Safety Study of Tivanisiran to Treat Dry Eye (SYL1001_VI): FYDES Study

Abbreviated Study Title:	FYDES Study
Protocol No:	SYL1001_VI
National Clinical Trial (NCT) No.:	Not applicable
Investigational New Drug (IND) No.:	130383
Study Phase:	3
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Medical Monitor:	[redacted]
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Protocol Synopsis

Title (Protocol No.):	Safety Study of Tivanisiran to Treat Dry Eye (SYL1001_VI): FYDES Study
Phase:	3
Study Design/Conduct:	Multicenter, double-masked, parallel, vehicle-controlled, randomized (2:1, 1.125% tivanisiran sodium ophthalmic solution: vehicle) study in approximately 300 subjects with mild to severe dry eye disease (DED).
Objectives:	Primary: Evaluate the safety, through adverse events (AEs), of tivanisiran sodium ophthalmic solution (1.125%) administered as 1 drop in both eyes (OU) once a day (QD) in treating DED signs and symptoms in subjects with a documented diagnosis of mild to severe DED. [redacted]
Endpoints:	Primary: 1. Frequency and percentage of subjects with ocular and non-ocular treatment emergent adverse events (TEAEs) for 1 year. Secondary: [redacted]
Population Studied:	Approximately 300 adult subjects with mild to severe DED will be studied. Inclusion Criteria: 1. Subject is age ≥ 18 years at Visit 1. 2. Has given written consent to participate in the study, after having received all information relating to the design, aims, and possible risks resulting therefrom. 3. Has used artificial tears (AT), autologous serum, or specific dry eye medications during the 6 months prior to Visit 1. [redacted]

	[redacted] Exclusion Criteria: 1. Currently participating or has participated in another clinical trial or has been exposed to an investigational product (IP) within the 2 months prior to inclusion. [redacted]. 2. Pregnant or breastfeeding females with a positive pregnancy test at Visit 1. 3. Women of childbearing potential (WOCBP) not willing to use a medically acceptable contraceptive method from enrollment until after the final visit. 4. Current, previous chronic, or recurrent medical condition that, according to the Investigator, might impact the interpretation of the study results or put the subject at risk. 5. Any concomitant treatment or prior ocular procedure or surgery in either eye or alteration of the dose of systemic medications at the time of entry into the study that could interfere in the assessment of the trial, per Section 5.5.1, Table 2, or per the Investigator's opinion. [redacted]
Investigational Products:	The IPs administered during the study will be: 1. Tivanisiran sodium ophthalmic solution, 1.125% (equivalent to tivanisiran ophthalmic solution, 1.05%) 2. Vehicle control (placebo: phosphate-buffered saline ophthalmic solution 0.97%)
Dosing Regimen:	1 drop (active or vehicle) OU QD in the morning
Assessments/Evaluations:	Safety: • AE monitoring • [redacted]

	[redacted]
Duration of Study:	Approximately 13 months
Statistical Methods:	Sample size is based on adequate safety exposure to support a potential New Drug Application (NDA) for tivanisiran ophthalmic solution in the United States (US). The assessment of safety will be performed on the Safety Analysis Set and based on the summary of ocular and non-ocular AEs, [redacted]

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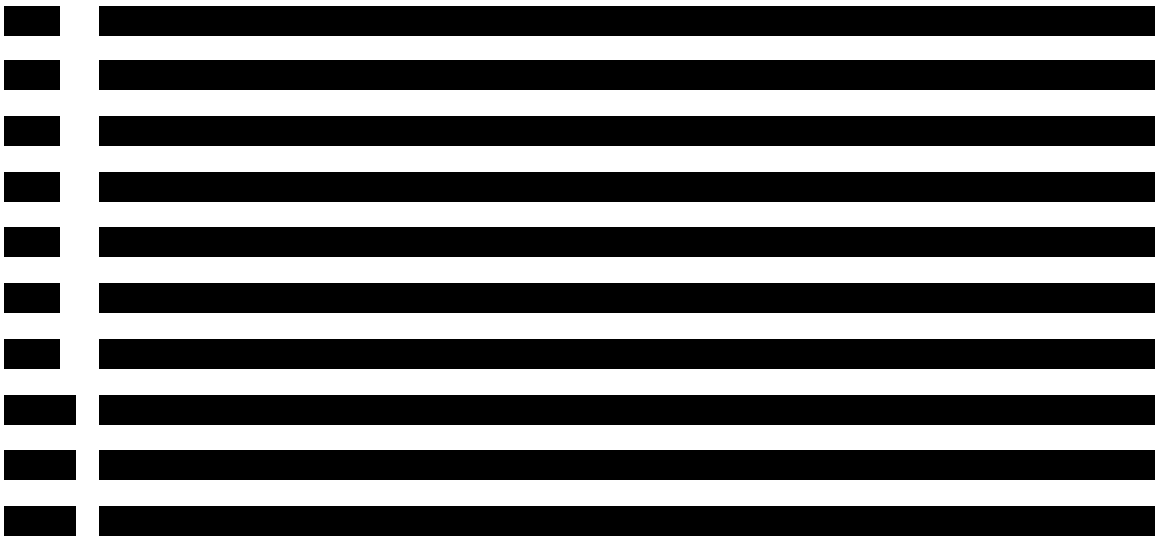

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1. Introduction

1.1 Background

Dry eye disease (DED) is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort such as burning sensation, itching, redness, stinging, pain, and foreign body sensation; visual disturbances; tear film instability; and often ocular surface damage (Perry, 2008; Schultz, 2014). Global prevalence of DED is estimated at 300 million, or 5% to 50% of select populations, with the disease generally more common in women than men and in Asian populations compared to Caucasian populations (Stapleton et al., 2017).

Current treatments include tear replacement, anti-inflammatory agents, serum or umbilical cord serum eye drops, and surgical interventions. According to Jones et al. (2017), it is "clear that many of the treatments available for the management of dry eye disease lack the necessary Level 1 evidence to support their recommendation" and there are "challenges . . . in predicting the relative benefits of specific management options." Topical treatments have been associated with side effects such as instillation pain and irritation (Schultz, 2014; Leonardi et al., 2016), ocular hypertension, and cataract formation (Marsh and Pflugfelder, 1999).

Tivanisiran sodium ophthalmic solution (eye drops) is a sterile, preservative-free solution being developed by Sylentis for treating and/or preventing signs and symptoms of DED. The active substance in the investigational product (IP) is tivanisiran sodium, a [redacted]-base pair, synthetic, oligonucleotide salt. Tivanisiran sodium is a small interfering ribonucleic acid (siRNA) inhibitor of transient receptor potential cation channel subfamily V member 1 (TRPV1) synthesis via an RNA interference (RNAi) mechanism. TRPV1 participates in ocular pain sensing, transmission, and regulation and acts as mediator of innate inflammatory response (Benítez-Angeles et al., 2020). These features are particularly relevant when treating DED.

[redacted]

1.2 Study Rationale

Tivanisiran sodium is a synthetic, double-stranded, [redacted] nucleotides in length, rationally designed siRNA that targets TRPV1 mRNA in a selective manner. DED is a very common disease and despite new advancements, few effective treatment options are available for patients.

