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Clinical Study VVN001-CS201
Protocol
17 June 2020

VIVAVISION BIOTECH, INC.
Clinical Protocol VVN001-CS-201
FINAL

Protocol Number:	VVN001-CS-201
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.
Medical Monitor:	
Issue Date:	Original: 17June2020

Approved:

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<<Other Signatories>> Date

VIVAVISION BIOTECH, INC.
Clinical Protocol VVN001-CS-201
Investigator Signature Page

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Contact for Serious Adverse Events:

Investigator Name (printed or typed):

_____

Investigator's Signature:

_____ _____
Date

SYNOPSIS

Protocol Number: VVN001-CS-201	**Investigational Product**: VVN001 Ophthalmic Solution
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	
The objectives of the study are: • Evaluate the safety and tolerability of VVN001, 1% ophthalmic solution and VVN001, 5% ophthalmic solution when administered BID compared to vehicle administered BID. • 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 Dry Eye Disease (DED).	
Study Population: The study population will consist of subjects with documented diagnosis of Dry Eye Disease.	
Number of Subjects/Study Sites: Approximately 165 subjects will be randomized to VVN001 or vehicle at approximately 10 centers in the United States (U.S.).	
Study Products: VVN001 ophthalmic solution or vehicle ophthalmic solution will be supplied as Investigational Product (IP).	
Route and Duration of Administration: IP will be instilled bilaterally in each eye BID (morning/evening) for up to 84 days.	
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 ophthalmic solution versus vehicle in subjects with dry eye disease. The study will consist of two periods over a 14-weeks total as follows: • Screening/Run-In period (Day -14 to Day -1) • Treatment period (Day 1 to Day 84) *Screening/Run-In Period.* At Visit 1 Screening (Day 1 minus 14 days), subjects who meet inclusion/exclusion criteria will begin a two-week run-in period during which they will be treated with 1 drop of single-masked vehicle per eye in each eye BID for a 14-day run-in period.	

Treatment Period. At Visit 2 Randomization (Day 1), subjects who continue to meet inclusion/exclusion criteria will be eligible for randomization to VVN001 Ophthalmic solution or vehicle.

Approximately 165 subjects will be randomized in this study at approximately 10 centers located in the United States. Subjects will be randomized to one of the following 3 treatment groups in a 1:1:1 ratio as follows:

Group A: 1% VVN001 administered BID (morning/evening)

Group B: 5% VVN001 administered BID (morning/evening)

Group C: Vehicle administered BID (morning/evening)

Following randomization, subjects will be instructed to self-administer 1 drop of IP per eye into each eye twice daily (morning/evening; Groups A, B, and C). Subjects will be instructed to return to the clinic to be evaluated at Study Visits 3, 4, 5 and 6 (Days 14, 28, 56 and 84 respectively). Subjects must take their morning eyedrop prior to Study Visits 3, 4 and 5. The last dose of IP and the final treatment visit (Visit 6) will occur upon completion of 84 (±2) days of treatment. Subjects will be 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. Subjects will be released from the study at the end of Visit 6 (Day 84).

Safety Assessments (OU):

- Slit-Lamp Biomicroscopy and external eye exam
- Dilated Ophthalmoscopy
- Intraocular Pressure (IOP) measurement
- Best Corrected Visual Acuity (BCVA)
- Conjunctival Hyperemia Evaluation
- Drop Comfort/Tolerability Assessment

Efficacy Assessments (OU):

Signs

- Total Corneal Fluorescein Staining (tCFS score (0-20 point scale) at each clinic visit.
- Inferior region corneal staining score (0-4 point scale) at each clinic visit.
- CFS score by each individual subregion (0-4) at each clinic visit.
- Tear production (Schirmer test without anesthesia, mm/5 min) at each clinic visit.

Symptoms (subject reported)

- Eye dryness score (0-100 point Visual Analog Scale (VAS)) evaluated at each clinic visit.
- Eye discomfort score (0-100 point VAS) evaluated at each clinic visit.

- Symptom Assessment Questionnaire iN Dry Eye (SANDE) will be administered at each clinic visit.

Safety Endpoints:

- Ocular and non-ocular adverse events
- Slit-lamp biomicroscopy and external eye exam
- Conjunctival hyperemia score
- IOP
- Dilated Ophthalmoscopy
- BCVA
- Drop Comfort/Tolerability Assessment

Efficacy Endpoints:

Primary Endpoint:

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

Secondary Endpoints:

The secondary endpoints will be evaluated in a hierarchical fashion and tested sequentially:

Key Secondary Endpoint:

1. 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 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), superior, nasal, temporal, and central) of CFS using modified NEI/Industry Workshop (0-4 scale; using 0.5 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.

Statistical Methods:

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

General Considerations

All continuous study assessments will be summarized by treatment and visit (as applicable) using descriptive statistics (sample size (n), mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

All study data will be listed by treatment, subject, and visit (as applicable).

Sample Size Rationale

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.

Eligibility Criteria:

At Visit 1 (Screening) and Visit 2 (Randomization) male or female subjects must meet the following criteria:

Inclusion Criteria:

1. Provide written informed consent prior to any study-related procedures and provide Health Insurance Portability and Accountability Act (HIPAA) authorization.
2. Are 18 years of age or older.
3. Are willing and able to follow instructions and willing to be present for the required study visits for the duration of the study.
4. Have a BCVA, using corrective lenses if necessary, in the qualifying eye(s) of +0.7 or better as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) at the screening visit and randomization visit.
5. If a woman of child-bearing potential (WOCBP) not pregnant or lactating and not sexually active (i.e. abstinent) for 14 days prior to Visit 1 and willing to remain so through 30 days following Visit 6 or the last administration of the IP. Alternatively, a WOCBP who is not abstinent must have been using acceptable methods of birth control.
6. Are women who have undergone one of the following sterilization procedures at least 6 months prior to Visit 1:
    a. Bilateral tubal ligation
    b. Hysterectomy
    c. Bilateral oophorectomy

7. Have a history of dry eye disease in both eyes supported by a previous clinical diagnosis or have a self-reported history of subjective complaints for at least 6 months prior to screening
8. Are currently using artificial tears and have been using within 30 days of the screening visit.
9. Have an Eye dryness score ≥40 at Visit 1 and ≥35 at Visit 2, one score for both eyes (0-100 point VAS)
10. Have ongoing dry eye disease in the same eye or both eyes, as defined by all of the following criteria in the study eye and the same eye at Visit 1 and Visit 2:
    a. Inferior CFS (iCFS) score of ≥ 2 (NEI; 0-4 scale; using 0.5 unit increments)
    b. Have a Schirmer score (without anesthesia) of ≥1 and ≤7 mm/5 min.
11. Have in the opinion of the Investigator, normal lid anatomy.
12. Are willing to withhold artificial tears for the duration of the study.

Exclusion Criteria:

1. Have a known hypersensitivity or contraindication to the IP or components of IP.
2. Have a Schirmer score (without anesthesia) of <1 or >7 mm/5 min in the study eye.
3. Within 14 days prior to screening (Visit 1) have taken:
    a. Topical ocular antibiotics or systemic antibiotics taken for an ocular condition
    b. Serum tears
    c. Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs)
    d. Topical ocular or oral antihistamines or mast cell stabilizers
    e. Topical ocular or nasal vasoconstrictors (Phenylepherine as part of an ocular evaluation is allowed)
4. Within 30 days prior to screening (Visit 1) have taken/used:
    a. Ocular, inhaled or intranasal or dermatologic corticosteroids
    b. Topical cyclosporine (Restasis® and Cequa®)
    c. Topical ophthalmic lifitegrast (Xiidra®)
    d. Intranasal Tear Neurostimulation
    e. Any topical ophthalmic medications or makeup for eyelash growth
5. Have any prior use of isotretinoin (Accutane®).
6. Within 60 days prior to screening (Visit 1), or during the study, have altered the dosage or anticipate alterations to the dose of the following:
    a. Anticholinergics (if used on a chronic basis)
    b. Antidepressants (if used on a chronic basis)
    c. Systemic immunosuppressive agents

d. Oral contraceptives

e. Oral or injectable corticosteroids (e.g., prednisone. Prednisone dose must be less than 11 mg/day)

