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A Phase 2a, Double-Masked, Randomized, Vehicle-controlled Trial of VVN001 in Subjects with Dry Eye Disease

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Keywords: Dry eye disease; VVN001; Cornea; Symptoms

ABSTRACT

Purpose:

Evaluate the initial ocular safety and tolerability and efficacy of VVN001 Ophthalmic Solution (VVN001), a small-molecule antagonist of lymphocyte function-associated antigen-1 (LFA-1), in subjects with dry eye disease (DED).

Methods:

This was a multi-center, double-masked, randomized, dose-response, vehicle-controlled, parallel-group study conducted in 170 subjects with DED. Subjects were randomized to receive VVN001 (1% or 5%) or its vehicle, twice-daily in both eyes for 84 days. The primary outcome measure was inferior region corneal fluorescein staining (iCFS, 0-4 scale) at Day 84. Visual Analogue Scale eye dryness (VAS, 0-100 scale) was a secondary outcome.

Results:

The primary and first secondary outcomes were not met. At Day 84 treatment effects in favor of VVN001 5% relative to its vehicle for iCFS were 0.29 units ($p = 0.054$), and for VAS were 3.18 units ($p = 0.533$). In other secondary outcomes, treatment effects in favor of VVN001 5% relative to its vehicle were seen in total CFS (1.61 units, 0-20 scale, $p = 0.004$) and Schirmer score (1.77 and 2.32 mm, $p = 0.049$ and $p = 0.17$ at Days 14 and 28 respectively). Adverse events of incidence 5% or greater in either active treatment group were instillation site pain (3/57, 5.3%), dysgeusia (3/56, 5.4%) and urinary tract infection (3/57, 5.3%).

Conclusions:

There were no major safety issues of note. Appropriately powered studies will be required with *a priori* selection of the efficacy endpoints to evaluate VVN001's therapeutic potential.

INTRODUCTION

"Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] In a recent review of the large volume of literature, "…the prevalence of DED in the general population ranged from 5 to 50%. The prevalence of signs was higher and more variable than symptoms…Women have a higher prevalence of DED than men…Risk factors were categorized as modifiable/nonmodifiable, and as consistent, probable or inconclusive…The economic burden and impact of DED on vision, quality of life, work productivity, psychological and physical impact of pain, are considerable, particularly costs due to reduced work productivity".[2] There are overlapping etiologies of aqueous deficient and evaporative dry eye. While evaporative dry eye may be more prevalent than aqueous deficient DED, as the disease progresses, these and other sources become apparent.[3] Desiccating stress ultimately results in ocular surface inflammation.[4]

Given that inflammation is a key aspect of the pathophysiology of DED at least in some patients, many approaches have been tried in the pharmacological treatment of DED. Approved pharmacotherapies in the U.S.A. include the immunomodulator cyclosporine, a corticosteroid (loteprednol etabonate), a lymphocyte function-associated antigen-1 (LFA-1) antagonist, lifitegrast, and an intranasal nicotinic agonist (varenicline). As well, medical devices marketed

in the U.S.A. for treatment of DED and other ocular surface disorders include a nasal neurostimulatory device and warming of the eyelids.

While safe and effective, not all patients with DED are fully served by these current therapies. The incidence of adverse reactions (including tolerability) in the package insert for lifitegrast ranges from 5-25%. In a controlled safety study, the incidence of instillation site irritation was 15%, and instillation site reaction was 13%.[5] In a real-world, retrospective study, White et al reported a relatively high discontinuation rate within 12 months for both cyclosporine (70.8%) and lifitegrast (64.4%) – although the reason for discontinuation rate was not explicitly provided.[6] In the package insert for one cyclosporine product, the most common adverse reaction was ocular burning (17%); and for another cyclosporine product, the most common adverse reactions were instillation site pain (22%) and conjunctival hyperemia (6%).[7, 8] It is well known that DED is associated with increased osmolarity.[9] High osmolarity usually results from higher salt content. Thus, there is a need for novel therapies to serve the needs of patients more broadly with this challenging disease.

VivaVision is developing VVN001, a small-molecule antagonist of LFA-1 for the treatment of dry eye disease. VVN001 was designed to have higher solubility then lifitegrast at the pH of natural tears, 7.0-7.4. We hypothesized that higher aqueous solubility may avoid the precipitation of drug when instilled into a high molarity environment, thus it may result in a more favorable ocular adverse events profile. In addition, the VVN001 structure is substantially different from lifitegrast, and the altered structure may lead to fewer users with altered sensation of taste – although it is not known what structural features caused dysgeusia. In an *in vitro*

study, VVN001 demonstrated concentration-dependent inhibition of Jurkat cell intercellular adhesion molecule-1 (ICAM-1) mediated adhesion, VVN001 had an IC_{50} of 3.2 nM, which was comparable to the reference compound, lifitegrast (4.8 nM). Further, VVN001 was found to inhibit cytokine release but not to inhibit integrins A2B1 and A4B1. Topical ocular VVN001 was evaluated in C57BL/6 mice placed in a low humidity environment and treated with subcutaneous scopolamine. In this in vivo model of DED, VVN001 was similar in efficacy and potency to the reference compound, lifitegrast (Data on File, VivaVision). This is the first-in-human study of VVN001 Ophthalmic Solution.

MATERIALS AND METHODS

Study design

This was a multi-center, double-masked, randomized, dose-response, vehicle-controlled, parallel-group study conducted in subjects with dry eye disease, conducted in accordance with Good Clinical Practices (GCP, Figure 1).

Clinical assessment

Study assessments were conducted in both eyes. At Screening (Visit 1, Day -14), subjects who met inclusion/exclusion criteria began a two-week run-in period with a single-masked vehicle. During the run-in period, subjects prescribed treatment with 1 drop of single-masked vehicle per eye twice daily (b.i.d.) in both eyes (O.U.) for 14 days (Day -14 to Day -1). At Visit 2 (Baseline; Randomization; Day 1), subjects who continued to meet inclusion/exclusion criteria were

eligible for randomization. Randomized subjects returned for visits with a ± 2 day window on Days 14, 28, 56 and 84.

Following randomization, subjects were instructed to self-administer 1 drop of double-masked medication (all treatments in the same container/closure system), b.i.d., O.U. Subjects were instructed to return to the clinic for their scheduled visits and to take their morning eyedrop prior to these visits. Subjects were instructed not to use any topical eyedrops (e.g., over the counter artificial tears or topical ocular medications) other than the study medication during the study.

Examinations included: Signs (OU): CFS score (0 – 4 point NEI scale) in each of five regions;[10] at each clinic visit; and tear production assessed with Schirmer Tear Test (STT, without anesthesia, mm/5 minutes) at each clinic visit. Symptoms (each clinical visit): Eye dryness score (0-100 point VAS); Eye discomfort score (0-100 point VAS); and SANDE questionnaire.[11]

Safety evaluations included: Adverse event (AE) monitoring (ocular and non-ocular); drop comfort/tolerability assessment; conjunctival hyperemia score; best corrected visual acuity; slit-lamp biomicroscopy; external eye exam, intraocular pressure measurement (by applanation) and dilated ophthalmoscopy. Safety laboratory tests included hematology, clinical chemistry, urinalysis, and urine pregnancy tests (for women of childbearing potential). Subjects recorded dosing information in a dosing diary.