The potential features of tivanisiran sodium are as follows:

- Tivanisiran sodium reduces specifically the expression of TRPV1. *In vitro* studies showed the silencing activity of tivanisiran sodium against TRPV1 without affecting cell viability. This specificity should greatly reduce any local or systemic related adverse events (AEs).
- Tivanisiran sodium has very limited systemic absorption. [redacted] These results were confirmed in pharmacokinetic studies, where low levels of tivanisiran were detected in few animal samples treated at high doses, as well as in human studies (SYL1001_I clinical trial), where no levels were detected at doses at least twice the proposed clinical dose. The low systemic exposure supports a very limited absorption outside the eye; therefore systemic side effects should be minimized.
- Non-clinical and clinical studies have shown that tivanisiran sodium decreases ocular pain discomfort without affecting corneal anesthesia. This is an essential feature for ocular chronic treatments.
- Data arising from two dose-finding clinical trials identified the dose of 1.125% tivanisiran sodium solution as the most efficient in reducing pain using Visual Analogue Scale (VAS) scoring, corneal fluorescein staining (CFS), and tear (film) break-up time (TBUT). [redacted]
- Tivanisiran sodium eye drops have been safe and very well tolerated in non-clinical and clinical studies (SYL1001_I to SYL1001_IV clinical trials). Tivanisiran sodium is formulated in the absence of antimicrobials such as benzalkonium chloride (BAC), a preservative that is associated with an increase in AEs related to problems with local tolerability and often a cause of discontinuation of medications.
- [redacted] Tivanisiran sodium affects the translation of a specific protein by degradation of the corresponding mRNA.

The dose of 1.125% was selected to continue with the clinical development program of this compound based on efficacy results obtained in phase 2 and 3 trials.

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

Not all risks of or problems with using tivanisiran sodium ophthalmic solution are known. No potential risks have been identified with tivanisiran during its clinical and non-clinical development, and no dose-limiting AEs have been reported during any of the clinical trials. Eye pruritus is the only AE replicated in both clinical trials where the dose level of 1.125% was tested (SYL1001_II and SYL1001_IV). Eye pruritus was reported in 2 patients (10%) in the SYL1001_II clinical trial and in 1 patient (0.70%) in SYL1001_IV.

1.3.2 Known Potential Benefits

Predictable benefits of tivanisiran sodium derive from the nature of the molecule. Treatment with siRNAs might result in a longer-lasting effect and restriction of the site of action to the eye. A longer-lasting effect could allow for less frequent dosing, a positive feature for patient compliance.

Tivanisiran sodium is an siRNA that specifically reduces the expression of TRPV1; this specificity should decrease the onset of local AEs related to its acute or chronic use. Finally, tivanisiran sodium has very limited systemic absorption, minimizing the occurrence of systemic AEs.

1.3.3 Assessment of Benefits and Risks

Tivanisiran sodium is demonstrated to be safe and well tolerated. No potential risks have been identified in association with tivanisiran sodium during its development. Furthermore, based on the results from dose escalation studies, no dose-limiting AEs have been identified during any of the clinical studies conducted with tivanisiran sodium. Continuing the clinical development program of tivanisiran sodium at 1.125% is justified by the anticipated benefits that may be afforded to patients suffering from exacerbated DED, especially for those patients with a more severe form of the disease.

2. Study Objectives and Endpoints

2.1 Study Objectives

The primary objective of this study is to evaluate the safety, through AEs, of tivanisiran sodium ophthalmic solution (1.125%) administered as 1 drop in both eyes (OU) once a day (QD) in treating DED signs and symptoms in subjects with a documented diagnosis of mild to severe DED. [redacted]

2.2 Study Endpoints

Safety analyses will be performed using both eyes. [redacted]

The study eye is defined as the eye meeting all inclusion criteria and no exclusion criteria, and with the highest CFS total scoring at Baseline/Randomization (Visit 1). If both eyes meet the inclusion criteria and no exclusion criteria and have the same CFS total score, the right eye will be used as the study eye.

2.2.1 Primary Endpoint

The primary endpoint is the frequency and percentage of subjects with ocular and non-ocular treatment emergent adverse events (TEAEs) for 1 year.

2.2.2 [redacted]

[redacted]

[redacted]

2.2.3 [redacted]

[redacted]

3. Study Design

3.1 Overall Design of the Study

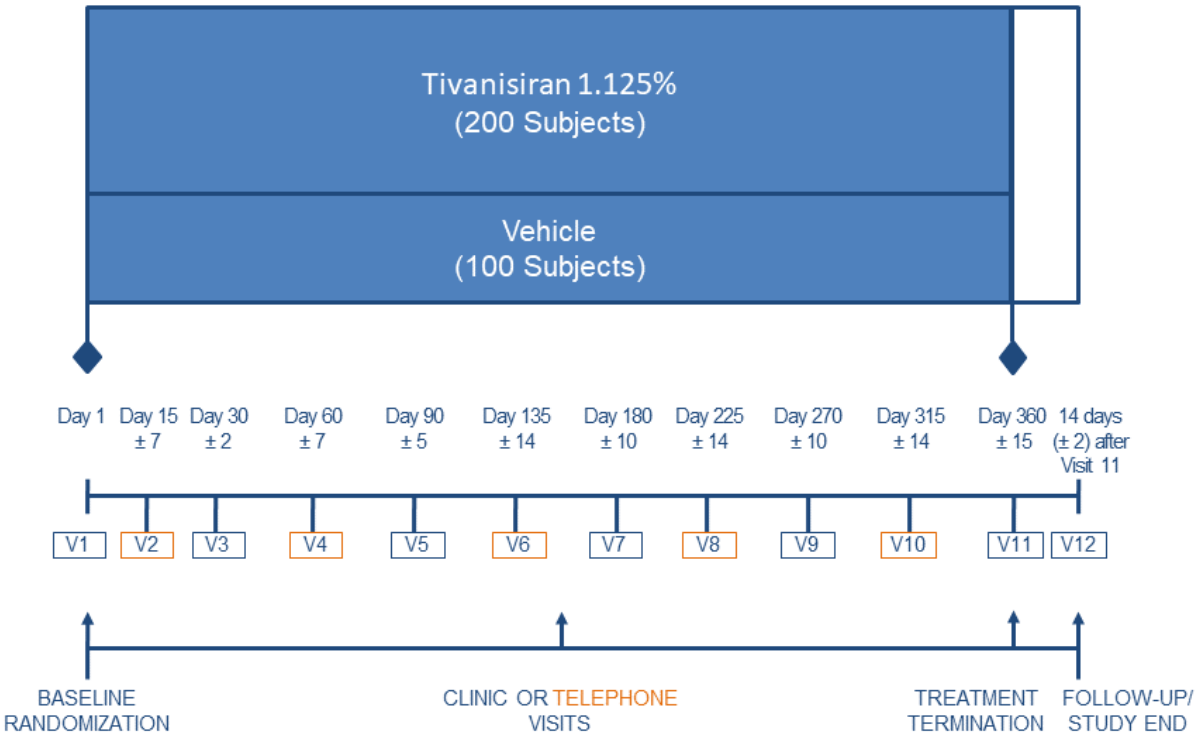
This is a phase 3, multicenter, double-masked, parallel, vehicle-controlled, randomized (2:1) trial comparing tivanisiran sodium ophthalmic solution to placebo (vehicle). Approximately 300 adult subjects will be enrolled in this study at approximately 25 sites in the United States (US). At Visit 1 (Baseline/Randomization), informed consent will be obtained from subjects and eligibility will be determined. Subjects will be randomly assigned in a 2:1 ratio to one of two double-masked treatment groups: either 1.125% tivanisiran sodium ophthalmic solution (approximately 200 subjects) or vehicle (approximately 100 subjects).

