NCT04556838

Clinical Study VVN001-CS201

Statistical Analysis Plan

13 January 2022

Sponsor:	VivaVision Biotech, Inc.		
Protocol:	VVN001-CS-201		
Document Version No.:	V3.0	**Document Date:**	13-JAN-2022

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Protocol VVN001-CS-201

A Phase 2a, Double-Masked, Randomized, Vehicle-controlled Trial Evaluating the Safety and Efficacy Activity of 1% and 5% VVN001 Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: **(Version Date)**	VVN001-CS-201 (17 June 2020)
Name of Test Drug:	1% and 5% VVN001 Ophthalmic Solution
Phase:	2a
Methodology:	Double-Masked, Randomized, Vehicle-controlled Trial
Sponsor:	VivaVision Biotech, Inc.

Sponsor Representative:

Document Date:	13 January 2022
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SIGNATURE PAGE

Protocol Title: A Phase 2a, Double-Masked, Randomized, Vehicle-controlled Trial Evaluating the Safety and Efficacy Activity of 1% and 5% VVN001 compared to Vehicle in Subjects with Dry Eye Disease

Sponsor: VivaVision Biotech, Inc.

Protocol Number: VVN001-CS-201

Document Date/Version: 17 June 2020/Final

Cytel, Inc. Author:

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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Sponsor Signatory:

Signature:_____

Date:_____

Signature:_____

Date:_____

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
AR	Adverse Reaction
BCVA	Best Corrected Visual Acuity
BID	Bis in die (twice per day)
CFB	Change from Baseline
CFS	Corneal Fluorescein Staining
CSR	Clinical study report
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICF	Informed Consent Form
iCFS	Inferior region of CFS
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
OD	Oculus Dextrus (right eye)
OU	Oculus Uterque (both eyes)
P	Probability
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAF	Safety Set
SANDE	Symptom Assessment Questionnaire iN Dry Eye
SAP	Statistical analysis plan
TEAE	Treatment-Emergent Adverse Events

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Abbreviation	**Definition**
tCFS	Total Corneal Fluorescein Staining
VA	Visual Acuity
VAS	Visual Analog Scale

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1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This document presents the statistical analysis plan (SAP) for VivaVision Biotech, Inc., Protocol VVN001-CS-201: "A Phase 2a, Double-Masked, Randomized, Vehicle-controlled Trial Evaluating the Safety and Efficacy Activity of 1% and 5% VVN001 compared to Vehicle in Subjects with Dry Eye Disease".

The SAP is based on the final protocol dated June 17,2020 and the purpose of this document is to outline the appropriate statistical approaches to be used in the analysis of study data in order to answer the study objectives. The populations for analysis defined, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will also provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Objectives of Statistical Analysis

1.2.1. Primary Objective

The primary objective of this trial is to evaluate the safety and tolerability of VVN001, 1% ophthalmic solution and VVN001, 5% ophthalmic solution when administered BID compared to vehicle administered BID.

1.2.2. Secondary Objective

The secondary objective is to evaluate the efficacy activity of VVN001, 1% ophthalmic solution and VVN001, 5% ophthalmic solution administered BID compared to vehicle administered BID in the treatment of signs and symptoms of DED.