7. Expect to use any Cannabidiol products during the study.
8. Have history of uncontrolled glaucoma, IOP over 21 mmHg in either eye at the screening visit or are being treated with eye drops for glaucoma in the study eye. Or the subject has had laser or surgery for glaucoma in the study eye within 90 days of the study.
9. Subjects who cannot suspend the use of contact lenses from Visit 1 and throughout the study.
10. Subjects who have a history of Anterior Basement Membrane Corneal Dystrophy.
11. Subjects who have had a corneal transplant or similar corneal surgery (DALK, DSEK, DMEK, etc.).
12. History of incisional ocular surface surgery, including but not limited to refractive, LASIK, Pterygium surgery within 6 months prior to Visit 1.
13. Any incisional intraocular surgical procedure within 12 months prior to Visit 1; or any planned ocular surgical procedure during the study period.
14. History of yttrium aluminum garnet-laser posterior capsulotomy or any laser ocular surgery in past 90 days prior to Visit 1.
15. Non-compliance (<80%) with Vehicle Run-In administration.
16. Have had eyelid surgery within the past 6 months.
17. Have a congenitally absent lacrimal gland or meibomian glands.
18. Have had cauterization of the punctum or have had non-dissolvable (silicone) or short term dissolvable punctal plugs inserted or removed within the 30 days prior to the screening or planned during the study. Have had long-term dissolvable plugs within 3 months of Visit 1.
19. Subjects who have active or have had an outbreak of herpetic keratitis within one year of Visit 1 or subjects who are on chronic oral antivirals for herpetic disease.
20. Have a diagnosis of:

    a. Ongoing ocular infection, lid margin disorders such as blepharitis (including staphylococcal, demodex or seborrheic) are allowed if not requiring treatment with ocular or systemic antibiotics at Visit 1 or intended treatment during the study.

    b. Meibomian gland disease requiring mechanical meibomian gland expression within the past 3 months.

    c. Excessive lid laxity, floppy eyelid syndrome, ectropion, entropion in either eye or moderate to severe pinguecula or pterygia in the study eye, per the opinion of the Investigator.

    d. Stevens-Johnson syndrome

e. Significant conjunctival scarring in the judgment of the Investigator

f. Severe/serious ocular condition that in the judgment of the Investigator opinion could confound study assessments or limit compliance.

g. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance.

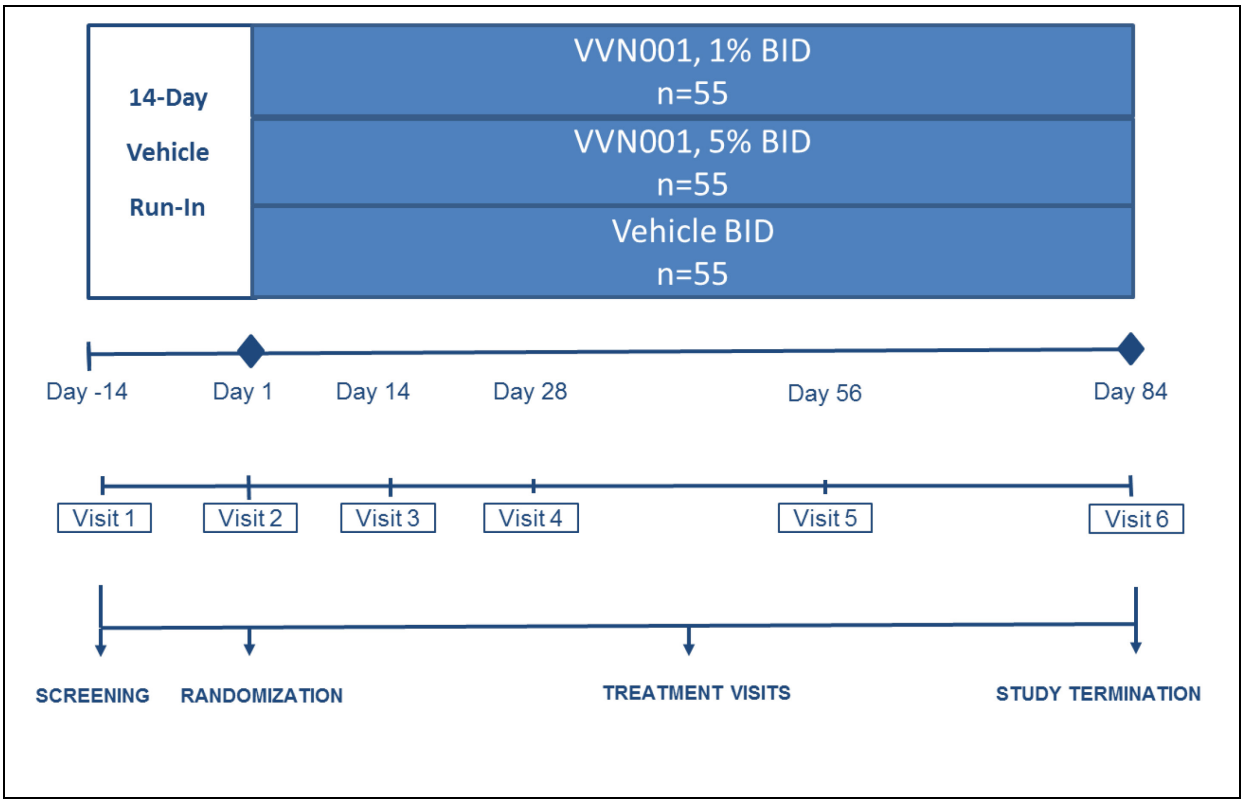
21. Have a documented history of ocular allergies, which, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.
22. Be current cigarette smokers.
23. Have been exposed to an investigational drug within the preceding 30 days or previously randomized in this study.
24. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.
25. Have a known history of alcohol and/or drug abuse within the past 5 years.
26. In the opinion of the Investigator or study coordinator, be unwilling or unable to comply with the study protocol or unable to successfully instill eye drops.

Randomization Criteria:

At Visit 2, the subject must continue to meet criteria outlined at Visit 1 except: Eye dryness score ≥35 one score for both eyes (0-100 point VAS) will qualify.

Study Schematic:

Figure 1 Study Schematic


14-Day
Vehicle
Run-In
VVN001, 1% BID
n=55
VVN001, 5% BID
n=55
Vehicle BID
n=55
Day -14
Day 1
Day 14
Day 28
Day 56
Day 84
Visit 1
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1.0 TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR	Adverse Reaction
BCVA	Best Corrected Visual Acuity
BID	Bis in die (twice per day)
CFS	Corneal Fluorescein Staining
CCLRU	Cornea and Contact Lens Research Unit
DALK	Deep Anterior Lamellar Keratoplasty
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
DMEK	Descemet's Membrane Endothelial Keratoplasty
DSEK	Descemet's Stripping Endothelial Keratoplasty
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICAM	Intercellular adhesion molecule
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ID	Identification
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LASIK	Laser-Assisted In Situ Keratomileusis
LFA	Lymphocyte function-associated antigen
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities

MGD	Meibomian Gland Dysfunction
n	Sample size
NEI	National Eye Institute
NSAID	Non-steroidal anti-inflammatory drug
OD	Oculus Dextrus (right eye)
OU	Oculus Uterque (both eyes)
PDF	Portable Document Format
P	Probability
pH	Potential of Hydrogen
PPS	Per Protocol Set
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAF	Safety Set
SANDE	Symptom Assessment Questionnaire iN Dry Eye
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
tCFS	Total Corneal Fluorescein Staining
UPT	Urine Pregnancy Test
VA	Visual Acuity
VAS	Visual Analog Scale
WOCBP	Women of Child Bearing Potential

1. INTRODUCTION

1.1. BACKGROUND

"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" (Craig 2017).

In a recent review of the large volume on literature, "the prevalence of DED 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, although differences become significant with age. 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" (Stapleton 2017).

One group of experts concluded that the mechanisms involved in the initiation and perpetuation of dry eye disease are evaporative water loss leading to hyperosmolar tissue damage. "Research in human disease and in animal models has shown that this, either directly or by inducing inflammation, causes a loss of both epithelial and goblet cells. The consequent decrease in surface wettability leads to early tear film breakup and amplifies hyperosmolarity via a Vicious Circle. Pain in dry eye is caused by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, while visual symptoms arise from tear and ocular surface irregularity" (Bron 2017).

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, both sources become apparent (DEWS II). In both groups, desiccating stress ultimately results in ocular surface inflammation (Stevenson 2012).

Given this pathophysiology, many approaches have been tried in the pharmacological treatment of DED. Approved pharmacotherapies in the U.S. include the immunomodulator cyclosporine (Restasis®, Cequa®) and the lymphocyte function-associated antigen-1 (LFA-1) antagonist, lifitegrast (Xiidra®). As well, medical devices marketed in the U.S. for treatment of DED and other ocular surface disorders include a nasal neurostimulatory device (TrueTear®) and warming of the eyelids (LipiFlow®). While safe and effective, not all patients with DED are fully served by these current therapies. Thus, there is a need for novel therapies to more broadly serve the needs of patients with this challenging disease.