Subject eligibility

The study was open to adult individuals with a documented history of dry eye disease in both eyes, or have a self-reported history of subjective complaints for at least 6 months prior to

screening. The study was approved by an Institutional Review Board, and all subjects gave written informed consent, and followed the Declaration of Helsinki.

Subjects were required to have the following findings in the same eye at Visits 1 and 2 in order to be considered for further study eligibility: 1) Inferior corneal fluorescein staining (CFS) score ≥ 2 (0 – 4 scale; using 0.5 increments) and 2) STT value without anesthesia of ≥ 1 and ≤ 7 mm/5 min.

In the case that both eyes were eligible for analysis, the eye with the greater inferior CFS (iCFS) score at Visit 2 was selected as the study eye. If both eyes had an equal iCFS score at Visit 2, the eye with the lowest STT value, without anesthesia, at Visit 2 was designated as the study eye. If both eyes had equal score in iCFS and equal STT values at Visit 2, the right eye (OD) was selected as the study eye. Excluded from the study were individuals with contraindications to the study medication or diagnostics, had recent use of topical ocular antibiotics, serum tears, topical ocular non-steroidal anti-inflammatory drugs (NSAIDs), topical ocular or oral antihistamines or mast cell stabilizers, topical ocular or nasal vasoconstrictors (other than diagnostics), ocular, inhaled, dermatologic or intranasal corticosteroids; topical cyclosporine, topical lifitegrast, intranasal tear neurostimulation, or any topical ophthalmic medications or makeup for eyelash growth. Also excluded were individuals with uncontrolled glaucoma, current contact lens use, previous refractive or other corneal surgery, or recent incisional ocular surgery.

Study drugs

The randomization schedule was generated by an independent unmasked statistician and maintained in a secure and limited-access location separate from the study investigator and

members of the project team. Qualified subjects were assigned to receive one of the following three double-masked products: VVN001 Ophthalmic Solution 1% or 5%, or vehicle, O.U., b.i.d for 12 weeks. Drug products were sterile, non-preserved, and formulated with sodium phosphate, sodium thiosulfate pentahydrate, sodium chloride and water for injection. All products used the same bottle and tip.

Statistics

The primary efficacy comparison in this study was between the active treatment group (VVN001, 5% ophthalmic solution or VVN001, 1% ophthalmic solution) and vehicle for the mean change from baseline (Visit 2) to Day 84 in inferior region corneal fluorescein staining (iCFS) using the modified National Eye Institute (NEI)/Industry Scale (0-4 scale using 0.5 increments).[10] Key secondary efficacy analyses based on the Eye Dryness Visual Analogue Scale (VAS) at Day 84 were similarly ordered with the high VVN001 concentration tested first followed by the low VVN001 concentration.

A priori, the repeated measures mixed model (RMMM) was utilized to compare the treatment group. This method assumed that any missing data was Missing at Random (MAR). The repeated measures were the absolute change from baseline score obtained at the scheduled visits. The model included treatment group, baseline score, visit number, the interaction term of treatment × visit as fixed effects, and the center as a random effect. A planned sample size of 55 subjects per treatment group (165 total) had 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 Day 84 using a t-test with α

= 0.05 (2-sided) significance level. All descriptive statistical analyses were performed using SAS statistical software (Version 9.4, SAS/STAT 15.1). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 23.0). Comparisons were conducted at the 5% significance level between each active treatment (VVN001, 5% and VVN001, 1%) and vehicle. No probability comparisons were made between the VVN001, 5% and VVN001, 1% treatment groups.

The primary population was the Full Analysis Set (FAS, defined as all randomized subjects who have received at least one dose of the investigational product. Prior to unmasking, a per protocol population was defined which excluded subjects with major protocol deviation or did not complete the study at Day 84.

All procedures for the handling and analysis of data were conducted using Good Clinical Practice and met International Conference on Harmonisation guidelines and FDA regulations for the handling and analysis of data for clinical trials.

RESULTS

Disposition, demographics and baseline characteristics

One hundred and seventy (170) subjects were randomized across 12 sites in the United States. Of these, 169 were dosed with VVN001, 5% (N = 56), VVN001, 1% (N = 57), or vehicle (N = 56). One subject was randomized to the VVN001 1% group, did not receive treatment. This subject was therefore excluded from all analysis populations.

Overall, 157 (92.4%) subjects completed the study, and 12 (7.1%) subjects prematurely discontinued the study [3 (5.4%) subjects from the VVN001, 5% treatment group; 4 (6.9%) subjects from the VVN001, 1% treatment group; 5 (8.9%) subjects from the vehicle treatment group]. The most common reasons for discontinuation of the study were subject withdrew consent (6 subjects), AEs (2 subjects), and lost to follow-up (2 subjects). The rates of premature study discontinuation were comparable between treatment groups.

The mean age of the study population was 63.4 years (range: 20 to 93 years). Overall, the majority of subjects [89 (52.7%) subjects] were ≥65 years of age. There were 80 (47.3%) subjects <65 years of age. Most study subjects [126 (74.6%) subjects] were female. The most common race was White [125 (74.0%) subjects], followed by Black/African American [29 (17.2%) subjects] and Asian [14 (8.3%) subjects]. Demographic characteristics were not appreciably different between the 3 treatment groups, with the possible exception of a higher percentage of females in the VVN001, 5% treatment group (Table 1).

Efficacy

Primary measure: Sign (iCFS): At baseline, mean iCFS scores were similar among treatment groups (range 2.44 to 2.45 units; scale of 0-4). Using the RMMM, calculated mean changes from baseline were -0.98 and -0.74 units for the VVN001 5% and VVN001 1% groups, respectively. This was a difference from vehicle of 0.29 ($p = 0.054$) and 0.06 units ($p = 0.714$), respectively ((Figure 2). Probability values throughout the study are also presented for this measure (Table 3).

Key secondary measure: Symptom: VAS eye dryness:

At baseline, mean VAS eye dryness scores were similar among treatment groups (range 66.2 to 66.5; scale of 0-100). Using the RMMM, calculated mean changes from baseline were -25.02 and -30.78 for the VVN001 5% and VVN001 1% groups, respectively. This was a difference from vehicle of 3.18 ($p = 0.533$) and 8.94 ($p = 0.079$), respectively (Figure 3). Probability values throughout the study are also presented for this measure (Table 4).

Other Secondary measures

Signs: Total CFS: At baseline, mean tCFS scores were similar among treatment groups (range 6.18 to 6.96 units; scale of 0-20). Using the RMMM, calculated mean decreases from baseline were 2.53 and 1.77 units for the VVN001 5% and VVN001 1% groups, respectively. This was a difference from vehicle of 1.61 ($p = 0.004$) and 0.85 ($p = 0.120$), respectively (Figure 4). Probability values throughout the study are also presented for this measure (Supplemental Table 1).

Signs: CFS: Other quadrants: In addition to inferior and total CFS, nasal, temporal, central and superior quadrants were analyzed. In general, the treatment effects were similar to inferior and total quadrants. Numerical improvements from baseline were generally more pronounced in the active treatment groups, particularly in the VVN001 5% treatment group. Probability values (unadjusted) for the improvements in CFS between VVN001, 5% and vehicle were ≤ 0.05 at Day 84 in the nasal, temporal and central quadrants ($p = 0.001$, 0.015 and 0.009, respectively) and at day 56 for the superior quadrant ($p = 0.04$).