At Visit 3 (Day 30 ± 2 days), Visit 5 (Day 90 ± 5 days), Visit 7 (Day 180 ± 10 days), Visit 9 (Day 270 ± 10 days), Visit 11 (Day 360 ± 15 days), and Visit 12 (14 days after Visit 11 ± 2 days), subjects will attend clinic visits where safety [redacted] evaluations will be performed. Visit 2 (Day 15 ± 7 days), Visit 4 (Day 60 ± 7 days), Visit 6 (Day 135 ± 14 days), Visit 8 (Day 225 ± 14 days), and Visit 10 (Day 315 ± 14 days) are telephone visits in which adverse events and concomitant medications (CMs) will be documented, IP instillation and diary completion instructions will be repeated, and the next appointment will be confirmed.

Treatment with double-masked IP will be discontinued at Visit 11. Subjects who discontinue prior to Visit 11 will undergo Visit 11 evaluations (Early Termination [ET]). Visit 12 (Follow-Up, 14 days [± 2] after Visit 11) will take place two weeks after the last dose of IP.

A study schematic follows (Figure 1).

Figure 1: Study Schematic



3.2 Rationale for the Study Design

This study will examine the safety [redacted] of 1.125% tivanisiran sodium ophthalmic solution versus vehicle dosed OU QD for 1 year in subjects with signs and symptoms and a diagnosis of mild to severe DED.

Tivanisiran sodium will be administered as a topical ophthalmic solution. Subjects will receive IP in the clinic on the first day and will self-administer either tivanisiran sodium ophthalmic solution or vehicle QD in the morning, instilled bilaterally, for up to 360 days. The concentrations of tivanisiran sodium ophthalmic solution and dosing schedule were chosen based on non-clinical toxicology studies and data reflecting relative safety multiples, as well as data from previous clinical studies. For details on the toxicology studies and the respective safety multiples, see the Investigator's Brochure (IB).

Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. Each dose will be delivered by administering a drop ([redacted]) in each eye from a single-use vial.

3.3 Dose Justification

One phase 1 study (SYL1001_I), to assess pharmacokinetics and safety, and three vehicle-controlled clinical trials (SYL1001_II, SYL1001_III, and SYL1001_IV), to assess the effect and tolerance of different dose levels of tivanisiran ophthalmic solution, have been conducted.

Observations from SYL1001_I indicate a good local and systemic tolerance for tivanisiran sodium at various ([redacted]) dose levels. Subjects participating in SYL1001_II received a daily dose of [redacted] (1.125%), [redacted] or vehicle in both eyes whereas patients participating in SYL1001_III received a daily dose of [redacted] mg ([redacted]), or vehicle in both eyes for 10 consecutive days. These dose finding studies demonstrated that 1.125% was the most suitable dose for continuing the clinical development.

Ultimately, the tivanisiran sodium ophthalmic solution dose of 1.125% ([redacted]) was selected to continue with the clinical development program of this compound, and the SYL1001_IV clinical trial indicated that tivanisiran has a greater effect in patients with a more severe form of the disease.

3.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Procedures and Assessments (Appendix 1). The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study globally.

4. Study Population

The study population will consist of adult males and females who have been/are diagnosed with mild to severe DED.

4.1 Inclusion Criteria

A subject must meet all of the following in order to be enrolled into the study:

1. Subject is age ≥ 18 years at Visit 1.
2. Has given written consent to participate in the study, after having received all information relating to the design, aims, and possible risks resulting therefrom.
3. Has used artificial tears (AT), autologous serum, or specific dry eye medications during the 6 months prior to Visit 1.

[redacted]

4.2 Exclusion Criteria

A subject with any of the following will not be allowed to participate in this study:

1. Currently participating or has participated in another clinical trial or has been exposed to an IP within the 2 months prior to inclusion. [redacted].
2. Pregnant or breastfeeding females with a positive pregnancy test at Visit 1.
3. Women of childbearing potential (WOCBP) not willing to use a medically acceptable contraceptive method from enrolment until after the final visit.
4. Current, previous chronic, or recurrent medical condition that, according to the Investigator, might impact the interpretation of the study results or put the subject at risk.
5. Any concomitant treatment or prior ocular procedure or surgery in either eye or alteration of the dose of systemic medications at the time of entry into the study that could interfere in the assessment of the trial, per Section 5.5.1, Table 2, or per the Investigator's opinion.

6. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3 Randomization Criteria

At the Baseline/Randomization visit (Visit 1), a study subject must meet all clinical inclusion criteria and none of the exclusion criteria as defined in Section 4.1 and Section 4.2.

4.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. Minimal information, including demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE), will be recorded.

Individuals who do not meet the criteria for participation in this trial (screen failure) at the completion of Visit 1 because of the following may be rescreened:

- Prohibited medications from which the subject may discontinue for purposes of screening eligibility (with approval from Investigator based on clinical safety).
- Exclusionary medical history status at time of screening that will change (e.g., ocular infection, surgical history duration, etc.).

Rescreened subjects should be assigned a new subject number.

5. Study Treatments or Interventions

5.1 Investigational Products

The IPs administered during this study will be:

1. Tivanisiran sodium ophthalmic solution, 1.125% (equivalent to tivanisiran ophthalmic solution, 1.05%)
2. Vehicle control (placebo: phosphate-buffered saline ophthalmic solution, 0.97%)

5.1.1 Description

Active IP: Tivanisiran sodium ophthalmic solution, 1.125%, is an siRNA targeting human TRPV1 mRNA.

The active IP is delivered as a preservative-free sterile ophthalmic solution contained in single-use [redacted] vials grouped in strips. The active IP will be administered via an ophthalmic route through instillation into the lower conjunctival sac. The active IP will be administered as one drop per eye, per day of treatment.

Placebo: The placebo control is a phosphate-buffered saline (PBS) and is the vehicle in the formulation of tivanisiran sodium ophthalmic solution. Placebo will henceforth be referred to as vehicle. The vehicle will be administered via an ophthalmic route through instillation into the lower conjunctival sac. The vehicle will be administered as one drop per eye, per day of treatment.

Identical packaging and labeling of the active and vehicle IP will maintain the double-masked nature of the trial.

Table 1: Active and Vehicle IPs

	Active Investigational Product	**Vehicle Control (Placebo)**
Product	Tivanisiran sodium ophthalmic solution	Phosphate-buffered saline ophthalmic solution 0.97%
Dosage form	[redacted] mL ophthalmic solution	[redacted] mL ophthalmic solution
Unit dose	[redacted] µL drop size; 1.125%; 100% tivanisiran sodium	[redacted] µL drop size
Route of administration	Topical ocular administration	Topical ocular administration
Physical description	Colorless and clear ophthalmic solution	Colorless and clear ophthalmic solution
Excipients	[redacted]	[redacted]
Manufacturer	[redacted]	[redacted]

Additional details may be found in the IB.

5.1.2 Dosage and Administration

Single daily administration of 1 drop [redacted] µL) of the double-masked IP in both eyes (in the morning) will occur over a 360-day treatment period.

At Visit 1, randomized subjects will be assigned to an IP kit of double-masked IP (tivanisiran sodium ophthalmic solution 1.125% or vehicle). [redacted]

Subjects will return the used and unused double-masked IP at Visit 3 and will receive new kits (2-month supply) of IP. Subjects will return the used and unused double-masked IP at Visit 5 and will receive new kits (3-month supply) of IP at Visits 5, 7, and 9, each time returning the used and unused portion. At Visit 11, subjects will dose in the clinic and then return all used and unused double-masked IP. The double-masked labels will contain the following information:

- Primary label: Protocol number, kit number, contents, storage temperature, lot number, and required statement(s) per regulatory agency.
- Secondary label: Protocol number, kit number, visit, contents, storage temperature, Sponsor, lot number, and required statement(s) per regulatory agency.