1.2. STUDY RATIONALE

VivaVision is developing VVN001, a small-molecule antagonist of lymphocyte function-associated antigen 1 (LFA-1) for the treatment of dry eye disease. VVN001 binds to (LFA-1, also known as CD11a/CD18), found on the cell surface of leukocytes. The binding blocks the interaction of LFA-

1 to its cognate ligand, intercellular adhesion molecule-1 (ICAM-1, also known as CD54), typically expressed on endothelial cells and cells of the immune system (T cells and B cells (Smith 2007).

One antagonist, lifitegrast has been approved for the treatment of dry eye disease. The clinical trials of lifitegrast showed that antagonizing the interaction of LFA-1 and ICAM-1 significantly improved both the symptoms and the signs of the disease. VVN001 is more potent than lifitegrast in antagonizing the LFA-1/ICAM-1 interaction. In addition, VVN001 showed better water solubility (13% weight/volume) than lifitegrast (~5%) at neutral pH. Better water solubility may result in greater ocular comfort upon instillation.

1.3. RISK/BENEFIT ASSESSMENT

Safety data from the pre-clinical studies with VVN001 demonstrate an excellent safety and tolerability profile. LFA-1/ICAM-1 antagonists (lifitgrast) have been studied and approved for human use and prior clinical trials with lifigrast have demonstrated no long-term safety issues with administration. Given the experience with this product in pre-clinical studies as well as with similar approved products used in a dry eye population, there is a favorable benefit-risk ratio. Further the risks of this trial will be mitigated via routine monitoring and reporting of potential new adverse events.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. OBJECTIVES

The objectives of this study are to:

1. Evaluate the safety and tolerability of VVN001, 1% ophthalmic solution and VVN001, 5% ophthalmic solution when administered BID compared to vehicle administered BID.
2. 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.

2.2. STUDY ENDPOINTS

2.2.1. Safety Endpoints

- Ocular and non-ocular adverse events
- Slit-lamp Biomicroscopy and external eye exam
- Conjunctival hyperemia score
- IOP
- Dilated Ophthalmoscopy
- BCVA
- Drop Comfort/Tolerability Assessment

2.2.2. 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)

2.2.3. Secondary Efficacy Endpoints:

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

Key Secondary Endpoint:

1. 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), superior, nasal, temporal, and central) 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. STUDY DESIGN

3.1. OVERALL DESIGN OF THE STUDY

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 Ophthalmic solution versus vehicle in subjects with dry eye disease. The study will consist of two periods over 14-weeks total as follows:

1. Screening/ run-in period (Day -14 to Day -1)
2. Treatment period (Day 1 to Day 84)

Screening/Run-In Period:

At Visit 1 Screening (Day 1 minus 14 days), subjects who meet screening inclusion/exclusion criteria will begin a two-week run-in period during which they will be treated with 1 drop of single-masked vehicle per eye in each eye BID for a 14-day run-in period.

Treatment Period:

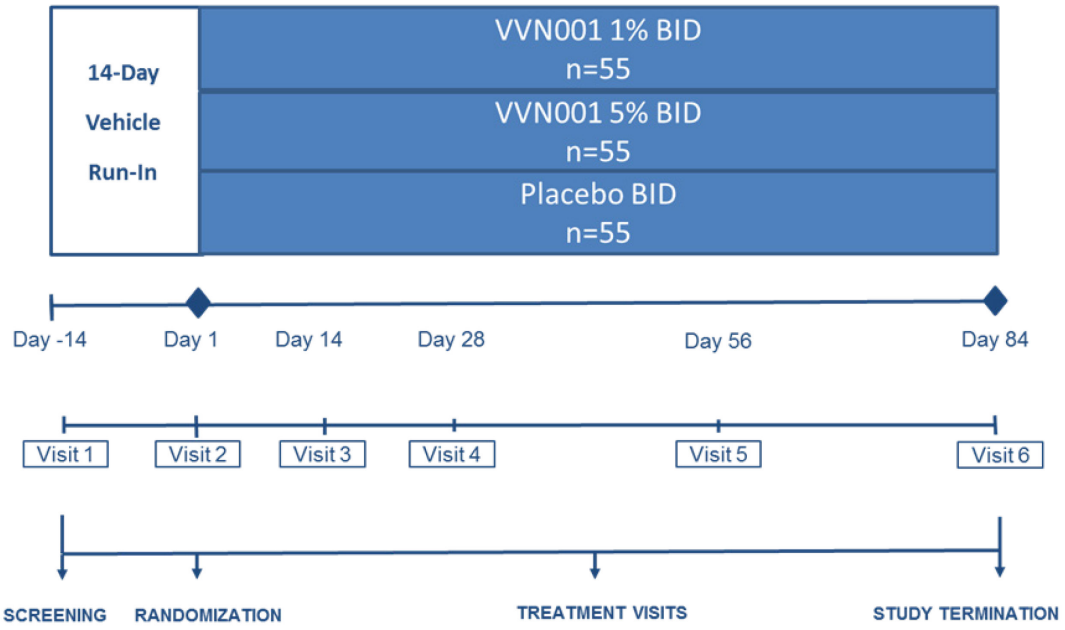
At Visit 2 Randomization (Day 1), subjects who continue to meet inclusion/exclusion criteria will be eligible for randomization to VVN001 Ophthalmic solution or vehicle.

Approximately 165 subjects will be randomized in this study at approximately 10 centers located in the United States (US). Subjects will be randomized to one of the following 3 treatment groups in a 1:1:1 ratio as follows:

- Group A: 1% VVN001 administered BID (morning/evening)
- Group B: 5% VVN001 administered BID (morning/evening)
- Group C: Vehicle administered BID (morning/evening)

Following randomization, subjects will be instructed to self-administer 1 drop of IP per eye into each eye twice daily (morning/evening; Groups A, B, and C). Subjects will be instructed to return to the clinic to be evaluated at Study Visits 3, 4, 5 and 6 (Days 14, 28, 56 and 84 respectively). Subjects must take their morning eyedrop prior to Study Visits 3, 4 and 5. The last dose of IP and the final treatment visit (Visit 6) will occur upon completion of 84 days of treatment. Subjects will be 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. Subjects will be released from the study at the end of Visit 6 (Day 84). See Figure 2 for a Schematic of the study visits.

Figure 2



Safety Assessments

Safety assessments in the study will be evaluated in both eyes (OU) and will include:

- Biomicroscopy and external eye exam
- Dilated ophthalmoscopy
- Intraocular pressure (IOP) measurement
- Best Corrected Visual Acuity (BCVA)
- Conjunctival Hyperemia Evaluation
- Drop Comfort/Tolerability Assessment

Efficacy Assessments

Efficacy assessments in the study will be evaluated OU for signs and symptoms of DED and will include:

Signs

- Total CFS score (0 – 20 point scale [using 0.5 increments] scale) at each clinic visit.
- Inferior subregion corneal staining score (0-4 point scale [using 0.5 increments]) at each clinic visit.
- CFS score by each individual (central, temporal, nasal and superior) subregion (0-4 point scale [using 0.5 increments]) at each clinic visit.

- Tear production (Schirmer test without anesthesia, mm/5 min) at each clinic visit.

Symptoms (subject-reported)

- Eye dryness score (0-100 point VAS) evaluated at each clinic visit.
- Eye discomfort score (0-100 point VAS) evaluated at each clinic visit.
- Symptom Assessment Questionnaire iN Dry Eye (SANDE) will be administered at each clinic visit.

3.2. END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including Visit 6 and has completed procedures shown in the Schedule of Procedures and Assessments (Appendix 1).

4. STUDY POPULATION

4.1. INCLUSION CRITERIA

At Visit 1 (Screening) and Visit 2 (Randomization) male or female subjects must meet the following criteria:

1. Provide written informed consent prior to any study-related procedures and provide Health Insurance Portability and Accountability Act (HIPAA) authorization.
2. Are 18 years of age or older.
3. Are willing and able to follow instructions and willing to be present for the required study visits for the duration of the study.
4. Have a BCVA, using corrective lenses if necessary, in the qualifying eye(s) of +0.7 or better as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) at the screening visit and randomization visits.
5. If a woman of child-bearing potential (WOCBP) not pregnant or lactating and not sexually active (i.e. abstinent) for 14 days prior to Visit 1 and willing to remain so through 30 days following Visit 6 or the last administration of the IP. Alternatively, a WOCBP who is not abstinent must have been using acceptable methods of birth control.
6. Are women who have undergone one of the following sterilization procedures at least 6 months prior to Visit 1:
    a. Bilateral tubal ligation
    b. Hysterectomy
    c. Bilateral oophorectomy
7. Have a history of dry eye disease in both eyes supported by a previous clinical diagnosis or have a self-reported history of subjective complaints for at least 6 months prior to screening
8. Are currently using artificial tears and have been using within 30 days of the screening Visit.
9. Have an Eye dryness score ≥40 at Visit 1 and ≥35 at Visit 2, one score for both eyes (0-100 point VAS)
10. Have ongoing dry eye disease in the same eye or both eyes, as defined by all of the following criteria at Visit 1 and Visit 2:
    a. Inferior CFS (iCFS) score of ≥ 2 (NEI; 0-4 scale; using 0.5 unit increments)
    b. Have a Schirmer score (without anesthesia) of ≥1 and ≤7 mm/5 min.
11. Have in the opinion of the Investigator, normal lid anatomy.
12. Are willing to withhold artificial tears for the duration of the study.