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2. STUDY DESIGN

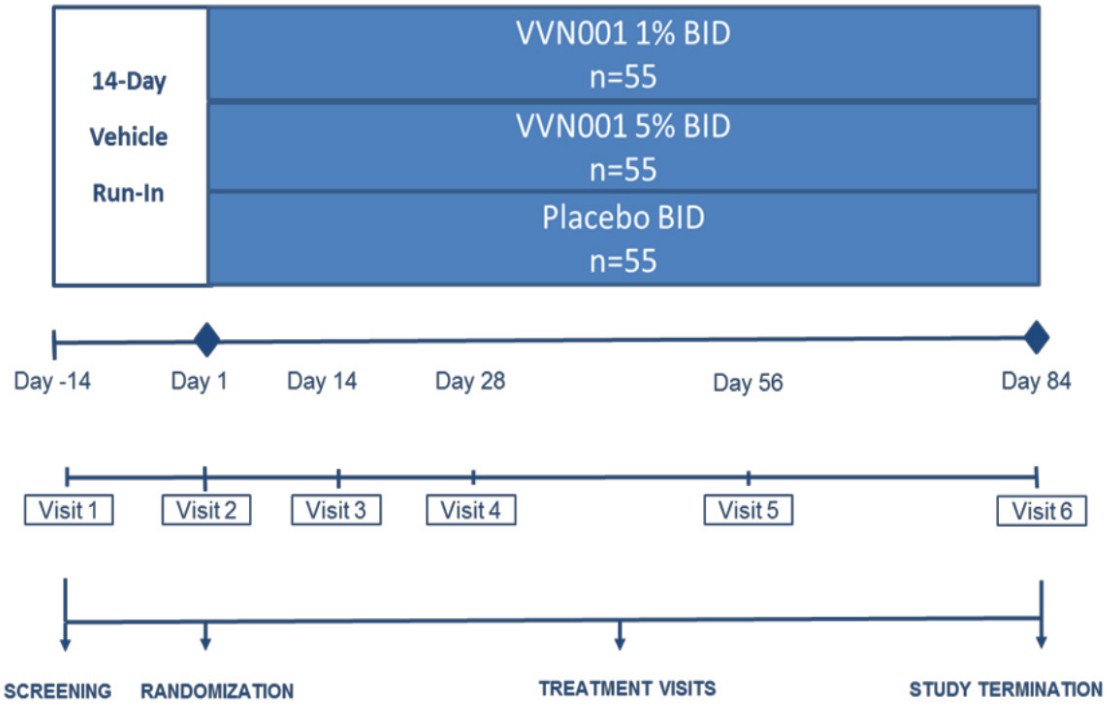
2.1. Synopsis of Study Design

This is a Phase 2a, multi-center, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and tolerability and to explore the efficacy activity of VVN001 1% and 5% Ophthalmic solution versus vehicle in subjects with dry eye disease. Approximately 165 subjects who meet inclusion/exclusion criteria will be eligible for randomization in 1:1:1 ratio to one of the 3 treatment groups: VVN001 Ophthalmic solution 1%, 5% or vehicle.

The study will consist of two periods over 14-weeks total: screening/run-in period (Day -14 to Day -1), and treatment period (Day 1 to Day 84).

2.1.1. Study Schematic

Figure 1. Study Visits Schematic



2.1.2. Study Eye

Subjects must replicate the following findings in the same eye at Visits 1 and 2 in order to be considered for further study eligibility: 1) Inferior CFS score ≥ 2 (0 - 4 scale) and 2) Schirmer score STT without anesthesia ≥ 1 and ≤ 7 mm, at Visit 1 and 2. If both eyes meet the two criteria above, the eye with the greater inferior CFS at Visit 2 will be selected as the study eye. If both eyes have an equal inferior CFS score at Visit 2, the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal score in inferior CFS scores and equal STT values at Visit 2, the right eye (OD) will be selected as the study eye.

2.1.3. Study Treatment

VVN001 Ophthalmic Solution 1%, 5% or Vehicle will be administered to the ocular surface twice daily as a single drop in each eye administered morning and evening. The first dose of Single-Masked Vehicle and the first dose of Double-Masked IP (VVN001 1%, 5% or Vehicle) will be self-administered in the morning dose for that day. Following Visit 1, the second dose of Single-Masked IP will be received in the evening for approximately 14 days. Following Visit 2, the subject will be instructed to self-administer the second dose of Double-Masked IP in the evening BID instilled into each eye bilaterally for approximately 84 days.

2.2. Randomization Methodology

Approximately 165 subjects will be randomized by permuted block in this study at approximately 10 centers located in the United States. Subjects will be randomized to one of the following 3 treatment groups VVN001 1%, 5% or Vehicle in a 1:1:1 ratio.

2.3. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

Table 1 Schedule of Assessments

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
	SCREENING	RANDOMIZATION	TREATMENT VISIT	TREATMENT VISIT	TREATMENT VISIT	FINAL TREATMENT VISIT
	DAY - 14 (+/-1 DAY)	DAY 1 (+/-2 DAYS)	DAY 14 (+/-2 DAYS)	DAY 28 (+/-2 DAYS)	DAY 56 (+/-2 DAYS)	DAY 84 (+/-2 DAYS)
INFORMED CONSENT AND MEDICAL HISTORY	X					
INCLUSION/EXCLUSION CRITERIA[D]	X	X				
CONCOMITANT MEDICATION QUERY	X	X	X	X	X	X
ASSESS PRIOR ARTIFICIAL TEAR USE	X					
CLINICAL SAFETY LABORATORIES AND HEMATOLOGY	X					X
ADVERSE EVENT QUERY		X	X	X	X	X
COLLECT STUDY DRUG		X[B]		X[C]	X[C]	X[C]
SUBJECT-REPORTED 2-SYMPTOM ASSESSMENT (EYE DRYNESS AND EYE DISCOMFORT; VAS)	X	X	X	X	X	X
SANDE	X	X	X	X	X	X
PREGNANCY TEST[A]	X					X
BCVA	X	X	X	X	X	X
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
	SCREENING	RANDOMIZATION	TREATMENT VISIT	TREATMENT VISIT	TREATMENT VISIT	FINAL TREATMENT VISIT