Signs: Schirmer score: The mean Schirmer's tear test score in the study eye at baseline was 4.1 ± 1.9 mm, 3.8 ± 1.9 mm, and 3.9 ± 1.9 mm in VVN001 5%, VVN001 1% and vehicle groups,

respectively. The proportion of subjects with a 10 mm/5 minutes increase in Schirmer *at any visit* was 33.9% (19/56), 8.8% (5/57) and 17.9% (10/56), respectively (p = 0.052 and 0.155). Compared to vehicle, the between group p-value was 0.052 and 0.155, respectively. Shown in Figure 5 is the mean change from baseline in Schirmer score. Probability values (unadjusted) at Days 14 and Day 28 for the difference in favor of VVN001 5% over vehicle (1.77 (95% confidence intervals, 0.01 to 3.54) and 2.32 (0.41 to 4.23) mm, respectively) ≤ 0.05 (p = 0.049 and p=0.017, respectively, Supplemental Table 2).

Symptoms: SANDE: At baseline, mean SANDE global scores were similar among treatment groups (range 57.23 to 64.34, scale 0-100). Using the RMMM, calculated mean changes from baseline were -17.55 and -18.34 for the VVN001 5% and VVN001 1% groups, respectively. This was a difference from vehicle of 6.81 (p = 0.106) and 7.61 (p = 0.069), respectively (Figure 6). Probability values throughout the study are also presented for this measure (Supplemental Table 3).

All efficacy measures were also evaluated for the non-study eye, as well as in a "per-protocol" population excluding 14 subjects (8.3%) either major protocol deviations (n=2) violations or early withdraws from the study (n=12). Results observed were similar to those in for the FAS in the study eye.

Safety

Overall, the incidence of treatment emergent adverse events (TEAEs) was relatively low in all treatment groups in this study. With respect to ocular TEAEs, 8 (14.3%) subjects in the VVN001, 5% treatment group; 3 (5.3%) subjects in the VVN001, 1% treatment group; and 7

(12.5%) subjects in the vehicle treatment group. Of these reports in 18 subjects, the investigator judged them a related to study medications in 8 subjects, and the severity was mild in 17 subjects. There were 2 (1.2%) subjects who experienced ocular TEAEs that resulted in the discontinuation of study medication (1 subject from the VVN001, 5% treatment group and 1 subject from the vehicle treatment group) and were not judged to be related to use of study medication. Overall, the most commonly reported ocular TEAEs were instillation site pain [6 (3.6%) subjects], chalazion [2 (1.2%) subjects], eye discharge [2 (1.2%) subjects], and eye pain [2 (1.2%) subjects]. All other ocular TEAEs were reported only in a single subject. The incidence of individual ocular TEAEs was low and generally similar between the 3 treatment groups. With respect to non-ocular TEAEs, the only adverse events seen in more than one subject were mild dysgeusia (3/56 subjects, 5.4%, in the VVN001 5% treatment group) and urinary tract infections (seen in 3/57 subjects, 5.3%, in the VVN001 1% treatment group). The dysgeusia was judged as related to study treatment.

Two subjects discontinued study medication – one in the vehicle group (allergic conjunctivitis), and one in the VVN001 5% group (chalazion), neither of which was judged related to treatment. There were no serious adverse events (SAEs) reported in this study.

There were no treatment-related changes of note in visual acuity, intraocular pressure, biomicroscopy or ophthalmoscopy. Mean ocular drop comfort values ranged from 2.8 to 3.8 (scale: 0=Comfortable to 10=Uncomfortable) in all treatment groups at baseline and last visit. Bulbar conjunctival hyperemia presented similarly between all treatment groups at baseline, with a slight trend in all 3 treatment groups for subjects to receive lower scores (indicative of

improvement) at subsequent visits through the study. There were no TEAE's associated with the clinical laboratory tests.

DISCUSSION

The objective of this first-in-human study was to evaluate the safety, tolerability, and efficacy activity of VVN001 Ophthalmic Solution in a vehicle-controlled study. From a safety and tolerability perspective, VVN001 was relatively well tolerated, with a safety profile similar to its vehicle, and relatively few adverse events. The reported dysgeusia was relatively mild, and a known adverse event of this class of compounds. There was no obvious dose-response for the 1% and 5% concentrations of VVN001 Ophthalmic Solution. Also, similar to many evaluations of novel treatments of DED, the effects on signs and symptoms do not always covary.

From an efficacy perspective, all three treatment groups showed improvement over the 84 days of the study in signs and symptoms. This is typical of controlled studies in the evaluation of pharmacological treatments for dry eye disease. It is probably both the "placebo effect" (seen with topical and oral products) and the "vehicle effect".[12-14] Further, numerical improvements from baseline were generally more pronounced in the active treatment groups, particularly in the VVN001 5% treatment group.

From a probability perspective, the primary efficacy measure, inferior corneal fluorescein staining at Day 84, the treatment effect of VVN001 5% from vehicle (0.58 units, 0-4 scale) did not meet the criterion of $p \leq 0.05$ ($p = 0.054$). For the VVN001 1% group, the difference from vehicle, 0.74 units also did not meet the statistical criterion ($p = 0.714$). Further, the key

245 secondary efficacy measure, VAS eye dryness score, did not meet this statistical criterion for the
246 VVN001 5% treatment group (25.02 units, 0-100 scale, p = 0.533) or the 1% treatment group
247 (30.78 units, p = 0.079). These treatment differences were on the order of the a priori power
248 calculation, so it is not unexpected that some were statistically significant and some were not.

249 A priori, we protected the alpha level of 0.05 in probability analysis by our hierarchal analysis.
250 However, as typical in early-stage studies of treatment of DED, we also analyzed a number of
251 other measures. We found unadjusted p-values ≤0.05 in favor of VVN001 for total CFS at day
252 84 for the VVN001 5% group of 2.53 units (0-20 scale) with p = 0.004. At Day 56, we also
253 found a treatment effect in favor of VVN001 on SANDE of 17.45 units (0-100 scale) with p =
254 0.031.

255 With the caveat that there was no direct comparison to the marketed product, we note the
256 package insert for lifitegrast ophthalmic solution states the most common adverse reactions
257 (incidence 5-25%) were instillation site irritation, dysgeusia and decreased visual acuity.[15] In the
258 present study, adverse events of incidence 5% or greater in either active treatment group were
259 instillation site pain (3/57, 5.3%), dysgeusia (3/56, 5.4%) and urinary tract infection (3/57,
260 5.3%).

261 As noted previously, there are many methodological challenges with conducting first in human
262 studies of pharmacological treatment for dry eye disease, including appropriate selection of key
263 endpoints a priori, and limited power in these initial relatively small studies. Nonetheless, the
264 observations of efficacy seen with VVN001 in the present study are consistent with early stage

studies of pharmacotherapies for dry eye disease, including those which were later approved for marketing.[16-20]

We also considered comparing VVN001 to an approved pharmacological therapy for the treatment of dry eye disease. However, we suggest that such a comparison is challenging from both a methodological perspective and prohibitive at this stage from a sample size requirement, at least 10-fold the size of the present study.[21] This is consistent with recommendations of the Dry Eye Workshop II,[13] and a recently published Phase 2 trial of a novel pharmacological therapy.[22] With respect to the impact of water solubility on tolerability, VVN001 ophthalmic was well tolerated. Unfortunately, the tolerability compared to approved pharmacotherapies for DED was not possible in this study. However, this may be able to be assessed in future studies.