4.2. EXCLUSION CRITERIA

At Visit 1, for subjects to be eligible for study participation they may not:

1. Have a known hypersensitivity or contraindication to the IP or IP components.
2. Have a Schirmer score (without anesthesia) of <1 or >7mm/5 min in the study eye.
3. Within 14 days prior to screening (Visit 1) have taken:
    a. Topical ocular antibiotics or systemic antibiotics taken for an ocular condition.
    b. Serum tears
    c. Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs)
    d. Topical ocular or oral antihistamines or mast cell stabilizers
    e. Topical ocular or nasal vasoconstrictors (Phenylephrine as part of an ocular evaluation is allowed)
4. Within 30 days prior to screening (Visit 1) have taken/used:
    a. Ocular, inhaled, dermatologic or intranasal corticosteroids
    b. Topical cyclosporine (Restasis® and Cequa®)
    c. Topical ophthalmic lifitegrast (Xiidra®)
    d. Intranasal Tear Neurostimulation
    e. Any topical ophthalmic medications or makeup for eyelash growth.
5. Have any prior use of isotretinoin (Accutane®).
6. Within 60 days prior to screening (Visit 1), or during the study, have altered the dosage or anticipate alterations to the dose of the following:
    a. Anticholinergics (if used on a chronic basis)
    b. Antidepressants (if used on a chronic basis)
    c. Systemic immunosuppressive agents
    d. Oral contraceptives
    e. Oral or injectable corticosteroids (e.g., prednisone. Prednisone dose must be less than 11 mg/day)
7. Expect to use any Cannabidiol products during the study.
8. Have history of uncontrolled glaucoma in either eye, IOP over 21 mmHg at the screening visit or are being treated with eye drops for glaucoma in either eye. Or the subject has had laser or surgery for glaucoma in the study eye within 90 days of the study.
9. Subjects who cannot suspend the use of contact lenses from Visit 1 and throughout the study.

10. Subjects who have a history of Anterior Basement Membrane Corneal Dystrophy.
11. Subjects who have had a corneal transplant or similar corneal surgery (DALK, DSEK, DMEK, etc.).
12. History of incisional ocular surface surgery, including but not limited to refractive, LASIK, Pterygium surgery within 6 months prior to Visit 1.
13. Any incisional intraocular surgical procedure within 12 months prior to Visit 1; or any planned ocular surgical procedure during the study period.
14. History of yttrium aluminum garnet-laser posterior capsulotomy or any laser ocular surgery in past 90 days prior to Visit 1.
15. Non-compliance (<80%) with Vehicle Run-In administration.
16. Have had eyelid surgery within the past 6 months.
17. Have a congenitally absent lacrimal gland or meibomian glands.
18. Have had cauterization of the punctum or have had non-dissolvable (silicone) or short term dissolvable punctal plugs inserted or removed within the 30 days prior to the screening or planned during the study. Have had long-term dissolvable plugs within 3 months of Visit 1.
19. Subjects who have active or have had an outbreak of herpetic keratitis within one year of Visit 1 or subjects who are on chronic oral antivirals for herpetic disease.
20. Have a diagnosis of:
    a. Ongoing ocular infection, lid margin disorders such as blepharitis (including staphylococcal, demodex or seborrheic) are allowed if not requiring treatment with ocular or systemic antibiotics at Visit 1 or intended treatment during the study.
    b. Meibomian gland disease requiring mechanical meibomian gland expression within the past 3 months
    c. Excessive lid laxity, floppy eyelid syndrome, ectropion, entropion in either eye, or moderate to severe pinguecula or pterygia in the study eye per the opinion of the Investigator.
    d. Stevens-Johnson syndrome
    e. Significant conjunctival scarring in the judgment of the Investigator
    f. Severe/serious ocular condition that in the judgment of the Investigator opinion could confound study assessments or limit compliance.
    g. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance.
21. Have a documented history of ocular allergies, which, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.

22. Be current cigarette smokers.
23. Have been exposed to an investigational drug within the preceding 30 days or previously randomized in this study.
24. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.
25. Have a known history of alcohol and/or drug abuse within the past 5 years.
26. In the opinion of the Investigator or study coordinator, be unwilling or unable to comply with the study protocol or unable to successfully instill eye drops.

4.3. RANDOMIZATION CRITERIA

At the Randomization Visit (Visit 2), an eligible subject must continue to meet all clinical inclusion/exclusion criteria as defined in Sections 4.1 and 4.2 with the exception of the Eye dryness score: Eye Dryness ≥35 one score for both eyes (0-100 point VAS) will qualify. Note: Subjects must meet all eye specific criteria from Visit 2 in the same qualifying eye as in Visit 1.

4.4. 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 Visits 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 at Visit 2, the right eye (OD) will be selected as the study eye.

4.5. SCREEN FAILURES

If the subject does not qualify at Visit 1 or Visit 2, he or she may be re-screened once after 14 days from the relevant visit provided that new informed consent to be signed, new subject number received and all the assessments are repeated as per protocol requirements.

4.6. STUDY TREATMENTS AND INTERVENTIONS

4.7. INVESTIGATIONAL PRODUCTS

4.7.1. IP Description

VVN001 Ophthalmic Solution is a non-preserved aqueous solution of VVN001 for topical ophthalmic use and will contain the active substance (VVN001) and Sodium Phosphate, monobasic monohydrate, Sodium Thiosulfate Pentahydrate, Sodium Chloride, and Water. The pH ranges from 7.0 to 7.4. The osmolarity ranges from 280-320 mOsm/kg.

The VVN001 Vehicle control has the same composition as VVN001 Ophthalmic Solution except that it does not contain VVN001.

4.7.2. Dosage and Administration

VVN001 will be administered as a topical ophthalmic solution. Subjects will be randomized to receive one of the following three treatment groups:

- Group A: 1% VVN001 Ophthalmic Solution BID
- Group B: 5% VVN001 Ophthalmic Solution BID
- Group C: Vehicle BID

Justification for Dose
The concentrations of VVN001 Ophthalmic solution and dosing schedule were chosen based on non-clinical pharmacokinetic (PK) and toxicology studies and data reflecting relative safety multiples. For details on the pharmacokinetic and toxicology studies and the respective safety multiples, see the Investigator's Brochure.

IP Dispensation Instructions
At Visit 1, eligible subjects will receive one kit of Single-Masked Vehicle Run-In.

At Visit 2, randomized subjects will be assigned to an IP Kit which contains 4 weekly cartons of Double-Masked IP (VVN001, 1%, VVN001, 5% or Vehicle). The kit will contain a sufficient supply of IP for approximately 28 days of dosing. Subjects will return the used IP at Visit 4 and will receive a second supply of IP which will be sufficient for another approximate 28 days of dosing. The subject will again return the used IP at Visit 5 at which time they will receive the last kit of IP which will contain a sufficient supply for dosing through the remaining duration of the study.

Timing of Self-Administration
IP (VVN001, 1%, VVN001, 5% or Vehicle) will be administered to the ocular surface twice daily as a single drop in each eye administered morning and evening. The subject should be instructed to ensure they instill at least one drop in each eye per each administration.

The first dose of Single-Masked Vehicle and the first dose of Double-Masked IP (VVN001, 1%, VVN001 5% or Vehicle) will be self-administered by the subject under supervision of the site staff. This will be considered the morning dose for that day.

Following Visit 1, the subjects will self-administer the second dose of Single-Masked IP in the evening and will be instructed to self-administer one drop into each eye bilaterally BID for approximately 14 days. Following Visit 2 the subjects will be instructed to self-administer the second

dose of Double-Masked IP in the evening and will be instructed to self-administer IP BID instilled into each eye bilaterally for approximately 84 days.

4.8. PREPARATION/STORAGE AND ACCOUNTABILITY

4.8.1. Product Appearance/Packaging and Labeling

VVN001 Ophthalmic solution is a sterile solution for topical application to the eye at either 1% or 5%. Placebo for VVN001 ophthalmic solution is a matching sterile vehicle solution.