	Day - 14 (+/-1 day)	Day 1 (+/-2 days)	Day 14 (+/-2 days)	Day 28 (+/-2 days)	Day 56 (+/-2 days)	Day 84 (+/-2 days)
Biomicroscopy/External Eye Exam	X	X	X	X	X	X
CFS Staining	X	X	X	X	X	X
Schirmer (without anesthesia)	X	X	X	X	X	X
IOP	X	X	X	X	X	X
Dilated Ophthalmoscopy	X					X
IP Administration in Clinic	X[B]	X[C]				X[C]
Drop Comfort Assessment	X	X				X
Dispense IP	X[B]	X[C]		X[C]	X[C]	
Dispense Dosing and Symptom Diary (as needed)	X	X		X	X	
Collect Daily Diary		X	X	X	X	X
Exit Study						X

[A]Women of childbearing potential only; [B]Run-In Drug; [C]Double-Masked IP;[D]Subjects must replicate the following findings in the same eye at Visits 1 and 2 in order to be considered for further study eligibility: 1) Inferior CFS score ≥ 2 (0 – 4 scale; using 0.5 increments) and (2) STT without anesthesia ≥ 1 and ≤ 7 mm, at Visits 1 and 2. If both eyes meet the two criteria above, the eye with the greater inferior CFS be selected as the study eye. If both eyes have an equal inferior CFS score at Visit 2, the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal score in inferior CFS and equal STT scores at Visit 2, the right eye (OD) will be selected as the study eye.

2.4. Safety and Efficacy Variables

2.4.1. Safety Variables

The safety variables including OU are as follows:

- Ocular and non-ocular adverse events
- Slit-lamp Biomicroscopy and external eye exam
- Conjunctival hyperemia score
- Intraocular Pressure (IOP) measurement
- Dilated Ophthalmoscopy
- Best Corrected Visual Acuity (BCVA)
- Drop Comfort/Tolerability Assessment

2.4.2. Efficacy Variables

2.4.2.1. Primary Efficacy Endpoint

Mean Change from baseline (Visit 2) to Day 84 (Visit 6) in inferior region of CFS (iCFS) using the modified NEI/Industry Workshop (0-4 scale, using 0.5-unit increments)

2.4.2.2. Secondary Efficacy Endpoints

The secondary endpoints will be evaluated in a hierarchical fashion and tested sequentially starting with the key secondary endpoint below:

- **Key Secondary Endpoint:**

  Mean change from baseline (Visit 2) to Day 84 (Visit 6) in the individual symptom of eye dryness (0 -100 VAS scale)

- **Other Secondary Endpoints:**

  1. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4), 56 (Visit 5) and 84 (Visit 6) in total CFS (**tCFS**) using the modified NEI/Industry Workshop (0-20 scale; using 0.5-unit increments)
  2. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4), Day 56 (Visit 5) and Day 84 (Visit 6) in each **individual subregion** (inferior (except for Day 84), nasal, temporal, central and superior) of CFS using modified NEI/Industry Workshop (0-4 scale; using 0.5 unit increments)

3. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4) and 56 (Visit 5) in the individual symptom of eye dryness (0-100 VAS scale)
4. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4) 56 (Visit 5) and 84 (Visit 6) in the individual symptom of eye discomfort (0-100 VAS scale)
5. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4), 56 (Visit 5) and Day 84 (Visit 6) in SANDE.
6. Mean Change from baseline (Visit 2) to Days 14 (Visit 3), 28 (Visit 4), 56 (Visit 5) and Day 84 (Visit 6) in Schirmer

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- **Full Analysis Set (FAS) -** includes all randomized subjects who have received at least one dose of the IP. The efficacy and baseline analysis will be performed on the FAS. Subjects in the FAS will be analyzed as randomized.
- **Per Protocol Set (PPS) -** includes subjects in the FAS who do not have protocol deviations that impact the primary efficacy variable, and who complete the study. The PPS will be analyzed using observed data only for efficacy variables. Subjects in the PPS will be analyzed as treated. Sensitivity analyses may be performed on the PPS.
- **Safety Set (SAF) -** includes all randomized subjects who have received at least one dose of the IP. The SAF will be analyzed for all safety assessments. Subjects in the SAF will be analyzed as treated.