5.2 Preparation/Storage/Handling/Accountability

5.2.1 Acquisition and Accountability

IP will be provided to the Investigator in cardboard boxes containing [redacted] foil pouches of [redacted] vials for the double-masked IP. The IP may be distributed by trained study staff. Used and unused IP will be maintained at the site for accountability by the clinical study monitor. When authorized by the Sponsor and after the clinical study monitor has verified drug accountability is complete and accurate, all used and unused double-masked IP will be returned to a specialized company designated by the Sponsor for destruction.

5.2.2 Product Formulation, Appearance, Packaging, and Labeling

Tivanisiran sodium will be supplied in conventional [redacted] single-use vials (or ampoules) with a nominal capacity of [redacted] mL filled with [redacted] mL of the ophthalmic solution. The single-use vials will be provided in strips [redacted] and packaged in [redacted] pouches.

Double-masked IP will be contained in monthly kits [redacted] of product sufficient for at least 30 days of treatment. Two kits will be dispensed for 60-day intervals between clinic visits; 3 kits will be dispensed for 90-day intervals.

5.2.3 Product Storage and Stability

IP will be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide investigational product to any subject not participating in this protocol.

Stability studies support tivanisiran sodium stability up to [redacted] at [redacted] (ongoing) in [redacted] single-use vials. IP should be protected from light and moisture. Before it is dispensed, IP should be stored between [redacted]. The clinical site staff will maintain a temperature log in the IP storage area, verifying the temperature each working day. Permitted temperature excursions occurring at the site are defined below; excursions outside the below parameters will be reported:

Assessment criteria in the event of a LOWER temperature excursion	
Criterion < [redacted]°C	
Documented lowest temperature (°C)	**Acceptable excursion period**
[redacted]	[redacted] hours

Assessment criteria in the event of an UPPER temperature excursion	
Criterion > [redacted]°C	
Documented highest temperature (°C)	**Acceptable excursion period**
[redacted]	[redacted]
[redacted]	[redacted]

Once IP has been dispensed, the subject may store it at room temperature [redacted] a safe, cool, and dry place at home.

5.2.4 Preparation

The double-masked IP will not require on-site preparation by the Investigator.

5.3 Measures to Minimize Bias: Randomization and Masking

To minimize bias, the study is randomized and double-masked.

Subjects will be randomized to treatment assignment. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data.

A randomization schedule will be generated by the electronic data capture (EDC) system. The EDC will be used for randomization and unmasking.

Double-masked IP, either tivanisiran sodium 1.125% or vehicle, assigned to subjects at randomization in the double-masked treatment phase, will be identical in appearance. Sponsor, subjects, and investigative staff will be masked to the identity of treatment until completion of the study and final database lock.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor after consultation with the Sponsor.

5.4 Treatment Compliance

Double-masked IP will be administered bilaterally once daily (in the morning) for 360 days. Compliance with application of IP will be reviewed and assessed at Visits 3, 5, 7, 9, and 11 via review of the subject dosing diary.

Adherence to the dosing protocol will be assessed and verified via subject dosing diary and IP return accountability by the site staff and study monitor.

All unused and/or used IP must be returned to the investigative site at Visits 3, 5, 7, 9, and 11. At the same visits, subjects will be queried regarding compliance with the dosing regimen. Any missed doses will be recorded on the subject electronic Case Report Form (eCRF) via the subject dosing diary.

5.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and supplements.

All medications that the subject has taken 1 month prior to Visit 1 and through Visit 12 or discontinuation from the study will be recorded in the eCRF and the subject chart. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an adverse event will be recorded for each medication. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug).

5.5.1 Prohibited Medications and Procedures

Table 2: Medications and Procedures NOT Permitted

Medication and Procedures Not Permitted	Minimum Washout Prior to Visit 1 (Unless Otherwise Noted)
Use of [redacted]	Prior history
Corneal transplant or similar corneal surgery ([redacted].)	Prior history
Any incisional intraocular surgical procedure	[redacted] months
Incisional ocular surface surgery, [redacted]	[redacted] months
Eyelid surgery	[redacted]months
Yttrium aluminum garnet (YAG) laser posterior capsulotomy or any laser ocular surgery	[redacted] months
Long-term dissolvable punctal plugs	[redacted] months
Mechanical treatments for meibomian gland dysfunction (MGD), [redacted]	[redacted] months
Any other IP	[redacted]months
Alter the dose of ○ Anticholinergics (if used on a chronic basis) ○ Antidepressants (if used on a chronic basis) ○ Systemic immunosuppressive agents ○ Systemic corticosteroids (oral or injectable). [redacted] ○ Chronic systemic or oral non-steroidal anti-inflammatory drugs (NSAIDs), painkillers, etc. ○ Oral contraceptives	[redacted] days
Topical ocular cyclosporine [redacted]	[redacted] days
Intranasal tear neurostimulation, external nasal neurostimulation	[redacted] days
Punctal cautery and/or short-term dissolvable punctal plugs inserted or removed	[redacted] days
Any topical ophthalmic medications (or makeup) [redacted]	[redacted] days

Tacrolimus, sirolimus (systemic or ophthalmic)	[redacted] days
Topical ocular, inhaled, or intranasal corticosteroids and topical dermatologic corticosteroids on the face. [redacted]	[redacted] days
Topical ocular or systemic antibiotics for the treatment of an ocular condition	[redacted] days
Serum tears, varenicline nasal spray	[redacted] days
Topical ocular NSAIDs	[redacted] days
Topical ocular or oral antihistamines or mast cell stabilizers	[redacted] days
Topical ocular or nasal vasoconstrictors ([redacted])	[redacted] days
Contact lenses/wetting solution	[redacted] days before each clinic visit
Sporadic use of NSAIDs or painkillers (including marijuana and cannabidiol [CBD] products)	[redacted] days before each clinic visit

5.5.2 Artificial Tears (AT) Therapy

Subject-supplied AT therapy is allowed during the study but limited to [redacted] *pro re nata* (PRN) (≤ [redacted] instillations daily, as needed). The subject will be queried about possible use of AT in the daily dosing diary and at each clinic visit.

6. Study Discontinuation/Participant Withdrawal

6.1 Discontinuation of Study Treatment or Intervention

The study IP may be discontinued by a subject at any time, although every effort will be made to ensure consistent subject participation for a full year. Subjects will be followed closely and the Investigator's staff will conduct telephone visits with each subject between clinic visits to assess AEs, review CMs, review IP and dosing diary protocols, and confirm next appointment. Reported AEs will be assessed by the Investigator.

In the event of discontinuation of IP by a subject, the Investigator will make every attempt to have the subject complete Visit 11 assessments as soon as possible. The subject will be discontinued following those assessments, and the reason for premature discontinuation will be recorded in the subject chart and entered in the eCRF.

6.2 Participant Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a subject from the study for the following reasons:

- Withdrawal of consent
- Study terminated by the Sponsor
- Lost to follow-up
- Pregnancy
- Significant study treatment/intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression that requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention may be replaced.

Those who sign the ICF, are randomized, receive the study treatment/intervention and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

In the event of study discontinuation, the Investigator will make every attempt to have the subject complete Visit 11 assessments as soon as possible. The reason for premature discontinuation will be recorded in the subject chart and entered in the eCRF.

6.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required clinic study visit:

- The site will attempt to contact the subject and reschedule the missed visit within 1 week, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7. Study Procedures

Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all subjects prior to any study-related procedures being performed. The Schedule of Procedures and Assessments (Appendix 1) lists the procedures that will occur at each study visit.

Ophthalmological examination will be performed in both eyes; [redacted] both eyes will be used for statistical analysis of safety.

Upon review of and signature of written informed consent, subjects may initiate the washout of prohibited medications.