Single-Masked and Double-Masked IP is contained in 3 mL single-use droppers. Subjects will be instructed to instill one drop in each eye and then place the used dropper back into the kit. All investigational products kits are labeled with the following information:

- Product name, Batch number, Protocol number, Kit number, Storage instructions, Sponsor city and state, manufacturing date • "New Drug - Limited by Federal (United States) Law to investigational Use"

Each Single-Masked Kit will contain two weekly cartons with 16 single-use droppers packaged in a weekly use kit (carton box with dividers) by VivaVision, or designee.

Each randomized, Double-Masked monthly IP kit contains four weekly cartons with 16 single-use droppers packaged in a weekly use kit (carton box with dividers).

Each site will be provided with emergency back-up kits of Double-Masked IP in case of contamination or other loss. The investigational sites will be directed to assign specific emergency kits to individual subjects using the Interactive Web Response System (IWRS).

4.8.2. Product Storage and Stability

Kits with packaged droppers are to be stored at 20-25 °C (68-77 °F), excursions permitted between 15-30 °C (59-86 °F) and protected from light.

4.8.3. Accountability

The Investigator must maintain accurate accounting of IP received from the sponsor via a detailed inventory. This includes the amount of IP received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the sponsor or designee upon completion of the trial. All IP administered during the course of the trial must be accounted for on a drug accountability form.

IP ordered, records of receipts, dispensing records, and inventory forms will be retained and reconciled by designated site personnel. At each visit, subjects will return all used and unused droppers of Run-In and double-masked IP to clinic staff for accountability purposes. Accountability will be ascertained by performing reconciliation between the amount of IP cartons (kits and their

components) sent to the site, the amount used and unused at the time of reconciliation. No investigative drugs or kits will be discarded prior to full accountability by Sponsor's monitor.

Site personnel will record the date and time of the first dose in the source documents and will record this information in electronic Case Report Form (eCRF). Subjects will record self-administered doses on a Daily Dosing Diary.

Sponsor study monitors or designees will conduct accountability of IP (VVN001 or Vehicle). Accountability will be ascertained by performing reconciliation between the number of kits and droppers sent to the site, accounted for at the time of reconciliation during routine monitoring and at the end of the study.

At the end of the study, all study materials, including any used and unused IP (VVN001 or Vehicle kits), as well as original vial containers (even if empty), will be destroyed or returned to the Sponsor (or designee) in accordance with Sponsor or designee's Standard Operating Procedures (SOPs), following approval by the Sponsor. All returns of IP will be documented. The study monitor or designee will verify drug accountability. All drug accounting procedures must be completed before the study is considered complete.

4.9. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

To minimize bias, the following measures will be taken:

- IP allocation (VVN001, 1% and 5% versus vehicle) will be randomized and masked to the Sponsor, subjects, and investigative staff.
- The randomization schedule will be generated by an independent unmasked statistician (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study Investigator and members of the project team.

4.10. TREATMENT COMPLIANCE

Compliance will be assessed by reviewing dosing information recorded daily in the daily dosing diary by the subject. A trained Site Coordinator will document this comparison along with verification of returned used single-use droppers and will counsel the subject regarding any observed compliance discrepancies. If compliance deviations are major (<80%), the site will record the deviation in the source documents and in the eCRF.

4.11. CONCOMITANT THERAPY

All medications that the subject has taken 6 months prior to Visit 1 and through Visit 6 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 AE will be recorded for each medication.

4.12. PERMITTED MEDICATIONS AND THERAPIES

Medications and therapies not specifically excluded in Section 4.2 may be taken as necessary. Omega-3 supplements are permitted if the dose is stable within 3 months of Visit 1 and expected to remain stable for the duration of the study.

Table 1 Medications and Procedures Not Permitted

Any incisional intraocular surgical procedure	12 months
Have had incisional ocular surface surgery, including but not limited to refractive LASIK, refractive, pterygium removal	6 months
Eyelid surgery	6 months
Yttrium aluminum garnet-laser posterior capsulotomy or any laser ocular surgery	3 months
Punctal plugs that are long-term dissolvable	3 months
Mechanical treatments for Meibomian Gland Dysfunction (MGD) including but not limited to thermal pulsation (Lipiflow), debridement of lid margin (BlephEx), thermal application (MeiBoFlo, Tear Care), or meibomian gland probing.	3 months
Topical ocular or systemic antibiotics for the treatment of an ocular condition	14 days
Serum tears	14 days
Topical ocular non-steroidal anti-inflammatory drugs (NSAIDS)	14 days
Topical ocular or oral antihistamines or mast cell stabilizers	14 days
Topical ocular or nasal vasoconstrictors (Phenylephrine to dilate is allowed)	14 days
Ocular, inhaled or intranasal or dermatologic corticosteroids	30 days
Topical ocular cyclosporine	30 days
Lifitegrast	30 days
Intranasal Tear Neurostimulation	30 days
Punctal cautery and short-term dissolvable punctal plugs	30 days

Any topical ophthalmic medications (or makeup) used for eyelash growth	30 days
Alter the dose of anticholinergics (if used on a chronic basis)	60 days
Alter the dose of antidepressants (if used on a chronic basis)	60 days
Alter the dose of systemic immunosuppressive agents (other than systemic corticosteroids)	60 days
Alter the dose of Oral Contraceptives	60 days
Alter the dose of systemic corticosteroids (oral or injectable) If taking oral corticosteroids (e.g. prednisone), prednisone dose must be less than 11mg/day	60 days
No prior use of isotretinoin. No prior corneal transplant or similar corneal surgery (DALK, DSEK, DMEK, etc.).	Prior history
Topical ocular corticosteroids and topical dermatologic corticosteroids on the face within 30 days prior to Visit 1 and during study participation. Topical dermatologic corticosteroids not used on the face are allowed if applied to less than 3 areas for less than 3 consecutive days.	30 days
Contact Lenses or current use of eye drops for glaucoma.	At Screening and throughout study

5. STUDY DISCONTINUATION/PARTICIPANT WITHDRAWAL

5.1. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Any subject who wishes to discontinue the IP use or withdraw from participation in the study for any reason is entitled to do so without obligation. The Investigator may also discontinue any subject from the IP use or from study participation, if deemed necessary.

Investigational Product use may be discontinued, and any subject may be discontinued from study participation at any time during the study at the discretion of the Investigator or the Sponsor for any reason including but not limited to:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
2. Any Serious Adverse Event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
3. Subject's decision to withdraw.
4. Any woman who becomes pregnant while participating in the study. Information on the pregnancy and outcome will be requested.
5. Subject’s failure to comply with protocol requirements or study related procedures.
6. Termination of the study by the Sponsor, Food and Drug Administration (FDA), or other regulatory authorities.

In the event study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have the subject complete Visit 6 assessments as possible. If a non-serious AE is unresolved at the time of the subject’s final study visit, an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow all SAEs to resolution. The reason for premature discontinuation should be entered into the eCRF and recorded in the subject chart.

Subjects who withdraw from the study will not be replaced.

Additionally, the trial or parts of the trial may be discontinued by the Sponsor or at the recommendation of the Investigator after consultation with VivaVision Biotech, Inc. This may be based on a significant number of AEs of a similar nature that warrant such action.

6. STUDY PROCEDURES

6.1. VISIT DESCRIPTIONS

6.1.1. Visit 1 (Screening): Day minus 14 (±2 days) prior to Visit 2

The following will be performed/assessed in the order suggested below and all ocular assessments will be conducted in both eyes (as applicable):

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent.
- Obtain information including demographics, concomitant medications, ocular and systemic medical and medication history and surgical history.*
- Assess for prior AT use.
- Evaluate eligibility
- A Screening Identification (ID) should be assigned to the Subject once any Visit 1 procedures (other than Informed Consent Form (ICF)) are performed.
- Subject-rated symptom assessments (in this order):
    - Individual eye dryness and discomfort symptom assessment via VAS
    - SANDE
- Urine Pregnancy Test (UPT) for all eligible women of childbearing potential.*
- Safety Lab Draw (Hematology, Serum Chemistry, Serology and Urinalysis).*
- BCVA
- Slit-lamp biomicroscopy and external eye exam
    - Includes evaluation of conjunctival hyperemia
- CFS (Wait 15 minutes prior to performing Schirmer test)
- Unanesthetized Schirmer test
- IOP
- Dilated Ophthalmoscopy
- Determine if the subject is eligible to continue in the study. Do not continue screening any subject who does not meet eligibility requirements. Any subject who does not meet eligibility requirements will be designated as a Screen Failure.
- If the subject is qualified, a kit containing a two-week supply of Single-Masked Run-In will be provided.
- Subject will self-administer first dose of Single-Masked IP observed by trained study staff.
- Administer the Drop Comfort Tolerability Assessment at 1-minute and 5-minutes post dose.