3.2. Protocol Deviations

At the discretion of the sponsor, major protocol deviations as determined by a review of the data prior to unmasking of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the PPS. This file will include a description of the protocol deviations, and clearly identify whether this deviation warrants exclusion from the PPS. It will be finalized prior to hard database lock and unmasking. All protocol deviations will be captured in the CRF and summarized by treatment group and overall. The data listing for the protocol deviations will be also presented.

4. STATISTICAL METHODS

4.1. Sample Size Justification

A sample size of 55 subjects per treatment group will have 80% power to detect a treatment difference of 0.43 units with a common standard deviation 0.80 in iCFS score, and a treatment difference of 13.75 units with a common standard deviation 25.5 in eye dryness score at Visit 6/Day 84 using a t-test with a 0.05 two-sided significance level.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented by treatment group and visit (as applicable). For continuous variables, the sample size (n), mean, median, standard deviation, minimum and maximum values will be summarized by treatment group and visit (as applicable). All study data will be listed by treatment group, subject and visit (as applicable).

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the 2-sided, 0.05 level of significance.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4, SAS/STAT 15.1), unless otherwise noted. Medical History and adverse events will be coding using MedDRA version 23.0. Concomitant medications will be coded using World Health Organization (WHO) Drug version B3 WHO Drug Global – Mar 2020.

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

Analyses of the change from baseline in primary and secondary efficacy endpoints utilizing repeated measures mixed model will adjust for the baseline score of the parameter of interest as a continuous covariate, treatment group as the main effect, and visit as a repeated measure on subject in the model.

4.2.5. Multiple Comparisons/Multiplicity

To avoid inflation of the type I error rate due to multiple hypotheses, the analysis of primary and key secondary efficacy endpoints will be conducted in the following hierarchical tests:

1) Primary (iCFS on Day 84, study eye) high concentration vs. vehicle
2) Primary (iCFS on Day 84, study eye) low concentration vs. vehicle
3) Key secondary (Eye Dryness VAS on Day 84) high concentration vs. vehicle
4) Key secondary (Eye Dryness VAS on Day 84) low concentration vs. vehicle

The comparisons will be conducted by using the repeated measure mixed model at the 5% significance level. Each comparison will be made in order until 2- sided p value > 0.05. If p value $\leq$ 0.05, then comparison is statistically significant, and testing is continued.

If both primary and key secondary efficacy endpoints demonstrate statistically significant superiority of each concentration of VVN001 versus vehicle at the two-sided 5% level, the similar hierarchical tests defined above will be conducted for the other secondary efficacy endpoints in the order of Day 84, Day 56, Day 28, Day 14 and in the order of presentation high concentration, low concentration within each endpoint specified in Section 2.4.2.2.

4.2.6. Subpopulations

No analyses of subgroups of subjects are planned.

4.2.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study were not to be replaced.

4.2.8. Missing, Unused, and Spurious Data

Any missing, unused, or spurious data will be noted in the final clinical study report. Missing data will be handled as follows. Missing data for other data points not covered below will be left as missing.

4.2.8.1. Imputation Method for Efficacy Endpoints

Sensitivity analyses specified in Section 4.7.1.1 for the primary endpoint on FAS population will be performed by imputing missing data in terms of using last observation carried forward (LOCF) as well as observed data only. Additional sensitivity analysis will be examined if needed.

4.2.8.2. Missing Dates

If the start date/time of an AE is partially or completely missing, the date/time will be compared as far as possible with the date/time of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Listings will display the available date data.

The following general rules will be used:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded as being treatment-emergent if the start date is before the date of study drug administration or if the stop date/time is before study drug administration.
- If the start time and day are missing but the start month and year are complete, an AE will only be excluded as being treatment-emergent if the start month/year is before the month/year of study drug administration or if the stop date/time is before study drug administration.
- If the start day and month are missing but the start year is complete, an AE will only be excluded as being treatment-emergent if start year is before the year of study drug administration or if the stop date/time is before study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date/time is before study drug administration.

The above general rules are applicable to the partially or completely missing worsening date/time of AE as well.

4.2.9. Visit Windows

Visit windows will be calculated based on the schedule of assessments in Table 1. Any visits or procedures performed outside the scheduled visits must be documented in the Unscheduled Visit page of the eCRF. Although there is a visit window of ±2 days around the expected visit date, nominal visits will be used for the per-visit analyses for all the endpoints. In addition, for primary and key secondary efficacy endpoints, the unscheduled visit or early termination visit

will be mapped to the scheduled visit which is closest to the midpoint of two consecutive visit windows.