In summary, in this double-masked, randomized, dose-response, vehicle-controlled trial of VVN001 Ophthalmic Solution in subjects with dry eye disease, there were no major safety or tolerability issues of note. Further studies will be required with *a priori* selection of the appropriate efficacy endpoints and adequate sample size to evaluate the therapeutic potential of VVN001.

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DISCLOSURES:

Joseph Tauber, M.D. None.
David Evans, O.D. None.
Bruce Segal, M.D. None.
Xiao-Yan Li, M.D. is an employee and stock holder of VivaVision Biotech, Inc.
Wang Shen, Ph.D. is an employee and stock holder of VivaVision Biotech, Inc.
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Figure Legends

Figure 1 Clinical trial design

Figure 2 Inferior Corneal Fluorescein Staining: Mean Change from Baseline

Figure 3 VAS Eye Dryness Score: Mean Change from Baseline

Figure 4 Total Corneal Fluorescein Staining: Mean Change from Baseline

Figure 5 Schirmer test (mm): Mean Change from Baseline

Figure 6 Global SANDE Score: Mean Change from Baseline

Table 1 Demographics and Baseline Characteristics (Full analysis set)

	VVN001, 5% (N=56)	VVN001, 1% (N=57)	Vehicle (N=56)	All Subjects (N=169)
Age (Years)				
Mean (SD)	62.5 (11.68)	65.2 (14.50)	62.6 (13.25)	63.4 (13.18)
Median	65.0	69.0	65.5	66.0
Min, Max	31, 82	34, 93	20, 85	20, 93
Age Categories, n (%)				
<65 years	26 (46.4)	27 (47.4)	27 (48.2)	80 (47.3)
≥65 years	30 (53.6)	30 (52.6)	29 (51.8)	89 (52.7)
Gender, n (%)				
Male	8 (14.3)	18 (31.6)	17 (30.4)	43 (25.4)
Female	48 (85.7)	39 (68.4)	39 (69.6)	126 (74.6)
Race, n (%)				
White	41 (73.2)	43 (75.4)	41 (73.2)	125 (74.0)
Black or African American	13 (23.2)	6 (10.5)	10 (17.9)	29 (17.2)
Asian	1 (1.8)	8 (14.0)	5 (8.9)	14 (8.3)
Other	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)

Ethnicity, n (%)				
Non-Hispanic or Latino	40 (71.4)	43 (75.4)	44 (78.6)	127 (75.1)
Hispanic or Latino	16 (28.6)	14 (24.6)	12 (21.4)	42 (24.9)

Table 2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (SAF)

System Organ Class Preferred Term	VVN001, 5% (N=56)		VVN001, 1% (N=57)		Vehicle (N=56)		All Subjects (N=169)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Ocular								
Subjects with any TEAEs	8 (14.3)	12	3 (5.3)	3	7 (12.5)	9	18 (10.7)	24
Eye disorders	6 (10.7)	9	0 (0.0)	0	6 (10.7)	7	12 (7.1)	16
Chalazion	2 (3.6)	2	0 (0.0)	0	0 (0.0)	0	2 (1.2)	2
Conjunctival haemorrhage	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Conjunctivitis allergic	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Eye discharge	1 (1.8)	1	0 (0.0)	0	1 (1.8)	1	2 (1.2)	2
Eye pain	1 (1.8)	1	0 (0.0)	0	1 (1.8)	1	2 (1.2)	2
Eye pruritus	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Eyelid cyst	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Eyelid margin crusting	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Eyelid pain	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Ocular hyperaemia	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Photophobia	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Swelling of eyelid	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Vitreous floaters	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
General disorders and administration site conditions	1 (1.8)	2	3 (5.3)	3	2 (3.6)	2	6 (3.6)	7
Instillation site pain	1 (1.8)	2	3 (5.3)	3	2 (3.6)	2	6 (3.6)	7
Product issues	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Device extrusion	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Non-ocular								
Subjects with any TEAEs	8 (14.3)	8	4 (7.0)	4	3 (5.4)	3	15 (8.9)	15
Blood and lymphatic system disorders	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Anaemia	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Ear and labyrinth disorders	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Vertigo	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
General disorders and administration site conditions	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Influenza like illness	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1

System Organ Class Preferred Term	VVN001, 5% (N=56)		VVN001, 1% (N=57)		Vehicle (N=56)		All Subjects (N=169)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Infections and infestations	0 (0.0)	0	3 (5.3)	3	0 (0.0)	0	3 (1.8)	3
Urinary tract infection	0 (0.0)	0	3 (5.3)	3	0 (0.0)	0	3 (1.8)	3
Injury, poisoning and procedural complications	1 (1.8)	1	0 (0.0)	0	1 (1.8)	1	2 (1.2)	2
Epicondylitis	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Hand fracture	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Nervous system disorders	3 (5.4)	3	0 (0.0)	0	1 (1.8)	1	4 (2.4)	4
Dysgeusia	3 (5.4)	3	0 (0.0)	0	0 (0.0)	0	3 (1.8)	3
Neuropathy peripheral	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Psychiatric disorders	0 (0.0)	0	1 (1.8)	1	0 (0.0)	0	1 (0.6)	1
Anxiety	0 (0.0)	0	1 (1.8)	1	0 (0.0)	0	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Dysphonia	0 (0.0)	0	0 (0.0)	0	1 (1.8)	1	1 (0.6)	1
Skin and subcutaneous tissue disorders	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
Rash	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1

Abbreviations: IP=Investigational Product; PT=Preferred Time; SOC=System Organ Class; TEAE=Treatment-Emergent Adverse Event
A TEAE was defined as an AE whose date of onset occurred after the first dose of study drug through the follow up visit.
Subjects with one or more AEs within a level of MedDRA were counted only once in that level. Events included all AEs
System Organ Class and Preferred Terms were sorted alphabetically.
MedDRA Dictionary (Version 23.0) was used for coding adverse events.
Percentages were based on the number of SAF patients in each treatment group and overall (N).
The device extrusion adverse event was a punctal plug which the subject had implanted prior to enrollment in the study.

Table 3 Inferior Corneal Fluorescein Staining: Baseline and Change from Baseline

Visit	Measure	5% VVN001 (N=56)	1% VVN001 (N=57)	Vehicle (N=56)
Baseline	Mean (SD)	2.45 (0.54)	2.45 (0.53)	2.44 (0.54)
Day 14	LSMeans	-0.51	-0.28	-0.47
	Difference of LSMeans (95% CI)	-0.04 (-0.28 ; 0.19)	0.19 (-0.04 ; 0.42)	
	P-value	0.710	0.113	
Day 28	LSMeans	-0.64	-0.58	-0.59
	Difference of LSMeans (95% CI)	-0.05 (-0.30 ; 0.21)	0.01 (-0.24 ; 0.27)	
	P-value	0.720	0.919	
Day 56	LS Means	-0.74	-0.68	-0.85
	Difference of LSMeans (95% CI)	0.12 (-0.18 ; 0.41)	0.17 (-0.12 ; 0.46)	
	P-value	0.440	0.252	
Day 84	LSMeans	-0.98	-0.74	-0.69
	Difference of LSMeans (95% CI)	-0.29 (-0.59; 0.01)	-0.06 (-0.35 ; 0.24)	
	P-value	0.054	0.714	

Scale: 0 (none) to 4 (severe); Study eye. Full analysis set; Mean for Baseline was observed mean. The LSMeans (Least Square Means), Difference of LSMeans (95% CI) and P-value were calculated from the repeated measures mixed model including the treatment, baseline iCFS and visit and the interaction term of treatment x visit as fixed effect and center as a random effect. An unstructured (UN) covariance structure was used. The treatment group comparison was tested in the order of 5% VVN001 vs. Vehicle, then 1% VVN001 vs. Vehicle.