- Dispense daily dosing diary.
- Instruct the subject to discontinue using all prohibited medications for the remainder of the study and schedule to return to the clinic for Visit 2 in two weeks.

*May be performed at any time during the visit in order to facilitate subject and site schedules.

6.1.2. Visit 2 (Randomization): Day 1

Visit 2 will occur 14 (±2 days) after Visit 1 (Screening). The following will be performed/assessed in both eyes (as applicable):

- Evaluate continued eligibility
- Subject-rated symptom assessments (in this order):
    - Individual eye dryness and eye discomfort symptom assessment via VAS
    - SANDE
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit *
- BCVA
- Slit-lamp biomicroscopy and external eye exam
    - Includes evaluation of conjunctival hyperemia
- CFS
- Wait 15-20 minutes after CFS before proceeding
- Unanesthetized Schirmer test
- IOP
- Collect used Run-In, Daily Dosing Diary and check compliance
- Determine if subject is eligible for randomization

For eligible subjects, the following is the process regarding administration of Double-Masked IP whereby the trained site staff will conduct the following procedures:

- Enter subject information into IWRS to determine randomization code and Kit Number.
- Subject will self-administer first dose of Double-Masked IP observed by trained study staff.
- Administer the Drop Comfort/Tolerability Assessment at 1-minute and 5-minutes post dose.

- Assess for occurrence of any IP related AEs
- Dispense 4 weeks supply of double masked IP and Daily Dosing Diary
- Collect used Single-Masked IP kit
- Schedule the subject to return for Visit 3 (Day 14±2 days)

6.1.3. Visit 3: Day 14 (±2 days)

This visit will occur on Day 14 as calculated from Visit 2: Day 1, and the following will be performed in both eyes (as applicable):

- Subject-rated symptom assessments (in this order):
    - Individual eye dryness and eye discomfort symptom assessment via VAS
    - SANDE
- Use of any concomitant medications since the last visit*
- Occurrence of any AEs since the last visit*
- BCVA
- Slit-lamp biomicroscopy and external eye exam
    - Includes evaluation of conjunctival hyperemia
- CFS
- Wait 15-20 minutes after CFS before proceeding
- Unanesthetized Schirmer test
- IOP
- DO NOT COLLECT IP kit at this visit
- Collect and Review Daily Dosing diary and check compliance
- Dispense new Daily Dosing Diary
- Schedule the subject to return for Visit 4 (Day 28 ±2 days).

6.1.4. Visit 4: Day 28 (±2 days)

This visit will occur on Day 28 as calculated from Visit 2: Day 1, and the following will be performed in both eyes (as applicable):

- Subject-rated symptom assessments (in this order):

    - Individual eye dryness and eye discomfort symptom assessment via VAS
    - SANDE
- Use of any concomitant medications since the last visit*
- Occurrence of any AEs since the last visit*
- BCVA
- Slit-lamp biomicroscopy and external eye exam
    - Includes evaluation of conjunctival hyperemia
- CFS
- Wait 15-20 minutes after CFS before proceeding
- Unanesthetized Schirmer test
- IOP
- Collect used kit of Double-Masked IP and completed Daily Dosing Diary and check compliance.
- Dispense new kit of Double-Masked IP and Daily Dosing Diary
- Schedule the subject to return for Visit 5 (Day 56 ±2 days).

6.1.5. Visit 5: Day 56 (±2 days)

This visit will occur on Day 56 as calculated from Visit 2: Day 1, and the following will be performed in both eyes (as applicable):

- Subject-rated symptom assessments (in this order):
    - Individual Symptom eye dryness and eye discomfort Assessment via VAS
    - SANDE
- Use of any concomitant medications since the last visit*
- Occurrence of any AEs since the last visit*
- BCVA
- Slit-lamp biomicroscopy and external eye exam
    - Includes evaluation of conjunctival hyperemia
- CFS
- Wait 15-20 minutes after CFS before proceeding
- Unanesthetized Schirmer test

- IOP
- Collect used kit of Double-Masked IP and completed Daily Dosing Diary and check compliance.
- Dispense new kit of Double-Masked IP and Daily Dosing Diary
- Schedule the subject to return for Visit 6 (Day 84 ±2 days) and remind them to bring used and unused IP to the next visit.

6.1.6. Visit 6: Day 84 (±2 days)

This visit will occur on Day 84 as calculated from Visit 2: Day 1, and the following will be performed in both eyes:

- Subject-rated symptom assessments (in this order):
  - Individual eye dryness and eye discomfort Symptom Assessment via VAS
  - SANDE
- Use of any concomitant medications since the last visit*
- Occurrence of any AEs since the last visit*
- UPT*
- Safety Lab Draw*
- Subject will self-administer last dose of Double-Masked IP observed by trained study staff
- Administer the Drop Comfort/Tolerability Assessment at 1-minute and 5-minutes post dose.
- Assess for occurrence of any IP related AEs
- BCVA
- Slit-lamp biomicroscopy and external eye exam
  - Includes evaluation of conjunctival hyperemia
- CFS
- Wait 15-20 minutes after CFS before proceeding
- Unanesthetized Schirmer test
- IOP

- Collect used kit of Double-Masked IP and completed Daily Dosing Diary and check compliance.*
- Dilated Ophthalmoscopy
- All subjects will be discharged from the study at this visit

6.1.7. Early Termination Visit

In the event of termination prior to Visit 6, every attempt will be made to ensure that all the Visit 6 assessments are performed in both eyes at the Early Termination Visit prior to discharge from the study.

6.1.8. Unscheduled Visit

Any visits or procedures performed beyond those specified within the protocol must be documented in the Unscheduled Visit pages of the electronic Case Report Form (eCRF). Unscheduled visits may include but are not limited to reporting AEs, changes in concomitant medications, or ophthalmic assessments as deemed appropriate by an appropriately qualified physician.

7. STUDY ASSESSMENTS

7.1. SAFETY ASSESSMENTS

Safety Parameters include (OU):

- Slit-Lamp Biomicroscopy and external eye exam
- Dilated Ophthalmoscopy
- Intraocular Pressure (IOP) measurement
- Best Corrected Visual Acuity (BCVA)
- Conjunctival Hyperemia Evaluation
- Drop Comfort/Tolerability Assessment

7.2. EFFICACY EVALUATIONS

Signs (OU)

- Total CFS score (0 – 20 point scale) at each clinic visit.
- Inferior region CFS score (0-4 point scale) at each clinic visit.
- CFS score by each individual subregion (0-4 point scale) at each clinic visit.
- Tear production (Schirmer test without anesthesia, mm/5 min) at each clinic visit.

Symptoms (subject reported)

- Eye dryness score (0-100 point VAS) evaluated at each clinic visit.
- Eye discomfort score (0-100 point VAS) evaluated at each clinic visit.
- Symptom Assessment Questionnaire iN Dry Eye (SANDE) will be administered at each clinic visit.

8. ASSESSMENT OF SAFETY

8.1. SAFETY PARAMETERS

- AE Monitoring
- Drop Comfort/Tolerability Assessment (Appendix 2)
- Conjunctival Hyperemia Score (Appendix 3)
- BCVA (Appendix 4)
- Slit-Lamp Biomicroscopy (Appendix 5)
- External Eye Exam (Appendix 5)
- IOP Measurement (Appendix 6)
- Dilated Ophthalmoscopy (Appendix 7)

8.1.1. Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence associated with the use of an IP in humans, whether or not considered drug related.

Adverse Reaction (AR): Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected Adverse Reaction (SAR): Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected: An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Life-threatening: An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

A **SERIOUS ADVERSE EVENT (SAE)** is any AE or suspected adverse reaction occurring at any dose that:

- Results in death.
- Is life-threatening.

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization.
- Prolongs inpatient hospitalization.
- Is a congenital anomaly/birth defect.
- Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).

A **NON-SERIOUS ADVERSE EVENT** is any AE that does not meet the definitions for SAEs as described above.

Each **AE** will be classified as **SERIOUS** or **NON-SERIOUS** using the definitions provided above.

The SEVERITY of each AE will be classified as MILD, MODERATE, or SEVERE.

The Investigator will review each event and assess its RELATIONSHIP to use of IP (unrelated, unlikely, possibly, probably, definitely). The AE will be assessed using the following definitions:

Unrelated:

- Event occurring before dosing.
- Event or intercurrent illness due wholly to factors other than IP use.

Unlikely:

- Poor temporal relationship with IP use.
- Event easily explained by subject's clinical state or other factors.

Possible:

- Reasonable temporal relationship with IP use.
- Event could be explained by subject's clinical state or other factors.

Probable:

- Reasonable temporal relationship with IP use.
- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by subject's clinical state or other factors.

Definite:

- Distinct temporal relationship with IP use.

- Known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot be explained by subject's clinical state or other factors.

