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

Protocol No:	SYL1001_VI
Protocol Date:	2021-11-17 (Original)
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AT	Artificial tears
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
[redacted]	[redacted]
[redacted]	[redacted]
CMP	Clinical Monitoring Plan
CS	Clinically significant
DED	Dry eye disease
eCRF	Electronic case report form
FAS	Full analysis set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council on Harmonisation
IOP	Intraocular pressure
IP	Investigational product
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non-clinically significant
NEI	National Eye Institute
OU	Oculus uterque (both eyes)
PP	Per protocol
PT	Preferred term
QC	Quality control
QD	Once daily

SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
TBUT	Tear break-up time
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
VFQ	Visual Function Questionnaire
WHODrug	World Health Organization Drug Dictionary

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] 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]
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]

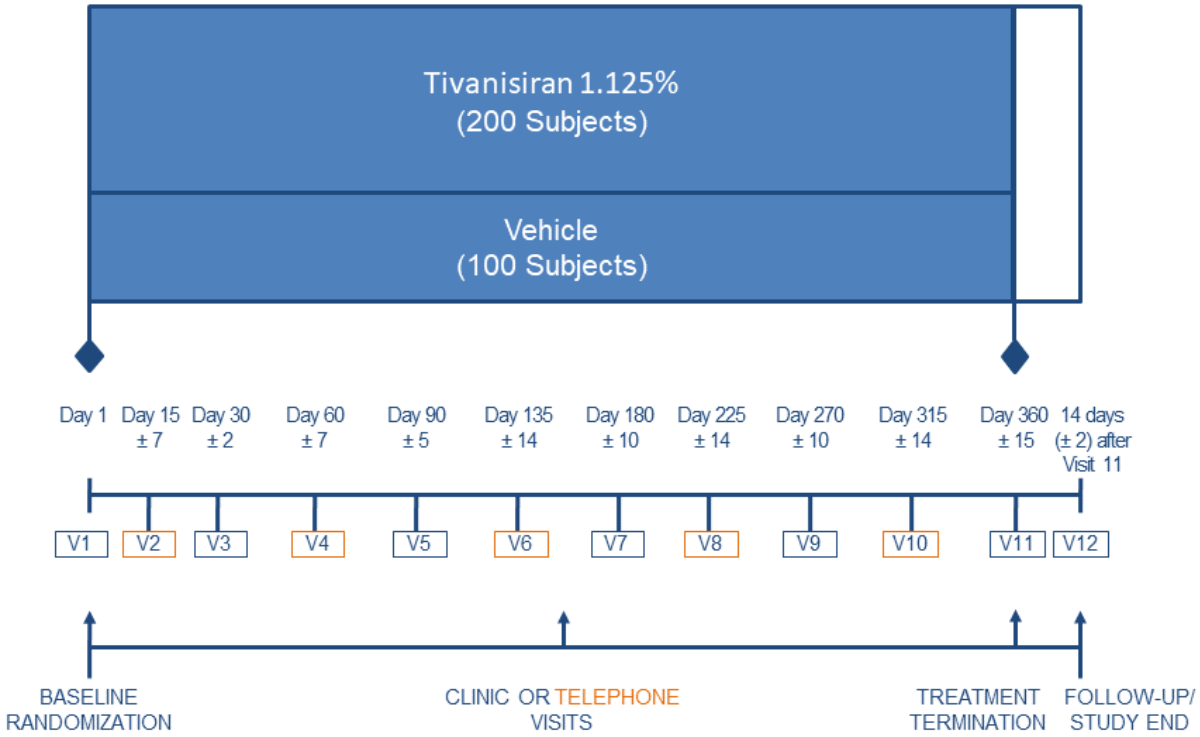
9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

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].

Figure 1 summarizes the design of the study.

Figure 1: Study Schematic



9.5.1.1. Visit and Procedure Schedule

See Table 1 in Appendix I for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), sex, race, and ethnicity will be collected at Visit 1. Baseline disease characteristics include CFS (total and by region), dry eye symptom score, TBUT, anesthetized Schirmer's score, and Sjögren's syndrome status.