Table 4 Visual Analog Scale: Eye Dryness Score: Baseline and Change from Baseline

Visit	Measure	5% VVN001 (N=56)	1% VVN001 (N=57)	Vehicle (N=56)
Baseline	Mean (SD)	66.2 (15.4)	66.5 (18.6)	64.9 (17.3)
Day 14	LSMeans	-14.80	-16.58	-14.32
	Difference of LSMeans (95% CI)	-0.48 (-8.46 ; 7.50)	-2.26 (-10.21 ; 5.68)	
	P-value	0.906	0.575	
Day 28	LSMeans	-16.70	-18.15	-16.50
	Difference of LSMeans (95% CI)	-0.20 (-8.56 ; 8.16)	-1.65 (-9.92 ; 6.62)	
	P-value	0.963	0.694	
Day 56	LS Means	-18.18	-23.57	-16.17
	Difference of LSMeans (95% CI)	-2.01 (-11.21 ; 7.19)	-7.40 (-16.56 ; 1.75)	
	P-value	0.667	0.112	
Day 84	LSMeans	-25.02	-30.78	-21.84
	Difference of LSMeans (95% CI)	-3.18 (-13.24 ; 6.88)	-8.94 (-18.93 ; 1.05)	
	P-value	0.533	0.079	

Scale: 0 (none) to 100 (severe); Study eye. Full analysis set; Mean for Baseline was the observed mean. LSMeans, Difference of LSMeans (95% CI) and P-value were calculated from the repeated measures mixed model including the treatment, baseline VAS and visit and the interaction term of treatment x visit as fixed effect and center as a random effect. An unstructured (UN) covariance structure was used. The treatment group comparison was tested in the order of 5% VVN001 vs. Vehicle, then 1% VVN001 vs. Vehicle.

Figure 1 Clinical trial design

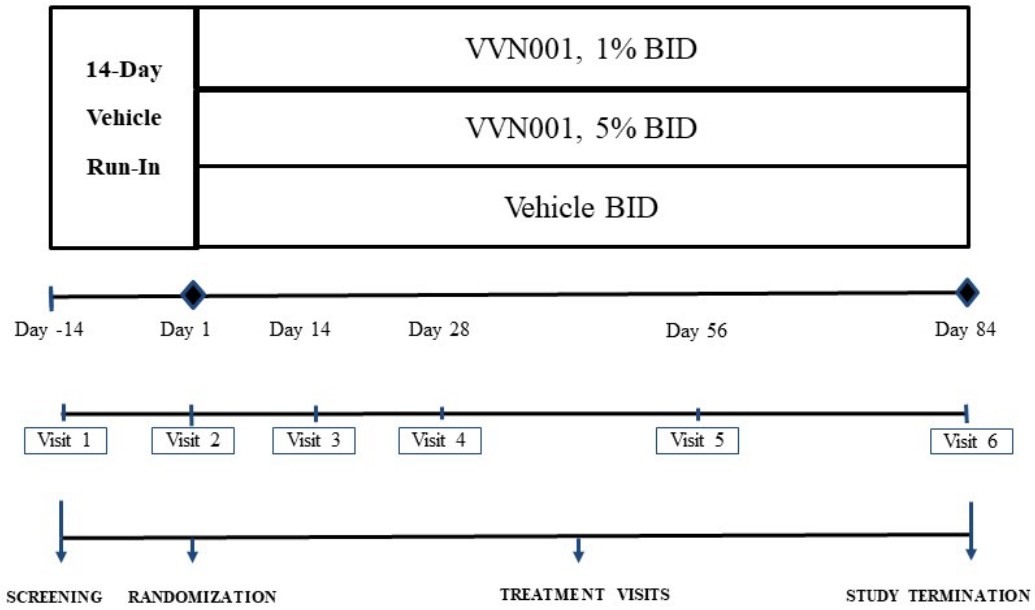
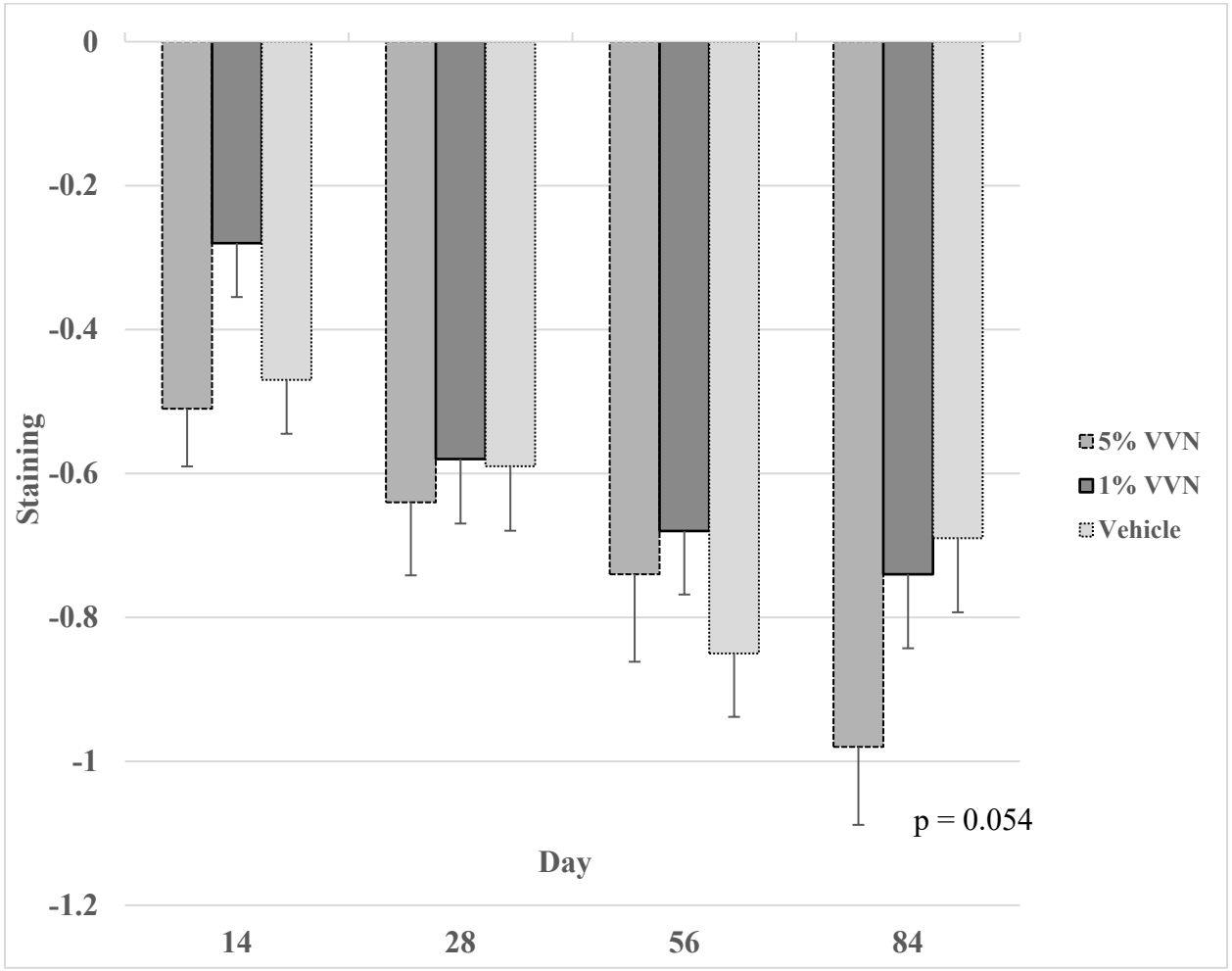
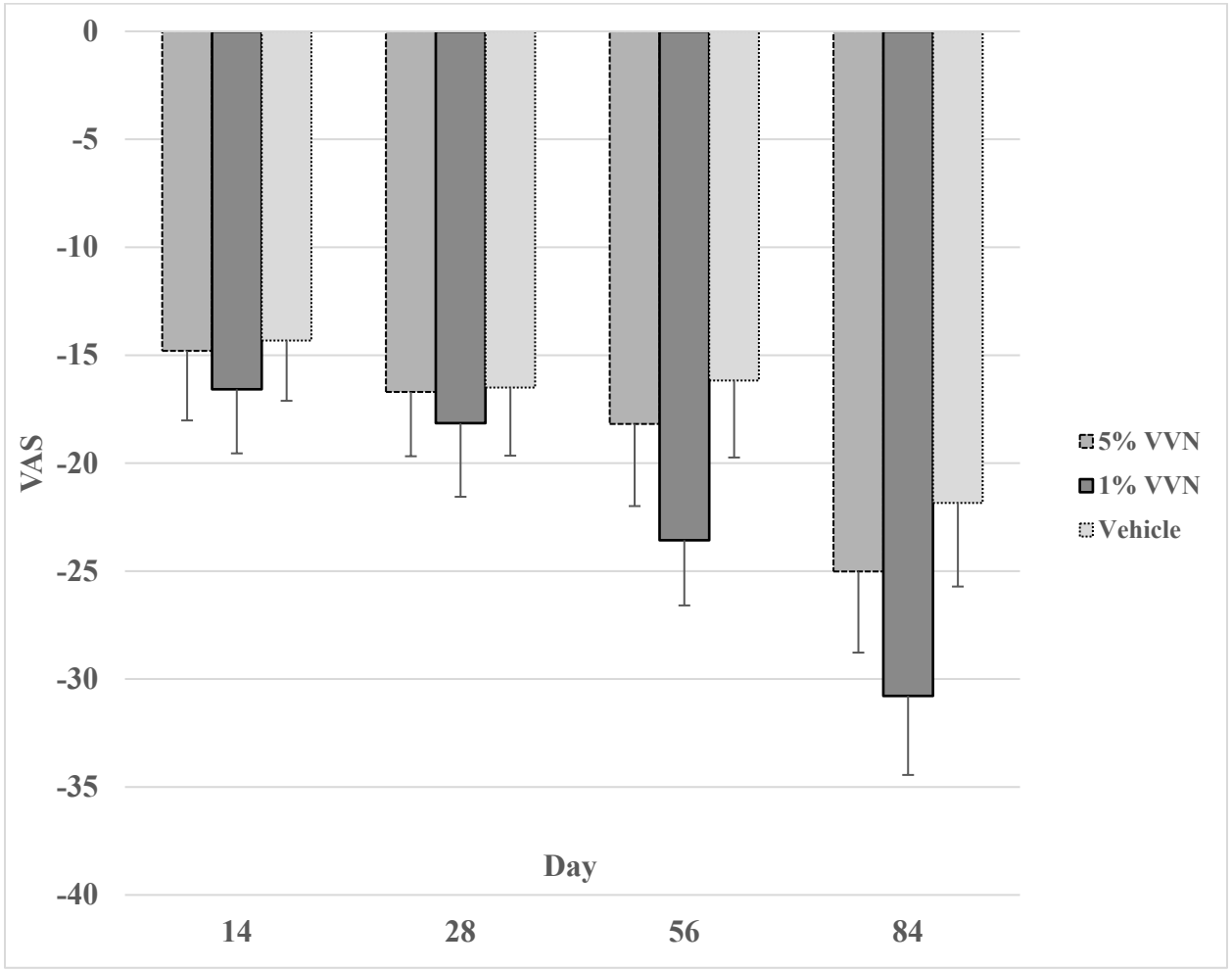