8.1.2. Procedures for AE Reporting by the Investigator

AEs will be monitored throughout the study and will be recorded on the eCRF with the date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to use of IP), treatment required, and the outcome.

To elicit AEs, simple questions with minimal suggestions or implications should be used as the initial questions at all evaluation points during the trial. For example:

- How have you felt since your last assessment?
- Have you had any health problems since your last assessment?

The severity of each AE should be categorized as mild, moderate, or severe.

The causality of use of IP in relation to the AE will be assessed by the Principal Investigator after careful medical consideration and categorized as unrelated, unlikely, possible, probable, or definite.

If an AE occurs, the Investigator will institute support and/or treat as deemed appropriate.
If a non-SAE is unresolved at the time of the last day of the study, an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow SAEs to resolution.

8.1.3. Serious Adverse Event Reporting by the Investigator

Serious Adverse Event Reporting

It is the responsibility of the Investigators or their designees to report any event of this nature to the Sponsor or a designee within 24 hours of the event being brought to the Investigators' or their staffs' attention. It is also the responsibility of the Investigator to report all SAEs reported at their site to their Institutional Review Board (IRB), as required. The Investigator should make every attempt to follow all SAEs to resolution.

The following information should be provided when an SAE is reported to the Sponsor or designee:

1. Protocol Number
2. Site Number
3. Subject Number
4. Subject Demographic information, including:
    - Date of Birth

- Sex
- Race

5. IP start date
6. Date of last dose of IP
7. Date investigational product reinitiated (if investigational product interrupted)
8. SAE information, including:
    - SAE term (diagnosis only; if known or serious signs/symptoms)
    - Description of SAE/narrative
    - Date/time of onset
    - Severity
    - Outcome
    - Date/time of resolution or death (if duration < 24 hours)
    - Relationship to IP
    - Action taken with IP
9. Criteria for classifying the event as serious, including whether the SAE:
    - Resulted in death.
    - Was life-threatening
    - Required inpatient hospitalization
    - Prolonged inpatient hospitalization
    - Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
    - Was a congenital anomaly/birth defect
    - Important medical events that may not result in death, were not life-threatening, or did not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
10. Concomitant medications

11. Relevant history
12. Possible causes of SAE other than IP
13. Copy of AE page from the eCRF

NOTE: If a SAE occurs in any study involving VVN001 or Vehicle that is unexpected and is determined to be definitely related, probably related or possibly related to IP, all sites will be notified by the Sponsor and each site should report it to its IRB.

9. STATISTICS

9.1. STATISTICAL METHODS

9.1.1. Analysis Populations

The following analysis populations will be considered:

Full Analysis Set (FAS) – The FAS includes all randomized subjects. The efficacy analysis will be performed on the FAS. Subjects in the FAS will be analyzed as randomized.

Per Protocol Set (PPS) – The PPS includes subjects in the FAS who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PPS will be analyzed using observed data only for efficacy variables. Subjects in the PPS will be analyzed as treated.

Safety Set (SAF) – The 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.

The statistical analysis of safety data will be performed for the SAF. The analysis of baseline and efficacy data will be performed for the FAS. Sensitivity analyses may be performed on the PPS.

9.1.2. Subject Disposition, Demographic and Background Characteristics

Subject disposition, demographic characteristics, and background variables will be summarized by treatment group.

9.1.3. Analysis of Efficacy effects

To assess whether VVN001 is more effective than Vehicle, exploratory efficacy will be performed. The unit of analysis for ophthalmic efficacy measures depends on the measure itself. Some endpoints will be analyzed per subject whereas others will be analyzed per eye (study eye and non-study eye, where study eye is defined in Section 4.4).

The following parameters will be assessed per eye (study eye and non-study eye):

- Total and Individual CFS score
- Tear production (Schirmer test without anesthesia, mm/5 min)

The following parameters will be assessed per subject (one score for both eyes):

- VAS for Eye Discomfort
- VAS for Eye Dryness
- SANDE

All efficacy parameters will be analyzed as continuous data. Analysis will be performed at each timepoint using summary statistics as well as a longitudinal model as appropriate.

Analyses of all efficacy endpoints will be done using the FAS. Analyses on the study eye will be repeated for all non-study eye as supportive analyses. Analyses may also be repeated on the PP set.

The primary analysis will utilize a repeated measures mixed model where the dependent variable is the change from baseline score, treatment group is a fixed effect, baseline score is a covariate, and visit is a repeated measure on subject. The repeated measures mixed model is utilized to account for the effect of missing data under the assumption that the data are missing at random. Least squares means will be used to test each concentration of VVN001 to vehicle. Sensitivity analyses for the primary endpoint will be performed using last observation carried forward (LOCF) as well as observed data only.

In order to minimize the impact of multiplicity, the following hierarchical tests will be conducted:

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 at the 5% significance level. Each comparison will be made in order until $P > 0.05$. If $P \leq 0.05$, the comparison is statistically significant and testing is continued.

The planned analyses for all outcomes will be described in detail in the SAP, which will be finalized and submitted prior to database lock.

9.1.4. Analysis of Safety

Analysis of safety data will be presented for all subjects in the Safety Population. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, most current version) and categorized by system organ class using preferred terms. AEs will be tabulated by treatment group with respect to their Severity and relationship to the IP. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, BCVA, dilated ophthalmoscopy, external eye exam and slit-lamp biomicroscopy will be summarized as safety outcomes.

The primary safety analysis will summarize ocular and non-ocular treatment-emergent adverse events (TEAEs) using discrete summaries at the subject level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring after the first dose of IP. Serious adverse events (SAEs) and treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity and relatedness.

9.1.5. Sample Size Estimation

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.

9.1.6. Level of Significance

Nominal P-values will be reported at the 5% level of significance if applicable.

9.1.7. Procedure for Accounting for Missing, Unused, or Spurious Data

Any missing, unused, or spurious data will be noted in the final clinical study report. The data will be analyzed as reported. The last observation carried forward approach will be used to analyze incomplete datasets.

9.1.8. Procedure for Reporting Deviations from the Statistical Plan

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Direct Access to Source Data/documents

The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the eCRF such as medical history) to the monitor or appropriate designee.

10.2. Quality Control

The progress of the study will be monitored by on-site, written, e-mail, and telephone communications between personnel at the study center and the Sponsor (or designated monitor). The Investigator will allow VivaVision Biotech, Inc. monitors or designees to inspect all eCRFs; subject records (source documents); signed informed consent forms; HIPAA authorizations; records of IP receipt, storage, and disposition; and regulatory files related to the study.

10.3. Good Clinical Practice (GCP)

This clinical trial will be conducted in compliance with the protocol, International Council on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements.

10.4. Collection of Data

Source documentation for data collected in this study will be maintained at the investigative site. In cases where no source will be used (e.g., dosing diary), it will be noted in the Investigator files. The CRF will be electronic (eCRF) and data will be entered from source documentation into the eCRF. After study completion, an archival copy [e.g., Portable Document Format (PDF)] of the eCRF data will be retained by the site.

10.5. Ethics

10.5.1. Institutional Review Board

This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the Sponsor or designee prior to the start of enrollment into the study. Materials used to recruit subjects will be approved by the appropriate IRB and the approvals made available to the Sponsor or designee prior to their use. In addition, the Investigator's Brochure should be submitted to the IRB. Written IRB approval must adequately identify the protocol and ICF. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to the Sponsor (or designated monitor).

Any modification of study procedures or amendments to the protocol must be approved by the IRB prior to implementation. In the event that a modification or amendment is considered by the Investigator to be immediately necessary to ensure subject safety, the Investigator will promptly notify his or her IRB and the Sponsor.

Investigators will report all SAEs reported at their site to their IRB, as appropriate.

10.5.2. Informed Consent Requirements

Written informed consent will be obtained from each participant prior to any study-related procedures being performed (prior to or upon Visit 1/Screening). A copy of the signed and dated informed consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigative site and be available for Sponsor or designee review.

Each informed consent will contain Investigator contact information with a telephone number the subject or the subject's authorized representative can call 24 hours a day if they have medical concerns.

10.6. Data Handling and Recordkeeping

All procedures for the handling and analysis of data will be conducted using GCP and will meet ICH guidelines and FDA regulations for the handling and analysis of data for clinical trials.

10.6.1. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and monitor(s) for resolution. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

10.6.2. Records Retention

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines.

10.6.3. Publication Policy

The Institution and Investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.