4.3. Interim Analyses

No interim analyses are planned for this study.

4.4. Subject Disposition

A tabulation of subject disposition will be tabulated for all screened subjects. The number of patients screened, and screened failure will be presented. The number and percentage of subjects included in each of the analysis populations (FAS, SAF, PPS) will be presented by treatment group and overall. Subject disposition events including randomization, treated, completed study, prematurely discontinued study and/or treatment, and reasons for premature study and/or treatment discontinuation will be summarized by treatment group and overall.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Demographic characteristics and medical history information will be summarized for the FAS populations using descriptive statistics by treatment group and overall. Demographic characteristic information will include age (years), age category (<65 vs. ≥ 65), gender, ethnicity and race.

Age will be calculated as an integer by using SAS function: Floor ((randomization date – date of birth) /365.25).

No formal statistical comparisons will be performed.

Demographic and Baseline data will be provided in data listings.

4.5.1. Baseline Ocular Assessments

The following baseline assessments will be presented using descriptive statistics for FAS population by treatment group and overall.

The assessments below will have one score for both eyes per subject.

- Eye dryness VAS score (0-100)
- Discomfort VAS score (0-100)

- SANDE global score
  - The SANDE is comprised of two 100mm VAS scales. One measures frequency of symptoms from rarely (0) to all the time (100). The other measures severity of symptoms from very mild (0) to very severe (100). The global score is calculated as square root of the product of the two measurements.

The assessments below will be assessed for each eye including study eye and non-study eye, where study eye is defined in Section 2.1.2:

- Total CFS score (0-20 scale)
- Individual subregion (inferior, superior, nasal, temporal, and central) of CFS score (0-4 scale)
- Schirmer test result without anesthesia (mm/5 min)

4.5.2. Medical and Surgical History

Medical history, including ocular medical history, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0). Non-ocular medical history will be summarized in the FAS population by system organ class (SOC) and preferred term (PT) by treatment group and overall. SOC will be sorted alphabetically. PT will be sorted by descending frequency overall within each SOC. Subjects with a particular medical history event or medical history class will be counted once at the PT level and once at the SOC level. Ocular medical history will be summarized at the subject and eye levels by treatment group and overall in the FAS with separate summaries for the study eye and non-study eye.

Surgical history will not be coded in this trial and thus all data as collected in the CRF will be provided in data listings. Data listings will be provided for medical history as well.

4.6. Treatment Exposure

Details of study drug administration, including duration on treatment and extent of exposure will be tabulated and presented in the SAF population. The duration of exposure will be calculated in days as *last dose date-first dose date +1* during the treatment period and summarized using descriptive statistics by treatment group and overall.

All dosing information will be presented in a data listing.

4.7. Efficacy Evaluation

Efficacy analysis will be conducted using the FAS and PPS populations. All the following efficacy parameters will be analyzed as continuous variables and summarized at each follow-up timepoint (Day 0, Day 1, Day 14, Day 28, Day 56 and Day 84) using descriptive statistics (the number of subjects, mean, SD, median, minimum and maximum) by treatment group and overall. The absolute change from baseline (Day 1) to each follow-up timepoint (Day 14, Day 28, Day 56 and Day 84) in the following efficacy parameters will be also presented using descriptive statistics by treatment group. The two-sample T test under the assumption of normality of the efficacy endpoints will be utilized for comparing VVN001 5% versus vehicle and VVM001 1% versus vehicle at each follow-up timepoint. If the normality is not met, the Wilcoxon rank sum test will be performed instead.

Efficacy parameters:

- Total CFS score (0-20 scale)
- Individual subregion (inferior, superior, nasal, temporal, and central) of CFS score (0-4 scale)
- Schirmer test result without anesthesia (mm/5 min)
- Eye dryness VAS score (0-100)
- Discomfort VAS score (0-100)
- SANDE global score defined in Section 4.5.1

4.7.1. Primary Analyses

The primary comparisons in this trial will be VVN001 5% versus vehicle and VVM001 1% versus vehicle on Day 84 in CFB of iCFS score on study eye. The repeated measures mixed model will be utilized to compare the treatment group. This method will assume that any missing data is Missing at Random (MAR). The repeated measures are the absolute change from baseline iCFS score obtained at the scheduled visit Day 14, 28, 56 and 84 respectively. The model will include treatment group (VVN001 5%, VVN001 1% and vehicle), baseline iCFS score, visit (Day 14, 28, 56 and 84), the interaction term of treatment × visit as fixed effects, the center as a random effect.