9.5.1.2.2. Medical History

Ocular and non-ocular medical history will be collected at Visit 1.

9.5.1.2.3. Prior and Concomitant Medications and Therapies

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).

AT therapy is allowed during the study but limited to quater in die (QID) pro re nata (PRN) (≤ 4 uses daily, as needed). The subject will be queried about possible use of AT in the daily dosing diary and at each clinic visit.

Restricted and prohibited prior and concomitant therapy are outlined in the protocol Section 5.5.1.

9.5.1.3. Efficacy Assessments

9.5.1.3.1. Primary Efficacy Assessment(s)

[redacted]

[redacted]

9.5.1.4. Safety Assessments

The safety of tivanisiran sodium ophthalmic solution (1.125%) will be evaluated using [redacted].

1. Adverse event (AE) monitoring

[redacted]

9.5.1.4.1. Adverse Events

An adverse event is any untoward medical occurrence in a subject or clinical study subject, 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Severity of adverse events are described with the following scale:

- **Mild**: requires minimal or no treatment and do not interfere with the subject's daily activities
- **Moderate**: results in a low level of inconvenience or concern and may cause some interference with functioning
- **Severe**: interrupts a subject'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 to study intervention are classified according to the following scale:

- **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 subject'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 subject'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.

9.5.1.4.2. [redacted]

[redacted]

9.5.2. Appropriateness of Measurements

All assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variable(s)

For this trial, the primary endpoint is based on safety.

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

9.5.4. Drug Concentration Measurements

No drug concentration measurements will be made for this study.

9.6. DATA QUALITY ASSURANCE

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.

9.6.1. Training and Education of Investigators and Study Site Personnel

An Investigator Meeting will be held before study initiation and attended by the Investigators and/or Sub-Investigators from each study site, study coordinators from each study site, if possible, and personnel from the sponsor and the Contract Research Organization ([redacted]). The purpose of this meeting is to train and instruct the Investigators and the study coordinators on the proper conduct of the clinical trial and ensure that all subjects are aware of their obligations set out by the protocol, ICH guidelines, GCP guidelines, and other applicable regulatory requirements.

9.6.2. Monitoring of Study Sites

[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.

This clinical trial will be monitored at regular intervals. All information dealt with during these visits will be treated as strictly confidential. All monitoring and study management will be conducted according to GCP and United States Code of Federal Regulations.

9.6.3. Data Entry and Verification of Database Used for Analysis and Reporting

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.

[redacted] will review the eCRFs entered by investigational site staff for completeness and accuracy and instructed the investigational site staff to make any required corrections or additions. After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Queries will be sent to the investigational site and designated investigational site staff are required to respond to the query and edit data, as necessary. All changes to the study database will be documented.

It is the responsibility of the monitor to make certain that all data are completed on the eCRFs. At the end of each study period, the Investigator will sign and date the eCRF to attest to the authenticity of the collected data and coherence between the data in the eCRF and the data in the source documents.

9.6.4. Clinical Study Report

The final clinical study report will be reviewed, audited, and approved by medical, clinical, statistical, and regulatory staff from the sponsor, and key study contributors from [redacted]

9.6.5. Inter-Laboratory Standardization Methods

Not applicable. A single, qualified, and certified central clinical laboratory will be used to analyze and report clinical laboratory data.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

This section of the analysis plan describes the analyses explicitly mentioned in the protocol as well as additional analyses not explicitly mentioned in the protocol but planned prior to breaking the treatment mask. Section 9.8 describes any changes to analyses that were explicitly mentioned in the protocol or statistical analysis plan.

9.7.1. Statistical and Analytical Plans

General Conventions

Summary statistics for the data collected during this study will be presented to give a general description of the subjects studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of subjects in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values.