7.1 Visit Descriptions

7.1.1 Visit 1 (Baseline/Randomization, Day 1), Clinic

The following procedures will be performed on all subjects at the Baseline/Randomization visit in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

Note: Randomization and IP initiation may proceed prior to receipt of lab results. A subject with clinically significant lab results may be exited from the study after Visit 1 upon Investigator consultation with the Sponsor and Medical Monitor.

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent and HIPAA authorization. (**Note:** This written ICF may be obtained prior to Visit 1 [e.g., for medication washout], but it is recommended that the ICF is reviewed and re-signed by the subject at Visit 1.)
- Assign Subject Identification Number: [redacted].
- Determine study eligibility based on Inclusion/Exclusion criteria.
- Obtain information including: demographics, prior and concomitant medications (CMs), ocular and systemic medical and medication history, and surgical history.
- *Urine pregnancy test (UPT) for WOCBP
- Administer the following subject-rated symptom assessments (in this order):
    - VAS for Dry Eye Symptom Score
    - NEI-VFQ-25
- BCVA
- [redacted]
- [redacted]

- CFS (NEI/Industry Workshop scale)
  - The Investigator should wait **approximately [redacted] minutes** after instillation of fluorescein before evaluating staining ([redacted]).
- Anesthetized Schirmer's test
  - Anesthetized Schirmer's test must be performed **at least [redacted] minutes** after fluorescein application and evaluation of CFS. Anesthetic eye drops should be administered during the 15-minute wait, approximately 3 minutes prior to the start of the Schirmer's test ([redacted]).
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- Determine if subject is eligible for randomization. For study subjects, the following is the process regarding administration of double-masked IP whereby the trained site staff will conduct the following procedures:
  - Enter subject information into Interactive Web Randomization System (IWRS) to determine randomization code and kit number.
  - Dispense dosing diary and train subject in daily completion.
  - Explain the method of IP administration.
  - Dispense double-masked kit ([redacted]) to the subject to take home.
  - Observe as the subject self-administers the first dose of double-masked IP at the clinic/site [redacted]. All remaining doses will be administered by the subject at home in the morning until Visit 11, when dosing will take place in clinic.
- [redacted]
- Assess for AEs
- Educate/remind subject:
  - Limit AT use [redacted].
  - If symptoms are not adequately controlled on IP, notify the study coordinator for instruction.
  - Complete dosing diary daily (see Appendix 17).
  - Return all medication and dosing diary at the next clinic visit.
  - Administer IP at least [redacted] minutes before the next (Visit 3) clinic assessments.
- Schedule the subject to return for Visit 3 (Day 30 ± 2 days).

7.1.2 Visit 2 (Day 15 ± 7 days), Telephone

The following procedures will be performed via phone call at Visit 2:

- Assess occurrence of AEs since last visit
- Update CMs since last visit
- Remind subject of IP instillation and diary completion instructions
- Confirm next clinic visit (Visit 3) and remind subject to administer IP at least 30 minutes prior to that visit

7.1.3 Visit 3 (Day 30 ± 2 days), Clinic

The following procedures will be performed in clinic at Visit 3. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- [redacted]
- Collect used and unused double-masked IP and subject dosing diary; evaluate compliance.
- Dispense new double-masked kits [redacted]) to the subject to take home for self-administration.
- Dispense new dosing diary.
- Remind subject:
    - Limit AT use to [redacted]
    - If symptoms are not adequately controlled on IP, notify the study coordinator for instruction.
    - Complete dosing diary daily.
    - Return all medication and dosing diary at the next clinic visit.
    - Administer IP [redacted] before the next (Visit 5) clinic assessments.
- Schedule the subject to return for Visit 5 (Day 90 ± 5 days).

7.1.4 Visit 4 (Day 60 ± 7 days), Telephone

The following procedures will be performed via phone call at Visit 4:

- Assess occurrence of AEs since last visit
- Update CMs since last visit
- Remind subject of IP instillation and diary completion instructions
- Confirm next clinic visit (Visit 5) and remind subject to administer IP at least 30 minutes prior to that visit

7.1.5 Visit 5 (Day 90 ± 5 days), Clinic

The following procedures will be performed in clinic at Visit 5 in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- *UPT for WOCBP
- [redacted]
- Collect used and unused double-masked IP and subject dosing diary; evaluate compliance.
- Dispense new double-masked kits (3-month supply) to the subject to take home for self-administration.
- Dispense new dosing diary.
- Remind subject:
    - Limit AT use [redacted].
    - If symptoms are not adequately controlled on IP, notify the study coordinator for instruction.
    - Complete dosing diary daily.
    - Return all medication and dosing diary at the next clinic visit.
    - Administer IP [redacted] next (Visit 7) clinic assessments.
- Schedule the subject to return for Visit 7 (Day 180 ± 10 days).

7.1.6 Visit 6 (Day 135 ± 14 days), Telephone

The following procedures will be performed via phone call at Visit 6:

- Assess occurrence of AEs since last visit
- Update CMs since last visit
- Remind subject of IP instillation and diary completion instructions
- Confirm next clinic visit (Visit 7) and remind subject to administer IP at least 30 minutes prior to that visit

7.1.7 Visit 7 (Day 180 ± 10 days), Clinic

The following procedures will be performed in clinic at Visit 7 in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- *UPT for WOCBP
- [redacted]
- Collect used and unused double-masked IP and subject dosing diary; evaluate compliance.
- Dispense new double-masked kits ([redacted]) to the subject to take home for self-administration.
- Dispense new dosing diary.
- Remind subject:
  - Limit AT use [redacted].
  - If symptoms are not adequately controlled on IP, notify the study coordinator for instruction.
  - Complete dosing diary daily.
  - Return all medication and dosing diary at the next clinic visit.
  - Administer IP [redacted] before the next (Visit 9) clinic assessments.
- Schedule the subject to return for Visit 9 (Day 270 ± 10 days).

7.1.8 Visit 8 (Day 225 ± 14 days), Telephone

The following procedures will be performed via phone call at Visit 8:

- Assess occurrence of AEs since last visit
- Update CMs since last visit
- Remind subject of IP instillation and diary completion instructions
- Confirm next clinic visit (Visit 9) and remind subject to administer IP at least 30 minutes prior to that visit

7.1.9 Visit 9 (Day 270 ± 10 days), Clinic

The following procedures will be performed in clinic at Visit 9 in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- *UPT for WOCBP
- [redacted]
- Collect used and unused double-masked IP and subject dosing diary; evaluate compliance.
- Dispense new double-masked kits ([redacted]) to the subject to take home for self-administration.
- Dispense new dosing diary.
- Remind subject:
    - Limit AT [redacted]
    - If symptoms are not adequately controlled on IP, notify the study coordinator for instruction.
    - Complete dosing diary daily.
    - Return all medication and dosing diary at the next clinic visit.
    - **Visit 11 dosing will happen in clinic; do not dose at home that morning.**
- Schedule the subject to return for Visit 11 (Day 360 ± 15 days). The final treatment should occur in the clinic on the morning of Visit 11.

7.1.10 Visit 10 (Day 315 ± 14 days), Telephone

The following procedures will be performed via phone call at Visit 10:

- Assess occurrence of AEs since last visit
- Update CMs since last visit
- Remind subject of IP instillation and diary completion instructions
- Confirm next clinic visit (Visit 11) and **remind subject to wait to administer IP in clinic** on that day

7.1.11 Visit 11 (Final Dose/Early Termination, Day 360 ± 15 days), Clinic

The following procedures will be performed in clinic at the Final Dose or ET Visit in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- *UPT for WOCBP
- Administer the following subject-rated symptom assessments (in this order):
    - Dry Eye Symptom Score (VAS)
    - NEI-VFQ-25
    - Global Impression/Assessment Questionnaires (Investigator/Subject-Rated)
- BCVA
- [redacted]
- [redacted]
- CFS
- Anesthetized Schirmer’s test
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Instillation of final dose [redacted]
- Collect used and unused double-masked IP and subject dosing diary; evaluate compliance.