11. REFERENCES

1. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. The TFOS Dry Eye Workshop II: Executive Summary. Ocul Surf. 2017;15:802-12.
2. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017;15(3):334-65.
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4. DEWS II Definition and Classification Report. 2017:276-283. Available at https://www.theocularsurfacejournal.com/article/S1542-0124(17)30119-2/pdf.
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7. Lemp, MA. Report of the National Eye Institute/Industry Workshop on clinical Trials in Dry Eyes. CLAO Journal.1995; 21(4):221-32.
8. Shimmura S, Ono M, Shinozaki K, et al. Sodium hyaluronate eyedrops in the treatment of dry eyes. Br J Ophthalmol. 1995; 79(11):1007-11.

12. APPENDICES

APPENDIX 1: SCHEDULE OF EVENTS

	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

	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)
	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.

APPENDIX 2: DROP COMFORT/TOLERABILITY ASSESSMENT

You will be asked to rate the comfort of the drop for both eyes as one score at 1-minute and 5-minutes post dose at Visits 1, 2 and 6.

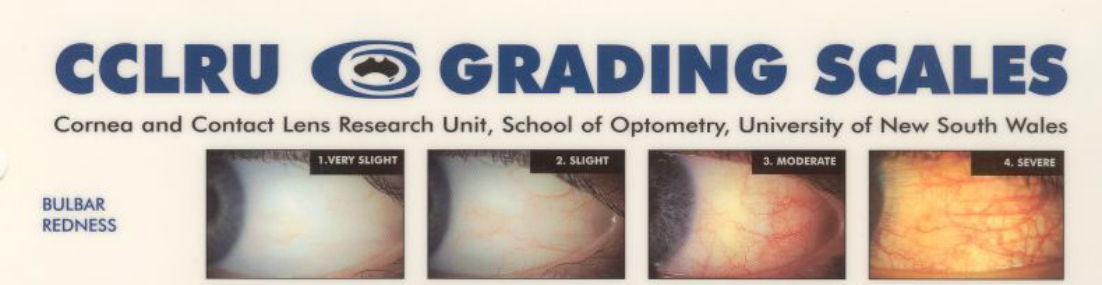
Drop Comfort/Tolerability

COMFORT/TOLERABILITY OF INVESTIGATIONAL PRODUCT
Overall Comfort of Investigational Product: 0=Comfortable and 10=Uncomfortable
0 5 10 |_____|

APPENDIX 3: INVESTIGATOR-RATED ASSESSMENT OF SIGNS OF CONJUNCTIVAL HYPEREMIA

Investigator-Rated Assessment of Bulbar conjunctival hyperemia

Investigators will rate overall bulbar conjunctival hyperemia using the Cornea and Contact Lens Research Unit (CCLRU) Grading Scale.



0 = None

1 = Very Slight

2 = Slight

3 = Moderate

4 = Severe

APPENDIX 4: ETDRS BEST CORRECTED VISUAL ACUITY

Visual Acuity (VA) testing should precede any examination requiring contact with the eye or instillation of study dyes, as is detailed in the order of assessments for each Visit in Section 6.1. Logarithm of the Minimal Angle of Resolution (LogMAR) visual acuity must be assessed using an ETDRS or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

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

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

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

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

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

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

APPENDIX 5: SLIT-LAMP BIOMICROSCOPY

The biomicroscopy exam should be performed with the slit lamp using a beam width and intensity that provide optimal evaluation of the anterior segment.

This procedure will be the performed in the same manner for all subjects observed at the Investigator's site. The site will record all ABNORMAL findings in the source document and the Investigator will evaluate the ABNORMAL findings as Non-Clinically Significant (NCS) or Clinically Significant (CS). CS and NCS ABNORMAL findings will be recorded in the source documentation. However, only ABNORMAL CS descriptions will be captured in the eCRF.

Lashes

0 = Normal
1 = Abnormal

Eyelid

Edema

0 = Normal, no swelling of the lid tissue
1 = Abnormal

Skin

0 = Normal, including but not limited to thinning, pigment changes, dermatitis
1 = Abnormal

Conjunctiva

Edema

0 = Normal, no swelling of the conjunctiva
1 = Abnormal

Cornea

Infiltrates

0 = Absent
1 = Present

Endothelial Changes

0 = Normal, None
1 = Abnormal, pigment, keratoprecipitates, guttata

Edema

0 = Normal, None, transparent and clear
1 = Abnormal

Anterior Chamber

Cells

0 = Normal, No cells seen
1 = Abnormal (+ to +++ cells)

Flare

0 = Normal, No Tyndall effect

1 = Abnormal, Tyndall beam in the anterior chamber

Lens Pathology

0 = Normal, no opacity in the lens

1 = Abnormal, existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings

Sclera

0 = Normal

1 = Abnormal

APPENDIX 6: IOP MEASUREMENT

IOP measurements will be performed utilizing Goldmann applanation tonometry according to the Investigator's standard procedure. All pressures will be recorded in mmHg.

APPENDIX 7: DILATED OPHTHALMOSCOPY

Dilated Ophthalmoscopy will include assessment of the optic nerve head for pallor and cupping (cup to disc ratio). After the Ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Visit 1, the Investigator will determine whether or not the abnormality would exclude subject from study participation.

APPENDIX 8: EYE DISCOMFORT, EYE DRYNESS SYMPTOM ASSESSMENT

Symptom Assessment Visual Analog Scale (VAS)

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

The subject will be asked to subjectively rate each ocular symptom (OU) by placing a vertical mark on the horizontal line to indicate the level of eye discomfort and dryness. 0 corresponds to "No Symptoms" and 100 corresponds to "Severe Symptoms"

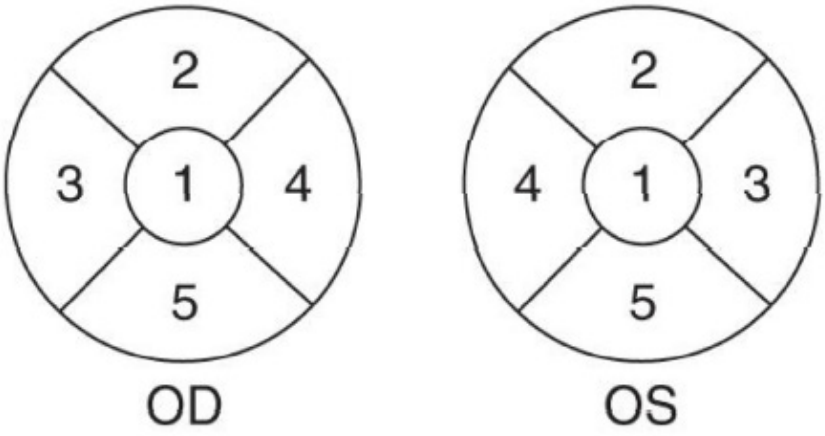
Subject Instructions: Please review the symptoms below. After your review, please rate how your eyes feel using 1 score for both eyes for each of the following symptoms by placing a single vertical mark that represents how your symptom feels at this moment.

0 = No Symptoms and 100 = Severe Symptoms

Eye Discomfort	**0**	**100**
	|_____|	
Eye Dryness	**0**	**100**
	|_____|	

APPENDIX 9: CORNEAL FLUORESCEIN STAINING (CFS) / NATIONAL EYE INSTITUTE / INDUSTRY WORKSHOP SCALE

The 5 areas of the cornea will be scored by the Investigator according to the following scoring system and the total score will also be calculated. Details regarding the procedure will be provided in the Manual of Procedures.



Score each of the five regions of each eye using the modified grading scale of 0–4 with 0.5 grade increments and the description provided.

None	0 = no staining
Trace	1 = few/rare punctate lesions
Mild	2 = discrete and countable lesions
Moderate	3 = lesions too numerous to count but not coalescent
Severe	4 = coalescent

Reference: modified from Lemp (1995) and Shimmura (1995)

APPENDIX 10: UNANESTHETIZED SCHIRMER TEST

The Schirmer test will be conducted on unanesthetized eyes. A 35 mm x 5 mm filter paper strip is used to measure the amount of tears that are produced over 5 minutes. The strip is placed in the lower eyelid margin of both eyes without the use of a preplaced ophthalmic anesthetic drop. After 5 minutes, the strip is removed and the amount of wetting is measured in millimeters.

APPENDIX 11: SANDE

PLEASE COMPLETE THE FOLLOWING QUESTIONS REGARDING THE FREQUENCY AND SEVERITY OF YOUR DRY EYE SYMPTOMS.

1. Frequency of symptoms:

Please place an 'X' on the line to indicate how often, on average, your eyes feel **dry and/or irritated**:

Rarely _____ **All the time**

2. Severity of symptoms:

Please place an 'X' on the line to indicate how severe, on average, you feel your symptoms of dryness and/or irritation are:

Very Mild _____ **Very Severe**

Appendix 12: Daily Dosing Diary

Subjects will be asked to record each day the following information related to administration of IP:

- Date
- Time
- Yes/No for administration of each dose