Number of subjects, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, standard deviations, standard errors, and quartiles will be calculated to one more decimal place than the source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%). Unless otherwise noted, summaries will be performed by the treatment group and presented in the order of Tivanisiran Sodium 1.125% and Vehicle.

Statistical tests will be presented as two-sided p-values rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' and p-values = 1 will be presented as '>0.9999' in all tables. Unless otherwise indicated, statistical testing will be carried out at the $\alpha = 0.05$ significance level.

Baseline values will be defined as the last measurement prior to dosing of double-masked study medication. Ocular measurements will use the most recent measurement for each eye.

Numeric laboratory data may be recorded at limits of detection (with a '<' or '>' sign, i.e., < 0.1 or > 0.1). To summarize the data, the original value will be converted to one unit less or more at the level of measured precision (e.g., 0.4 in the case of < 0.5 and to 0.6 in the case of > 0.5). The actual values will be presented in the data listings.

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

Computations for all results will be performed using SAS (Version 9.4, SAS/STAT 15.2) computer software package (SAS Institute, Inc, 2013, 2020), unless otherwise specified.

[redacted]

[redacted]

Missing Data and Outliers

Every attempt will be made to capture all study data. [redacted]. Safety analyses will use observed data only.

Visit Windows

The nominal visits listed in the eCRF will be used in the summaries. In general, unscheduled visits will not be summarized in tables unless otherwise noted.

Missing Dates

Missing dates that occur for prior or concomitant medications or adverse events will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as ’01-01’ (or ’01’).
- For stop dates, missing months will be imputed as ‘12’ and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Imputed dates will only be used to classify events or medications, such as occurring before or after the start of treatment. Imputed dates will only be used in tables. Listings will display the available date data.

Interim Analysis

There is no unmasked efficacy or futility interim analysis for this study.

9.7.1.1. Analysis Populations

9.7.1.1.1. 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. This [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 how they were treated. If the PP Analysis Set is the same as the FAS, separate summaries using the PP Analysis Set will not be provided.

The Safety Analysis Set will include all subjects who took at least one dose of double-masked 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). If the safety analysis set is the same as the FAS, then safety results will be provided using the FAS.

9.7.1.1.2. Analysis Eyes

Subjects in the FAS and PP Analysis Set will have at least one eye that qualifies based on the criteria in the protocol. Both eyes may qualify based on the criteria.

[redacted]

Safety analyses will be presented for both eyes.

9.7.1.2. Analysis of Subject Disposition

The number of subjects randomized at each site will be summarized by treatment group.

Subjects' enrollment and disposition during the study will be summarized by treatment group and overall based using the FAS, PP, and Safety Analysis Sets. The reasons for discontinuation will be displayed in the order as they appear on the eCRF.

Summary tables will include the following. The percentages will be calculated based on the number of subjects in each Analysis Set.

- Number of subjects screened
- Number and percentage of subjects randomized
- Number and percentage of subjects randomized with any protocol deviation
- Number and percentage of subjects treated
- Number and percentage of subjects treated with any protocol deviation
- Number and percentage of subjects treated who completed the study
- Number and percentage of subjects treated who discontinued from the study
- The reasons for study discontinuation
- Number and percentage of subjects attending each scheduled study visit

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), age group (<65 years, ≥65 years), sex, race, ethnicity, qualifying eyes, study eye (OD/OS), and baseline CFS score total and by region, dry eye symptom score, TBUT, anesthetized Schirmer's score, will be summarized descriptively by treatment group and overall using the FAS, PP, and Safety Analysis Sets. For categorical parameters, the percentages will be calculated overall and based on the number of subjects in each treatment group based on non-missing observations. The baseline characteristic parameters will be summarized for both the study eye and the non-study eye if the assessments were done on each eye separately.

[redacted].

9.7.1.3.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 24.1, Mozzicato, 2009). The frequency and percentage of subjects with any medical history will be summarized by treatment group using the FAS. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within active;
2. Descending frequency within vehicle;
3. PT in alphabetical order.