7.1.12 Visit 12 (End of Study/Follow-Up, 14 days [± 2] after Visit 11), Clinic

The following procedures will be performed in clinic at End of Study/Follow-Up visit in the order presented below. Procedures that may be conducted at any point in the visit are marked with an asterisk (*).

- *Assess occurrence of AEs since last visit
- *Update CMs since last visit
- Dry Eye Symptom Score (VAS)
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- CFS
- [redacted]
- [redacted]

Subject may resume normal therapies for DED.

7.1.13 Unscheduled Visits

At times outside of normally scheduled visits, assessments will be conducted at the discretion of the Investigator.

7.1.14 Early Termination

In the event that a subject exits or is terminated from the study prior to the End of Study/Follow-Up visit (Visit 12), every attempt (per Section 6.1) will be made to ensure that all of the Visit 11 assessments are performed before the subject is discharged from the study.

8. Study Assessments

The Schedule of Procedures and Assessments (Appendix 1) provides a list of study assessments and evaluations to be performed and the timing of each.

8.1 [redacted]

[redacted]

8.2 Safety Evaluations

Safety assessments will be performed at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1) and as detailed below.

- AE monitoring
- [redacted]

8.2.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

AEs will be monitored throughout the study. Participants will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: “Have you noticed anything different since you started the study; began the IP, etc.?”

All AEs will be captured on the appropriate eCRF. Information to be collected at minimum includes event description, onset, assessment of severity, relationship to IP, and outcome. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most current version).

SAEs will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

8.2.1.1 Definitions

An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.1.2 Classification of Adverse Events

Severity of Adverse Events

The severity of all AEs will be assessed by the Investigator and graded as follows:

- **Mild:** requires minimal or no treatment and do not interfere with the participant's daily activities

- **Moderate:** results in a low level of inconvenience or concern and may cause some interference with functioning
- **Severe:** interrupts a participant's usual daily activity. Severe events are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious."

Relationship of Adverse Events

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

- **Unrelated:** the AE is completely independent of IP administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the Investigator.
- **Unlikely:** a clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Possibly:** some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Probably:** evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the IP, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Definitely:** clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to IP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Possibly, probably, and definitely AEs will be considered related to IP for reporting purposes. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a *class of drugs* (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator will be responsible for determining whether an AE is unexpected, i.e., if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

8.2.1.3 Adverse Event Reporting Requirements

According to federal regulations, an Investigator must immediately report within 24 hours to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor Safety Department (See 21 Code of Federal Regulations [CFR] 312.64(b)).

According to federal regulations, the Sponsor must notify the US Food and Drug Administration, Department of Health and Human Services (FDA) and all participating Investigators as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that a potential serious risk arising from a clinical study qualifies for reporting. Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event (See 21 CFR 312.32(c)(1)).

Furthermore, the Sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (See 21 CFR 312.32(c)(2)).

8.2.1.4 Other Events of Interest

Not applicable.

8.2.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period.

Any report of pregnancy for any female study patient must be reported within 24 hours to the Sylentis Safety Department or its delegate using the Pregnancy Report Form. The pregnant female study patient must be withdrawn from the study.

Every effort will be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days after delivery.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sylentis Safety Department using the Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Sylentis Safety Department.

- [redacted]
  - [redacted]

9. Statistical Considerations

Continuous measures will be summarized descriptively by the mean, standard deviation, median, minimum, and maximum values. Categorical measures will be summarized by the frequency and percentage of subjects.

A separate Statistical Analysis Plan (SAP) will be prepared prior to unmasking of study data. Any amendments or changes to the planned analyses will be described in the SAP.

9.1 Statistical Hypothesis

Because this is primarily a safety study of tivanisiran sodium ophthalmic solution (1.125%), no formal hypotheses for efficacy have been defined.

9.2 Sample Size Determination

Sample size is based on adequate safety exposure to support a potential New Drug Application (NDA) for tivanisiran ophthalmic solution in the US.

9.3 Analysis Populations

The Full Analysis Set (FAS) consists of all subjects who were randomized. Subjects will be analyzed in the group to which they were randomized. [redacted]

The Per Protocol (PP) Analysis Set will include all subjects who completed study-required treatment and who followed the protocol without significant deviations. The determination of significant protocol violations will be made prior to locking the final database and unmasking. Subjects will be analyzed in the group according to the treatment received.

The Safety Analysis Set will include all subjects who took at least one dose of investigational product as indicated on the dosing record. Subjects will be analyzed in the group according to the treatment received. All safety variables will be analyzed using the Safety Analysis Set and only observed data will be included (i.e., missing data will remain missing for the safety analysis).

9.4 Statistical Analyses

The statistical analysis of the study will be performed on the data through Visit 11 and will be performed after all subjects have either completed Visit 11 or discontinued early from the study and after the study database has been cleaned, verified, and locked. It is planned that the data from all clinical sites that participate in this study will be combined so that the target sample size will be available for analysis.

9.4.1 Baseline Descriptive Analyses

Demographic characteristics including age (years), sex, race, and ethnicity will be summarized by treatment group and overall. Medical history (coded using the most recent version of MedDRA), and prior and concomitant medications (coded using the most recent version of the WHODrug) will be summarized by treatment and overall.

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance, rescue due to lack of efficacy). A list of discontinued subjects, protocol deviations, and subjects excluded from the analysis sets will be provided as well.

Exposure and compliance to study treatment will be summarized by treatment and overall.

[redacted]

[redacted]

[redacted].

[redacted]

9.4.3 Safety Analyses

Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, [redacted]. Summaries will be provided by treatment group, and for ocular assessments separately by study eye and non-study eye.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA (most current version) and categorized by system organ class using preferred terms. Separate summaries of AEs related to treatment (as reported by the Investigator) and by severity will be presented. The number of deaths and SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

[redacted]

[redacted]

9.5 Subgroup Analyses

Subgroup analyses will be described in the SAP.

9.6 Exploratory Analyses

Not applicable.

9.7 Missing or Unused Data

Only observed data will be analyzed at each visit. [redacted]

9.8 Tabulation of Individual Participant Data

All data collected in this study will be presented in individual patient data listings for all subjects.

9.9 Data Safety Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1 Regulatory Issues, Ethical Concerns, and Study Oversight

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent Documents

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any procedures being done specifically for the study.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor, and regulatory authorities as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants,

the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension may include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB, and/or the FDA.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality will be extended to cover testing of laboratory samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The Study Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product will be able to inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (i.e., office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at [redacted] This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by [redacted] research staff

will be secured and password protected. At the end of the study, all study databases will be de-identified and archived [redacted]

10.1.4 Clinical Monitoring

[redacted]., will conduct the clinical monitoring for this study. A Clinical Monitoring Plan (CMP) is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.5 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practice [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.6 Data Handling and Record Keeping

10.1.6.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, CMs, and expected adverse reactions data) and clinical laboratory data will be entered into [redacted], a 21 CFR Part 11-compliant data capture system provided by [redacted]. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.6.2 Study Records Retention

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 25 years, to meet international registration requirements. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of major deviations, corrective actions are to be developed by the site and implemented promptly. Details concerning minor, major, and critical protocol deviations will be outlined in a CMP or MOP.