Figure 2 Inferior Corneal Fluorescein Staining: Mean Change from Baseline



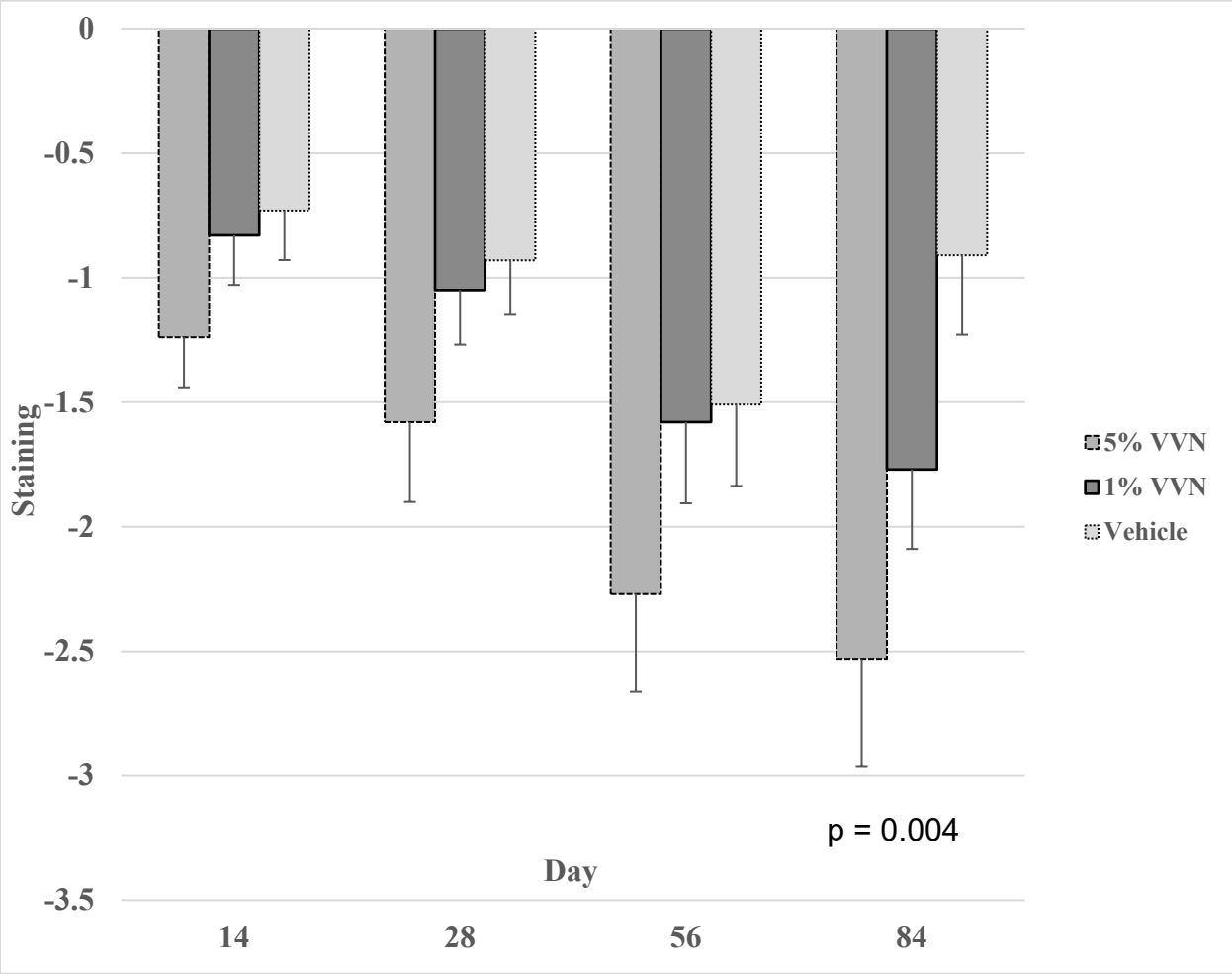
Scale: 0 (none) to 4 (severe); P = 0.054 for VVN001 5% vs. vehicle at Day 84