SAS *PROC MIXED* with restricted maximum likelihood estimation (REML) and an unstructured (UN) within-subject covariance structure will initially be used. The sample SAS analysis code will use the following structure:

```
PROC MIXED DATA=indata;
    CLASS subject center visit treatment(REF='Vehicle');
```

```
    MODEL change = treatment visit baseline_value treatment × visit
/Solution DDFM=KR;
    REPEATED visit / SUBJECT=subject TYPE=UN;
    RANDOM center;
    LSMEANS treatment treatment × visit /PDIFF CL;
    SLICE treatment × visit / SLICEBY=visit PDIFF CL;
RUN;
```

If the model fails to converge, compound symmetry (CS) will be implemented. From this model, the least squares mean (LSMEANS) for each treatment group and the estimated treatment differences for treatment comparisons will be presented together with 95% 2-sided confidence intervals for the differences and two-sided p-values for the treatment comparisons of the overall analysis. For assessments performed by eye, study eye and non-study eye will be summarized separately.

4.7.1.1. Sensitivity Analyses

Sensitivity analyses will be performed on the FAS population by using last observation carried forward (LOCF) imputation methodology to compare the treatment group on Day 84. LOCF will be used to impute missing data for the analysis of covariance (ANCOVA) model with terms for baseline iCFS score and treatment group as covariate. The model assumptions such as Shapiro-Wilk's test of normality; Levene's test of homogeneity of variance will be validated. The estimates of least squares mean for each treatment group and for the difference between treatment groups will be presented together with 95% confidence intervals and two-sided p-value. The sample SAS ANCOVA code would be:

```
PROC GLM DATA= indata;
  CLASS treatment(REF='Vehicle');
  MODEL change = treatment baseline_value;
  LSMEANS treatment / PDIFF CL;
RUN;
```

4.7.2. Secondary Analyses

The secondary efficacy endpoints listed below will be analyzed using repeated measure mixed model by adjusting for covariates that include treatment group, baseline value, visit and interaction term of treatment × visit as the fixed effects. The center will be considered as random effect. The treatment group comparison for each secondary endpoint at each timepoint (Day 84, Day 56, Day 28 and Day 14) will be tested using hierarchical fixed sequence testing followed by the sequential order below:

- CFB in eye dryness VAS on Day 84
- CFB in total CFS (tCFS) on Day 84, Day 56, Day 28, Day 14
- CFB in inferior of CFS (iCFS) on Day 56, Day 28, Day 14
- CFB in nasal of CFS on Day 84, Day 56, Day 28, Day 14
- CFB in temporal of CFS on Day 84, Day 56, Day 28, Day 14
- CFB in central of CFS on Day 84, Day 56, Day 28, Day 14
- CFB in superior of CFS on Day 84, Day 56, Day 28, Day 14
- CFB in eye dryness VAS on Day 56, Day 28, Day 14
- CFB in eye discomfort VAS on Day 84, Day 56, Day 28, Day 14
- CFB in SANDE global score on Day 84, Day 56, Day 28, Day 14
- CFB in Schirmer test result on Day 84, Day 56, Day 28, Day 14

For each sequential order of endpoint and each timepoint, the least squares mean (LSMEANS) for each treatment group and the estimated treatment differences for the treatment comparisons (VVN001 5% vs. vehicle and VVM001 1% vs. vehicle) will be reported together with two-sided p-values and 95% 2-sided confidence intervals. The endpoints on study eye and non-study eye will be summarized in the separate model.

The sample code of SAS *PROC MIXED* would be:

```
PROC MIXED DATA=indata;
    CLASS subject center visit treatment(REF='Vehicle');
    MODEL change = treatment visit baseline_value treatment × visit
                    /Solution DDFM=KR;
    REPEATED visit / SUBJECT=subject TYPE=UN;
    RANDOM center;
    LSMEANS treatment treatment × visit /PDIFF CL;
    SLICE treatment × visit / SLICEBY=visit PDIFF CL;
RUN;
```

The model convergence and the choice of covariance structure will be handled as similar to the primary analyses mentioned in section 4.7.1.

In addition, the frequency and percentage of subjects achieving a 10-milimeter increase or more in Schirmer test scores from baseline will be presented at each post-baseline visit and any visits

by treatment group. The analyses on study eye and non-study eye will be summarized separately. The flag of this achievement will be also reported in the listing. The chi-square test will be performed to compare VVN001 5% versus vehicle and VVM001 1% versus vehicle.