It is the responsibility of the site's Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to IRB and [redacted]., and/or Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.8 Publication and Data Sharing Policy

All information provided concerning the drug and clinical trial is confidential and belongs to the Sponsor. The Investigator may use this information only in relation to the trial. He/she will also be obliged to provide the Sponsor with all data generated in the study.

All results, data, and information developed, generated, and derived from this clinical trial, including any inventions, processes, or improvements that may arise from conducting the clinical

trial, shall be the sole property of the Sponsor and, therefore, the Investigator agrees to treat this information as confidential and secret as mentioned above. The Investigator agrees not to disclose the information in any way without the prior written consent of the Sponsor.

Sylentis and the Investigators agree to the publication and wide dissemination of the results of this study. This study constitutes a joint effort between Sylentis and the Investigators and, as such, both parties agree that either party can make recommendations on articles or texts which shall be considered in preparing final scientific documents for publication or presentation. All publications and presentations proposed by the Investigators or their staff and associates that are derived or are related to this study must be sent to Sylentis for review 90 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable aspects that, at the discretion of Sylentis alone, justify the protection of intellectual or industrial property, Sylentis may delay any publication or presentation for a maximum of 90 days in order to request such protection.

In accordance with national and local regulations, this study protocol shall be presented in a clinical trial register for public access and shall receive a unique identification number. In addition, the results of this clinical study shall be revealed in an accessible clinical trial results database, regardless of the outcome.

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12. Appendices

12.1 Appendix 1: Schedule of Procedures and Assessments

	Baseline (Randomization)	Treatment									Final Dose/ET	Follow-Up
Visit No.[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study Days	**1**	**15 (±7)**	**30 (±2)**	**60 (±7)**	**90 (±5)**	**135 (±14)**	**180 (±10)**	**225 (±14)**	**270 (±10)**	**315 (±14)**	**360 (±15)**	**14 (± 2) days after Visit 11**
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics/Medical History	X											
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Reminders: IP and Diary Protocol, Next Visit	X	X	X	X	X	X	X	X	X	X		
UPT (WOCBP)	X				X		X		X		X	
Dry Eye Symptom Score (VAS)	X		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	X
NEI-VFQ-25 (QoL)	X										X	
Global Impression/Assessment Questionnaire (Investigator/ Subject-Rated)											X	
BCVA	X		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	X
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
CFS[2]	X		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	X
Anesthetized Schirmer's Test[3]	X		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]				[redacted]						[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]

	Baseline (Randomization)	Treatment									Final Dose/ET	Follow-Up
Visit No.[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study Days	**1**	**15 (±7)**	**30 (±2)**	**60 (±7)**	**90 (±5)**	**135 (±14)**	**180 (±10)**	**225 (±14)**	**270 (±10)**	**315 (±14)**	**360 (±15)**	**14 (± 2) days after Visit 11**
[redacted]	[redacted]						[redacted]				[redacted]	
[redacted]	[redacted]				[redacted]						[redacted]	
Randomization	X											
Dispense Double-Masked IP[5] and Dosing Diary	X		X		X		X		X			
Collect Used/Unused Double-Masked IP and Dosing Diary			X		X		X		X		X	
Double-Masked IP Administration in Clinic[6]	X										X	
[redacted]	[redacted]										[redacted]	
[redacted]			[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Key: BCVA=best corrected visual acuity; CFS=corneal fluorescein staining; ET=early termination; [redacted] IP=investigational product; [redacted]; [redacted]
UPT=urine pregnancy test; VAS=visual analog scale, WOCBP = women of childbearing potential.

[1] Visits 1, 3, 5, 7, 9, 11, and 12 will take place in clinic. Visits 2, 4, 6, 8, and 10 will take place via telephone call.
[2] Investigator should wait approximately 2 minutes after instillation of fluorescein before evaluating staining.
[3] Anesthetized Schirmer's test must be performed at least 15 minutes after fluorescein application and evaluation of CFS. Anesthetic eye drops should be administered during the 15-minute wait, approximately 3 minutes prior to the start of the Schirmer's test.
[4] [redacted].
[5] A 1- to 3-month supply of medication is provided on these visits.
[6] At Visit 1 and Visit 11, IP is to be administered QD into both eyes at the clinic at least 15 minutes after completion of the last ocular assessment. IP is to be administered by the subject at home for the remainder of the study (Day 2 through Day 359), and at least 30 minutes prior to clinic Visits 3, 5, 7, and 9.

12.2 Appendix 2: Abbreviations and Definition of Terms

°C	Celsius
°F	Fahrenheit
AE	Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]transferase Test, Serum Glutamic-Oxaloacetic Transaminase
AT	Artificial Tears
BAC	Benzalkonium Chloride
BCVA	Best-Corrected Visual Acuity
[redacted]	[redacted]
[redacted]	[redacted]
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
CMs	Concomitant Medications
CMP	Clinical Monitoring Plan
[redacted]	[redacted]
DED	Dry Eye Disease
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

ET	Early Termination (visit)
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	US Food and Drug Administration, Department of Health and Human Services
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Randomization System
LASIK	Laser-Assisted in Situ Keratomileusis
[redacted]	[redacted]
LogMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing at Random
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities

MGD	Meibomian Gland Dysfunction
mL	Milliliter
[redacted]	[redacted]
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
NCT	National Clinical Trial
NDA	New Drug Application
NEI	National Eye Institute
NEI-VFQ-25	NEI-Visual Function Questionnaire-25
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NZW	New Zealand White
OD	*Oculus Dexter* (right eye)
OS	*Oculus Sinister* (left eye)
OU	*Oculus Uterque* (both eyes)
PBS	Phosphate-Buffered Saline
PI	Principal Investigator
PP	Per Protocol
PRN	*Pro Re Nata* (as needed)
QC	Quality Control
QD	*Quaque Die* (one time per day)
QID	*Quater in Die* (four times per day)
QoL	Quality of Life
RBC	Red Blood Cell Count
[redacted]	[redacted]
RNAi	Ribonucleic Acid Interference

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
siRNA	Small Interfering Ribonucleic Acid
SOP	Standard Operating Procedure
[redacted]	[redacted]
[redacted]	[redacted]
TBUT	Tear (film) Break-Up Time
TEAE	Treatment Emergent Adverse Event
TRPV1	Transient Receptor Potential Cation Channel Subfamily V Member 1
µL	Microliter
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
VAS	Visual Analogue Scale
[redacted]	[redacted]
WHODrug	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential
YAG	Yttrium Aluminum Garnet

12.3 Appendix 3: Dry Eye Symptom Score (0–100 VAS)

Subjects will be asked the following questions regarding their current dry eye symptoms (unrelated to IP instillation) at each clinic visit.

The subject will be asked to subjectively rate dry eye symptoms (OU) by placing a vertical mark on the horizontal line to indicate the level of dry eye symptoms they are experiencing at this time. 0 corresponds to "No Symptoms" and 100 corresponds to "Severe Symptoms."

Subject Instructions: Please review the scale below. After your review, please rate how your eyes feel by placing a single vertical mark that represents the level of your dry eye symptoms at this moment.

0 = No Symptoms and 100 = Severe Symptoms

Dry Eye Symptoms	**0**	**100**
	|_____|	

12.4 Appendix 4: NEI-VFQ-25

National Eye Institute
Visual Function Questionnaire-25
(Version 2000)

PART 1: GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

	Circle One
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

	Circle One
Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

3. How much of the time do you worry about your eyesight?

	Circle One
None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

	Circle One
None	1
Mild	2
Moderate	3
Severe	4
Very Severe	5

PART 2: DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4

Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Are you currently driving, at least once in a while?