Figure 3 VAS Eye Dryness Score: Mean Change from Baseline



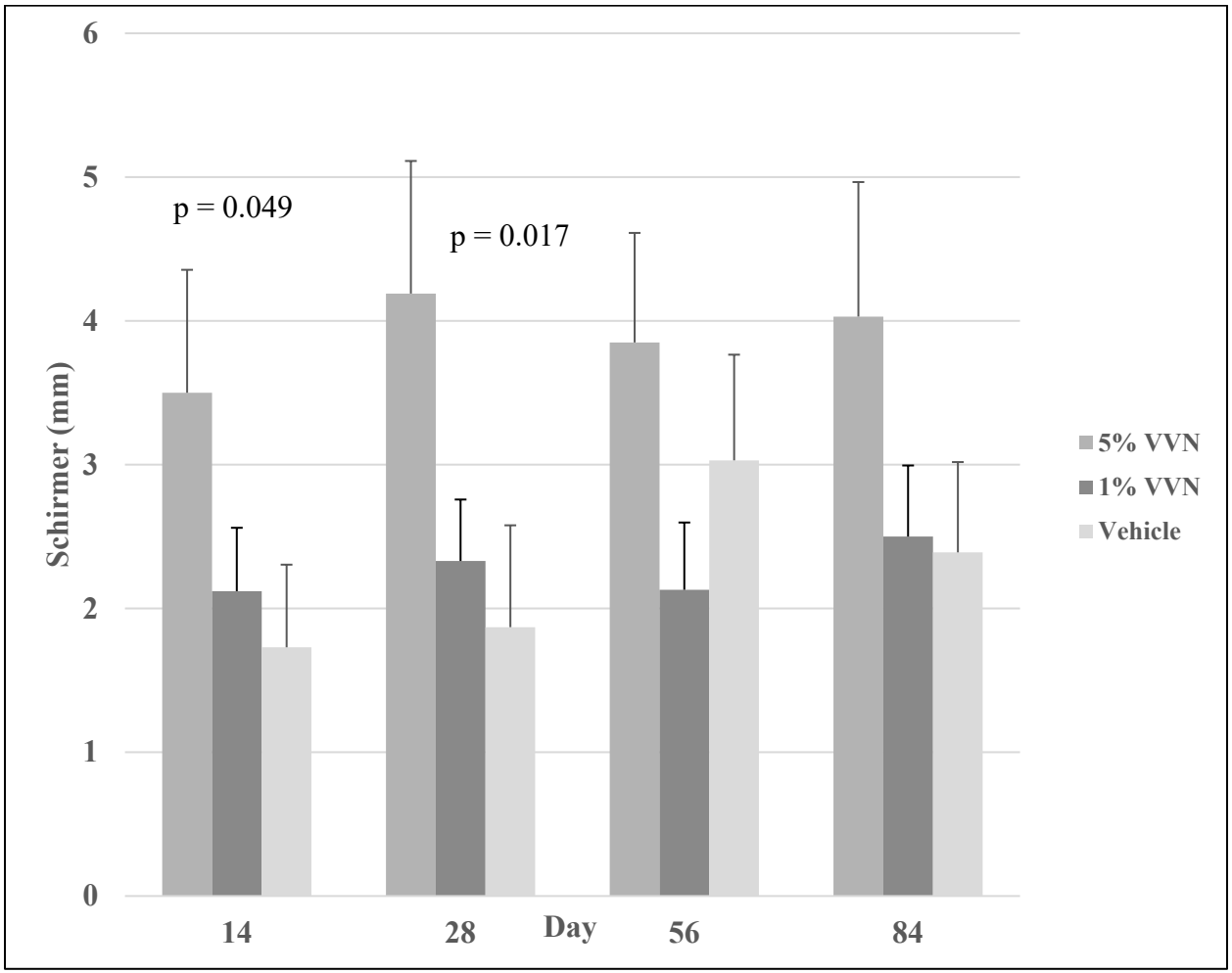
Scale: 0 (none) to 100 (severe)

Figure 4 Total Corneal Fluorescein Staining: Mean Change from Baseline



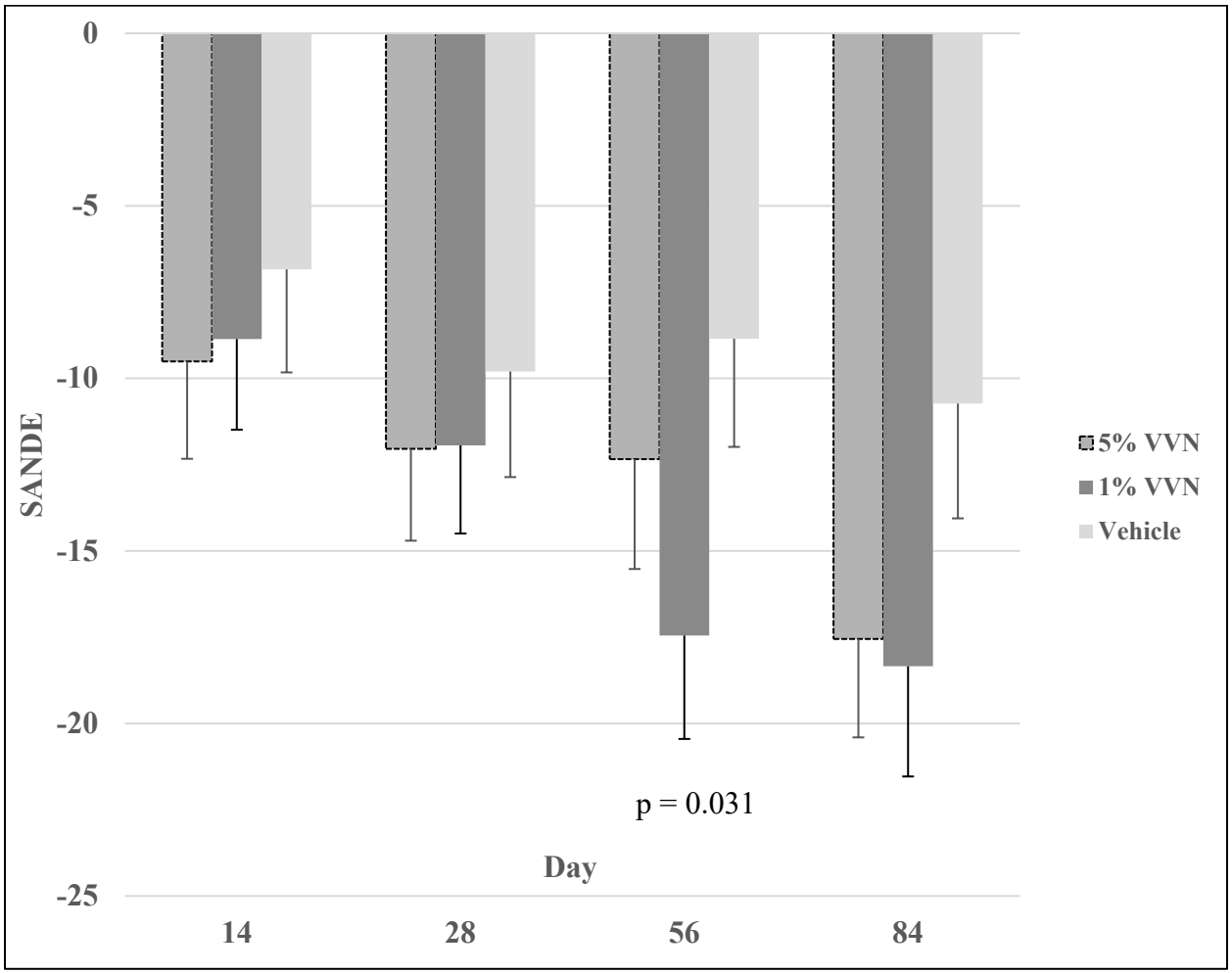
Scale: 0 (none) to 20 (severe): P = 0.004 for VVN001 5% vs. vehicle at Day 84