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical histories are identified according to which CRF the event is recorded. Ocular medical history will be summarized separately for study eye, non-study eye, and either eye.

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (Version 2021-09, Lagerlund et al., 2020) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of subjects with coded medications will be summarized by treatment group using the Safety Analysis Set. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup is sorted alphabetically, and preferred term is sorted by descending frequency overall within each Level 3 term according to:

1. Descending frequency within active;
2. Descending frequency within vehicle;
3. and PT in alphabetical order.

Prior and concomitant medications will be summarized separately. Ocular medications are defined as those medications for which an eye has been specified (OD, OS, or OU). Ocular and non-ocular medications will be summarized separately. Ocular medications will be summarized separately for study eye, non-study eye, and either eye.

Prior medications are defined as any medications that started and stopped prior to the first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the first dose of double-masked study drug. Medications taken after Visit 12 or withdrawal from the study are not considered concomitant.

Use of excessive AT (> 4 instillations daily) during the double-masked study period will be summarized by treatment group overall and by visit based on Safety Analysis Set. The by-visit analysis will include AT taken after the preceding in-clinic visit and up to and including the current in-clinic visit date or early withdrawal date (whichever is earliest), though the Visit 1 date is included in the first period (i.e., Visit 1 through Visit 3 or early withdrawal). No inferential statistics will be calculated for this summary.

9.7.1.4. [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

9.7.1.5. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

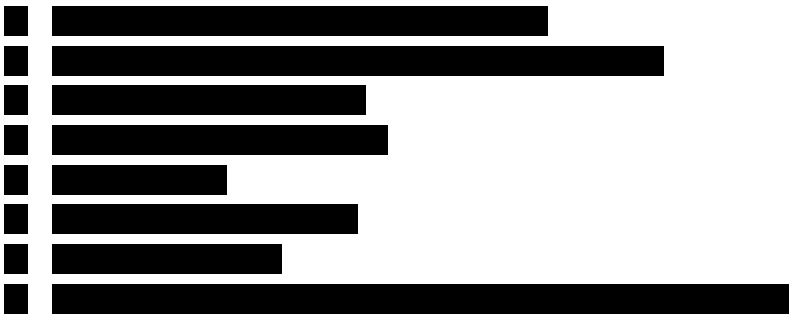
[redacted]

[redacted]

9.7.1.6. Analysis of Safety

Safety will be evaluated by:

1. Adverse event (AE) monitoring



The Safety Analysis Set will be used for all safety analyses. All data will be summarized as observed and no data imputation will be performed. No statistical treatment group comparisons will be performed, unless otherwise specified. Analyses will be presented by study eye and non-study eye, if applicable.

9.7.1.6.1. Adverse Events

AEs are coded using MedDRA Version 24.1. If a subject reported multiple events mapped to a single preferred term, the greatest severity and strongest Investigator assessment of relationship to study drug will be reported for the applicable summaries. Treatment-emergent adverse events (TEAE) are defined as events that start on or after first dose administration of double-masked study drug up to and including the last dose of double-masked study medication plus 30 days.

9.7.1.6.1.1.Overall Adverse Events

Though the study does not have a powered primary endpoint for efficacy, a description of estimands for adverse events is provided.

Estimands: The estimands are the proportion of subjects on tivanisiran sodium ophthalmic solution (1.125%) or vehicle experiencing individual treatment-emergent adverse events (TEAEs).

Target Population: Subjects with dry eye disease who meet the study entry criteria.

Endpoints: The proportion of subjects on tivanisiran sodium ophthalmic solution (1.125%) or vehicle experiencing individual TEAEs from Visit 1 to Visit 11.

Treatment Condition: Treatment condition is based on the treatment that was received.

Population-Level Summary: The proportion of subjects on tivanisiran sodium ophthalmic solution (1.125%) or vehicle experiencing individual TEAEs.