	(Circle One)
Yes	1 (Skip to Q 15c)
No	2

15a) IF NO: Have you never driven a car or have you given up driving?

	Circle One
Never drove	1 (Skip to Part 3, Q 17)
Gave up	2

15b) IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

	Circle One
Mainly eyesight	1 (Skip to Part 3, Q 17)
Mainly other reasons	2 (Skip to Part 3, Q 17)
Both eyesight and other reasons	3 (Skip to Part 3, Q 17)

15c) IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4

16. How much difficulty do you have driving at night? Would you say you have:

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or are you not interested in doing this	6

16a) How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

	Circle One
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

Read Categories	Circle One on Each Line				
	All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false or you are not sure.

	Circle One on Each Line				
	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me.	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

12.5 Appendix 5: INVESTIGATOR Global Impression Questionnaire

Screening number |__|__|__| |__|__|__| Site No. | Subject No.	☐ Final/Early termination visit (V11)	Assessment date |__|__| / |__|__| |__|__| / |__|__| (dd/mmm/yy)

INVESTIGATOR Global Impression Questionnaire

We would like you (Investigator) to answer the following question by putting a circle around the response that corresponds the best to your global impression.

Question:

In general, compared with the patient's dry eye signs at Visit 1/Baseline, how would you characterize his or her overall signs at this moment?

1. Marked worsening
2. Moderate worsening
3. Minimal worsening
4. Unchanged
5. Minimal improvement
6. Moderate improvement
7. Marked improvement

Date and Signature of the Investigator:

Date: ____ /____ / _____ (mm/dd/yyyy) Signature:_____

12.6 Appendix 6: SUBJECT Global Assessment Questionnaire

Screening number |__|__|__| |__|__|__| Site No. | Subject No.	☐ Final/Early termination visit (V11)	Assessment date |__| |__| / |__| |__| |__| / |__|__| (dd/mmm/yy)

SUBJECT Global Assessment Questionnaire

We would like you to answer the following question by putting a circle around the response that corresponds the best to your global impression.

Question:

Compared with Visit 1 (before starting study eye drops), how are your dry eye symptoms at this moment?

1. Much worse
2. Worse
3. About the same
4. Improved
5. Much improved

Date and Signature of the Subject:

Date: ____ /____ / _____ (mm/dd/yyyy) Signature:_____

12.7 Appendix 7: BCVA

Visual Acuity (VA) testing should precede any examination requiring contact with the eye or instillation of study dyes, as is detailed in the order of assessments for each visit in Section 7.1. LogMAR visual acuity must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

An ETDRS or modified ETDRS chart may be used. If a Lighthouse chart is used (24.5" by 25"; either reflectance or retro-illuminated), the subject must view the chart from a distance of exactly 4 meters (13.1 feet). If smaller reproductions (18" by 18", e.g., Prevent Blindness) are used, the subject viewing distance should be exactly 10 feet. Reflectance wall charts should be frontally illuminated (60-watt bulb or a well-lit room).

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the subject should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessments of visual acuity during the study, the same lighting conditions must be used consistently throughout the study

Calculations: LogMAR VA = Baseline value + (n × 0.02)

where: the baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and "n" is the total number of letters missed up to and including the last line read, and "0.02" is the value for each letter.

12.8 Appendix 8:

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

12.9 Appendix 9: [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

12.10 Appendix 10: CFS (NEI/Industry Workshop Scale)

The Investigator should wait approximately 2 minutes after instillation of fluorescein before evaluating staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The 5 areas of the cornea will be scored by the Investigator according to the following scoring system and the total score will also be calculated.

Note: The TBUT and the CFS may be performed in right eye then left eye or staggered, with the TBUT for the left eye being done during the waiting period before completing the CFS for the right eye.

12.11 Appendix 11: Anesthetized Schirmer's Test

Schirmer's test will be conducted on anesthetized eyes. A 35 mm x 5 mm filter paper strip is used to measure the amount of tears that are produced over 5 minutes. The strip is placed in the lower eyelid margin of both eyes with the use of a preplaced ophthalmic anesthetic drop. After 5 minutes, the strip is removed and the amount of wetting is measured in millimeters.

Anesthetized Schirmer's test must be performed at least 15 minutes after fluorescein application and evaluation of CFS. Anesthetic eye drops should be administered during the 15-minute wait, approximately 3 minutes prior to the start of the Schirmer's test.

12.12 Appendix 12: [redacted]

[redacted]

12.13 Appendix 13:

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

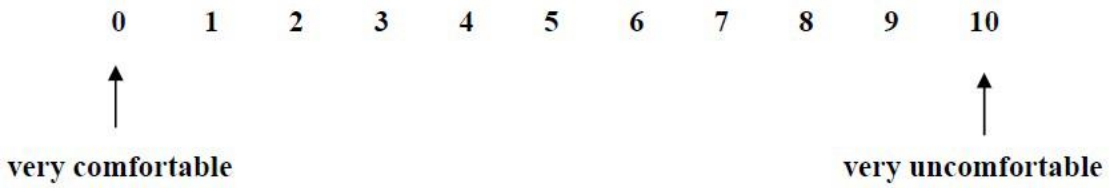
[redacted] If a third measurement is taken, all three measurements should be entered in the EDC.

12.15 Appendix 15: [redacted]

[redacted].

12.16 Appendix 16: Drop Comfort Assessment

At Visits 1 and 11, evaluation of the comfort of the eye drop will be conducted at least 15 minutes after completion of the last ocular assessment. Each eye will be evaluated immediately and at 1, 2, and 3 minutes following instillation of the IP at the site by trained study personnel. If the score is not ≤ 3 at minute 3, the drop comfort should be repeated every 5 minutes or until the score is ≤ 3.



12.17 Appendix 17: Subject Dosing Diary

The following is a sample of the content/information that will be collected in the daily subject dosing diary.

<table>
<tr><td colspan="5">FYDES Study (SYL1001_VI) Daily Subject Study Product Dosing Diary (Visit X – Visit X)</td></tr>
<tr><td>Subject ID #:</td><td colspan="4">___ ___ ___ - ___ ___ ___</td></tr>
<tr><td colspan="5">Diary Distribution/Review/Return</td></tr>
<tr><td>Date dispensed to subject:</td><td>__ __ / __ __ __ / 20 __ __
DD MMM YY</td><td>Date reviewed/returned to site:</td><td colspan="2">__ __ / __ __ __ / 20 __ __
DD MMM YY</td></tr>
<tr><td colspan="5">Section above to be completed by study personnel only.</td></tr>
<tr><td colspan="4">You are required to administer the study product <u>ONCE</u> a day in <u>BOTH</u> eyes.
Each time you administer study product in your eyes, record the date and time.</td><td>If you have used AT, please indicate below.</td></tr>
<tr><td>Record Date
<u>MM/DD/YYYY</u></td><td colspan="2">Time of Dose: ___:___ HH:MM ☐ AM ☐ PM
☐ Dose Not Taken Why:
_____</td><td>If dose not taken, indicate for which eye(s):
☐ Left ☐ Right ☐ Both</td><td>☐ Check if > 4 instillations of artificial tears</td></tr>
</table>

12.18 Appendix 18: Investigator Agreement

Protocol SYL1001_VI (FYDES Study)

Version No.: 1.0

Issue Date: 17 November 2021

I have read the clinical study protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with Good Clinical Practice Guidelines, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator:

Name (printed)	Signature	Date

12.19 Appendix 19: Compliance Statement

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki (2013) with respect to the use of human subjects in clinical studies and investigations.

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor's Representative:

[redacted] Signature Date

Medical Monitor:

[redacted] Signature Date