4.8. Safety Analyses

All safety analyses will be conducted on the SAF Population.

4.8.1. Safety Assessments

The following safety assessments will be summarized at each visit if applicable using descriptive statistics for SAF population by treatment group and overall. Assessments will be presented for study eye and non-study eye separately.

- Slit-Lamp biomicroscopy and external eye exam
  - For each anterior segment such as lashes, eyelid, conjunctiva, cornea, anterior chamber, lens pathology and sclera, the summary tabulations of the frequency and percentage for evaluation category such as normal, abnormal CS (clinically significant) and abnormal NCS (non-clinically significant) will be presented. The worsening (from normal to abnormal CS\NCS) change from baseline will be flagged in the data listing.
- Dilated Ophthalmoscopy
  - The evaluation of normal and abnormal for each eye in retina and optic nerve exam will be tabulated by using the frequency and percentage. The cup-to-disc ratio by visits and absolute change from baseline at Visit 6 (Day 84) will be presented using descriptive statistics.
- Intraocular Pressure (IOP) measurement (mmHg)
  - Absolute change from baseline at post-baseline visits will be summarized using descriptive statistics. The frequency and percentage of subjects with increase in IOP $\geq$ 10 mmHg from baseline at each post-baseline visits and any visit will be summarized and presented in the data listing as well.
- Best Corrected Visual Acuity (BCVA)
  - LogMAR Visual Acuity (VA) score and change from baseline will be calculated and summarized using descriptive statistics. The frequency and percentage of

subjects with loss in VA ≥ 0.3 LogMAR (3 lines) from baseline at each post-baseline visits and any visit will be summarized and presented in the data listing.

- Conjunctival Hyperemia Evaluation
  - Overall bulbar conjunctival hyperemia grading scale: none, very slightly, slight, moderate and severe will be tabulated by using the frequency and percentage for each eye. The worsening (from low to high grading scale) change from baseline will be flagged in the data listing.
- Drop Comfort/Tolerability Assessment
  - The one scored for both eyes on VAS range from 0 to 10 at 1-minute and 5-miniute post dose and absolute change from baseline at Visit 6 (Day 84) will be summarized using descriptive statistics.

4.8.2. **Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term (PT).

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the first dose of study medication through the end of the study or any event that was present at baseline but worsened in severity.

Adverse events are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term) by treatment group and overall. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count based on the total column.

The frequency and percentage of subjects with any treatment-related ocular and non-ocular TEAE, with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), with any TEAE by severity (mild, moderate or severe), and with any serious adverse event (SAE) will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most severe occurrence) to each of the incidence rates in the descriptive analysis, regardless of the frequency of episodes. Furthermore, the frequency and percentage of subjects with any TEAEs by outcome, with any TEAEs by action taken, with any TEAEs by action taken related to study drug will be also summarized in the table by treatment group and overall. Separate summaries will be performed for ocular and non-ocular TEAEs by the most severity and strongest relationship by SOC and PT by treatment group and overall.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to withdrawal.

4.8.3. Laboratory Data

Safety laboratory tests will be collected in the central laboratory at Visit 1 and Visit 6. The actual continuous value and change from Visit 1 to Visit 6 will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, and urinalysis . All laboratory data will be provided in data listings. Urine pregnancy test results will be captured at Visit 1 and Visit 6. Urine pregnancy test results will be provided in data listing.

4.8.4. Vital Signs and Physical Examinations

Vital signs and physical examinations data will not be collected.

4.8.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term.

Concomitant medications will be defined as those medications that were initiated after study drug administration or those that were ongoing at the time of study drug administration. If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period.

Non-ocular prior and concomitant medications will be summarized by higher ATC level 3 (therapeutic subgroup) and preferred term by treatment group and overall in the SAF population. ATC Level 3 terms will be sorted alphabetically. Preferred terms will be sorted by descending frequency overall within ATC Level 3 term. Subjects receiving a particular medication or medication of ATC Level 3 will be counted once at the preferred term level and once at ATC Level 3.

Ocular prior and concomitant medications will be summarized at the eye level, separately for study and non-study eyes, and at the subject level by ATC Level 3 and preferred term by treatment group and overall in the SAF.

All concomitant medications information will be presented in the data listing.