The proposed procedures to handle missing data and intercurrent events are as follows:

- Discontinuation of study therapy with continued participation in the study without receipt of rescue therapy
    - Treatment Policy – no imputation; use observed data.
- Use of excessive artificial tears (> 4 instillations daily)
    - Treatment Policy – no imputation; use observed data.
- Missing data with or without withdrawal, regardless of reason
    - Treatment Policy – no imputation; use observed data.

Frequency and percentage of individual TEAEs will be summarized by treatment group.

System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within active;
2. Descending frequency within vehicle;
3. PT in alphabetical order.

Subjects are counted only once for each SOC and PT. The percentages are calculated based on the number of subjects in each treatment group of the Safety Analysis Set.

Treatment-emergent adverse events are those events that start on or after the first dose administration of double-masked study medication up to and including the last dose of double-masked study medication plus 30 days. Pretreatment adverse events are events that begin prior to first dose administration of double-masked study medication.

Ocular and non-ocular AEs are summarized separately, and will each be summarized separately for pretreatment and treatment-emergent adverse events, though an overall summary of ocular and non-ocular events will be provided. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU). Ocular AEs will be presented by study eye and non-study eye and overall (OU) if an event occurs in either eye.

All AEs are displayed in listings.

- Subjects with any treatment-emergent adverse event
- Subjects with severe treatment-emergent adverse event
- Subjects with any study drug related treatment-emergent adverse event

Treatment-emergent adverse events with closest relationship to study drug according to the categories specified in the protocol (Unrelated, Unlikely, Possibly, Probably, and Definitely) will be summarized for related events by SOC, PT, and treatment group. The summary will be repeated for TEAEs with the closest relationship group (Unrelated or Unlikely; Possibly, Probably, or Definitely Related).

A study drug related AE is defined as any AE that is assessed by the investigator with the relationships of possibly, probably, and definitely-related. A study drug non-related AE is defined as any AE that assessed by investigator with the relationships of “Unrelated” or “Unlikely”. Any treatment-emergent AEs that have a missing relationship will be presented as “Definitely Related” in the summary table but will be presented with a missing relationship in the data listing.

Treatment-emergent adverse events with maximum investigator-reported severity (mild, moderate, severe) will be summarized by SOC, PT, and treatment group. Any treatment-emergent AEs that have a missing severity will be presented as severe in the summary table but will be presented with a missing severity in the data listing.

9.7.1.6.1.2.Deaths, Serious Adverse Events and Other Significant Adverse Events

Any treatment-emergent adverse event leading to study drug discontinuation or study termination, serious adverse event (treatment-emergent or otherwise), or subject deaths will be provided in separate listings.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.7.2. Determination of Sample Size

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

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Protocol Amendments

Not applicable.

9.8.2. Changes from Protocol-Specified Analyses

[redacted].

Some changes due to protocol clarification memos were also added to this SAP. [redacted].

REFERENCES

1. Mangione CM. (2000). NEI VFQ-25 Scoring Algorithm. Available at: https://www.nei.nih.gov/sites/default/files/2019-06/manual_cm2000.pdf.
2. Mozzicato P. (2009). MedDRA: An overview of the medical dictionary for regulatory activities. Pharmaceutical Medicine 23: 65-75.
3. Lagerlund O, Strese S, Fladvad M & Lindquist M. (2020). WHODrug: A global, validated and updated dictionary for medicinal information. Therapeutic Innovation & Regulatory Science 54: 1116–1122.
4. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
5. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

APPENDIX I: SCHEDULE OF ASSESSMENTS

Table 1: Schedule of 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]										X
NEI-VFQ-25 (QoL)	X										X	
Global Impression/Assessment Questionnaire (Investigator/ Subject-Rated)											X	
BCVA	X	[redacted]										X
[redacted]												
CFS[2]	X	[redacted]										X
Anesthetized Schirmer's Test[3]	X											
[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]												
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]												

Key: BCVA=best corrected visual acuity; CFS=corneal fluorescein staining; ET=early termination; [redacted] IP=investigational product; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire-25; QoL=quality of life; [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.
[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.