Figure 5 Schirmer test (mm): Mean Change from Baseline



P = 0.049 and 0.017 for VVN001 5% vs vehicle at Days 14 and 28, respectively.

Figure 6 Global SANDE Score: Mean Change from Baseline



Scale: 0 (none) to 100 (severe); P = 0.031 for VVN001 5% vs. vehicle at Day 56

Supplemental Table 1 Total Corneal Fluorescein Staining: Baseline and Change from Baseline

Visit	*Measure*	*5% VVN001 (N=56)*	*1% VVN001 (N=57)*	*Vehicle (N=56)*
Baseline	Mean (SD)	6.96 (2.97)	6.64 (3.24)	6.18 (2.92)
Day 14	LSMeans	-.1.24	-0.83	-0.73
	Difference of LSMeans (95% CI)	-0.51 (-1.18, 0.16)	-0.09 (-0.76; 0.57)	
	P-value	0.138	0.780	
Day 28	LSMeans	-1.58	-1.05	-0.93
	Difference of LSMeans (95% CI)	-0.66 (-1.41 ; 0.09)	-0.12 (-0.86 ; 0.62)	
	P-value	0.085	0.749	
Day 56	LS Means	-2.27	-1.58	-1.51
	Difference of LSMeans (95% CI)	-0.76 (-1.70 ; 0.18)	-0.07 (-1.00; 0.87)	
	P-value	112	0.891	
Day 84	LSMeans	-2.53	-1.77	-0.91
	Difference of LSMeans (95% CI)	-1.61 (-2.70 ; -0.53)	-0.85 (-1.93, 0.22)	
	P-value	0.004**	0.120	

Scale: 0 (none) to 20 (severe); Study eye. Full analysis set; Mean for Baseline was the observed mean. The LSMeans, Difference of LSMeans (95% CI) and P-value were calculated from the repeated measures mixed model including the treatment, baseline tCFS and visit and the interaction term of treatment x visit as fixed effect and center as a random effect. An unstructured (UN) covariance structure was used. The treatment group comparison was tested in the order of 5% VVN001 vs. Vehicle, then 1% VVN001 vs. Vehicle. ** $P < 0.01$

Supplemental Table 2 Schirmer Score: Baseline and Change from Baseline

Visit	*Measure*	*5% VVN001 (N=56)*	*1% VVN001 (N=57)*	*Vehicle (N=56)*
Baseline	Mean (SD)	4.1 (1.88)	3.8 (1.93)	3.9 (1.92)
Day 14	LSMeans	3.50	2.12	1.73
	Difference of LSMeans (95% CI)	1.77 (0.01, 3.54)	0.40 (-1.36, 2.16)	
	P-value	0.049*	0.655	
Day 28	LSMeans	4.19	2.33	1.87
	Difference of LSMeans (95% CI)	2.32 (0.41, 4.23)	0.46 (-1.42, 2.34)	
	P-value	0.017*	0.627	
Day 56	LS Means	3.85	2.13	
	Difference of LSMeans (95% CI)	0.82 (-1.02, 2.66)	-0.90 (-2.73, 0.93)	
	P-value	0.381	0.331	
Day 84	LSMeans	4.03	2.50	2.39
	Difference of LSMeans (95% CI)	1.64 (-0.39, 3.66)	0.11 (-1.91, 2.13)	
	P-value	0.112	0.916	

Scale: 0 (none) to 100 (severe); Study eye. Full analysis set; Mean for Baseline was observed mean. The LSMeans, Difference of LSMeans (95% CI) and P-value were calculated from the repeated measures mixed model including the treatment, baseline Schirmer and visit and the interaction term of treatment x visit as fixed effect and center as a random effect. An unstructured (UN) covariance structure was used. The treatment group comparison were tested in the order of 5% VVN001 vs. Vehicle, then 1% VVN001 vs. Vehicle. *P < 0.05

Supplemental Table 3 Global SANDE Score: Baseline and Change from Baseline

Visit	*Measure*	*5% VVN001 (N=56)*	*1% VVN001 (N=57)*	*Vehicle (N=56)*
Baseline	Mean (SD)	66.34 (19.60)	57.23 (22.40)	58.19 (22.32)
Day 14	LSMeans	-9.51	-8.86	-6.84
	Difference of LSMeans (95% CI)	-2.67 (-9.65 ; 4.31)	-2.02 (-8.92; 4.88)	
	P-value	0.451	0.564	
Day 28	LSMeans	-12.04	-11.94	-9.80
	Difference of LSMeans (95% CI)	-2.24 (-9.30 ; 4.82)	-2.14 (-9.07; 4.79)	
	P-value	0.532	0.543	
Day 56	LS Means	-12.34	-17.45	-8.85
	Difference of LSMeans (95% CI)	-3.50 (-11.39 ; 4.40)	-8.60 (-16.41 ; -0.79)	
	P-value	0.383	0.031*	
Day 84	LSMeans	-17.55	-18.34	-10.73
	Difference of LSMeans (95% CI)	-6.81 (-15.08 ; 1.45)	-7.61 (-15.80; 0.58)	
	P-value	0.106	0.069	

Scale: 0 (none) to 100 (severe); Study eye. Full analysis set; *P < 0.05. Mean for Baseline is observed mean. The LSMeans, Difference of LSMeans (95% CI) and P-value were calculated from the repeated measures mixed model including the treatment, baseline SANDE and visit and the interaction term of treatment x visit as fixed effect and center as a random effect. An unstructured (UN) covariance structure was used. The treatment group comparison was tested in the order of 5% VVN001 vs. Vehicle, then 1% VVN001 vs. Vehicle.