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Protocol:	VVN001-CS-201		
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5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

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6. REFERENCES

7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be Generated

Tables Number	**Title**
Table 14.1.1	Overall Disposition and Subject Accountability – All Subjects Screened
Table 14.1.2	Overview of Analysis Sets – All Subjects Randomized
Table 14.1.3	Major Protocol Deviations – FAS
Table 14.1.4	Demographic and Baseline Characteristics - FAS
Table 14.1.5	Ocular Characteristics at Screening - FAS
Table 14.1.6.1	Study Eye Ocular Medical History - FAS
Table 14.1.6.2	Non-Study Eye Ocular Medical History – FAS
Table 14.1.6.3	Subject Level (Both Eyes) Ocular Medical History - FAS
Table 14.1.6.4	Non-ocular Medical History – FAS
Table 14.1.7.1	Study Eye Ocular Prior Concomitant Medications - SAF
Table 14.1.7.2	Non-Study Eye Ocular Prior Concomitant Medications – SAF
Table 14.1.7.3	Subject Level (Both Eyes) Prior Ocular Concomitant Medications – SAF
Table 14.1.7.4	Non-ocular Prior Concomitant Medications – SAF
Table 14.1.7.5	Study Eye Ocular Concomitant Medications – SAF
Table 14.1.7.6	Non-Study Eye Ocular Concomitant Medications – SAF
Table 14.1.7.7	Subject Level (Both Eyes) Ocular Concomitant Medications - SAF
Table 14.1.7.8	Non-ocular Concomitant Medications – SAF
Table 14.1.8	Study Medication Exposure - SAF
Table 14.2.1.1	Summary of Individual Subregion of CFS and Change from Baseline on Study Eye by Visit – FAS
Table 14.2.1.2	Summary of Individual Subregion of CFS and Change from Baseline on Study Eye by Visit - PPS
Table 14.2.1.3	Summary of Individual Subregion of CFS and Change from Baseline on Non-Study Eye by Visit - FAS
Table 14.2.1.4	Summary of Individual Subregion of CFS and Change from Baseline on Non-Study Eye by Visit - PPS
Table 14.2.2.1	Repeated Measures Mixed Model for Change from Baseline (CFB) in Inferior Region of CFS (iCFS) on Study Eye on Day 84 – FAS
Table 14.2.2.2	Repeated Measures Mixed Model for Change from Baseline (CFB) in Inferior Region of CFS (iCFS) on Study Eye on Day 84 – PPS

7.2. Data Listings to be Generated

Listings Number	**Title**
Listing 16.2.1.1	Subject Disposition – All Subjects Screened
Listing 16.2.2.1	Major Protocol Deviations – All Subjects Randomized
Listing 16.2.3.1	Subjects Excluded from the Efficacy Analysis – All Subject Randomized
Listing 16.2.4.1	Demographic and Baseline Characteristics - FAS
Listing 16.2.4.2	Ocular Medical History - FAS
Listing 16.2.4.3	Non-Ocular Medical History - FAS
Listing 16.2.4.4	Ocular Surgery History - FAS
Listing 16.2.4.5	Non-Ocular Surgery History - FAS
Listing 16.2.5.1	Treatment Exposure - SAF
Listing 16.2.5.2	Dispense Investigational Product - SAF
Listing 16.2.6.1	Corneal Fluorescein Staining (CFS) Assessment - FAS
Listing 16.2.6.2	Ocular VAS Score - FAS
Listing 16.2.6.3	SANDE Assessment - FAS
Listing 16.2.6.4	Schirmer's Test without Anesthesia Result- FAS
Listing 16.2.7.1	All Adverse Events - SAF
Listing 16.2.7.2	Serious Adverse Events - SAF
Listing 16.2.7.3	Adverse Events leading to Discontinuation of Treatment - SAF
Listing 16.2.7.4	Subject Deaths - SAF
Listing 16.2.8.1	Urine Pregnancy Test - SAF
Listing 16.2.9.1	Slit-lamp Biomicroscopy and External Eye Exam - SAF
Listing 16.2.9.2	Conjunctival Hyperemia Score - SAF
Listing 16.2.9.3	Intraocular Pressure (IOP) Measurement - SAF
Listing 16.2.9.4	Dilated Ophthalmoscopy - SAF
Listing 16.2.9.5	Best Corrected Visual Acuity (BCVA) - SAF
Listing 16.2.9.6	Drop Comfort/Tolerability Assessment - SAF
Listing 16.2.9.7	Prior and Concomitant Medications - SAF
Listing 16.2.9.8.1	Laboratory Results: Hematology - SAF
Listing 16.2.9.8.2	Laboratory Results: Chemistry - SAF
Listing 16.2.9.8.3	Laboratory Results: Urinalysis - SAF