A Randomized, Double-Masked, Vehicle-Controlled, Dose Ranging Study to Assess the Efficacy and Safety of Voclosporin Ophthalmic Solution (VOS) in Subjects with Dry Eye Syndrome

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DECLARATION OF SPONSOR

Title: A Randomized, Double-Masked, Vehicle-Controlled, Dose Ranging Study to Assess the Efficacy and Safety of Voclosporin Ophthalmic Solution (VOS) in Subjects with Dry Eye Syndrome

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study treatment, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) on Good Clinical Practice (GCP).

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Date (i.e., DD Month Year)

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INVESTIGATOR AGREEMENT FORM

I have read the attached protocol titled: A Randomized, Double-Masked, Vehicle-Controlled, Dose Ranging Study to Assess the Efficacy and Safety of Voclosporin Ophthalmic Solution (VOS) in Subjects with Dry Eye Syndrome

I agree to comply with the current International Council for Harmonisation Guidelines on Good Clinical Practice and applicable regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children);
- my Sub-Investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Aurinia Pharmaceuticals Inc.

Signature by the Investigator on this form documents review, agreement, and approval of the requirements contained within this protocol.

_____

Name

_____ _____

Signature Date (i.e., DD Month Year)

SYNOPSIS

Title:	A Randomized, Double-Masked, Vehicle-Controlled, Dose Ranging Study to Assess the Efficacy and Safety of Voclosporin Ophthalmic Solution (VOS) in Subjects with Dry Eye Syndrome
Study Product:	Voclosporin Ophthalmic Solution (VOS)
Indication:	Dry Eye Syndrome (DES)
Phase:	2/3
Sponsor:	Aurinia Pharmaceuticals Inc.
Study Code:	AUR-VOS-2019-01
Objectives:	To assess the efficacy and safety of three different concentrations of VOS (0.05%, 0.10%, and 0.20%) when administered twice a day (BID) in both eyes (OU) over 12 weeks compared to vehicle in subjects with DES.
Design:	This is a Phase 2/3, multi-center, randomized, double-masked, vehicle-controlled study to assess the efficacy and safety of three different concentrations of VOS when administered OU BID over 12 weeks in subjects with mild to moderate DES. Subjects will undergo a 2-week run-in period in which VOS vehicle will be self-administered OU, BID. Subjects will be re-assessed to confirm that all participants meet all of the inclusion criteria and none of the exclusion criteria. It is estimated that the study will enroll approximately 480 subjects across approximately 9 study centers. Eligible subjects will be randomized in a 1:1:1:1 ratio to one of the following study treatment groups after the 14- to 17-day run-in period.
Treatment:	Subjects will be randomized to one of the following treatment groups: Investigational product (IP): one drop 0.05% VOS, OU BID over 12 weeks, one drop 0.10% VOS OU BID over 12 weeks, or one drop 0.20% VOS OU BID over 12 weeks. Comparator: one drop VOS vehicle OU BID over 12 weeks.
Inclusion Criteria	Subjects are eligible for participation if they: 1. Provide written informed consent before any study-specific procedures are performed. 2. Are male or female, with a minimum age of 18 years (or legal age of consent if >18 years), at the time of screening. 3. Have a documented history of DES in both eyes supported by a previous clinical diagnosis prior to Visit 1 4. Are willing and able to follow protocol procedures and instructions and can be present for the required study visits for the duration of the study. 5. Have a symptom severity score of ≥30 mm for Eye Dryness on the Individual Symptom Severity Assessment Visual Analog Scale (VAS) (0-100 mm) at both Visit 1 and Visit 2. 6. Have a best corrected visual acuity (BCVA) in both eyes of +0.7 logarithm of the Minimum Angle of Resolution (logMAR) or better as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at Visit 1. 7. Have ongoing DES, as defined by at least one eye (if one eye, the same eye) meeting both of the following criteria at both Visit 1 and Visit 2: a) Have an unanesthetized Schirmer Tear Test (STT) score of ≥1 mm and ≤10 mm per 5 minutes.

	b) Have a total fluorescein corneal staining (FCS) score of at least 3 [National Eye Institute (NEI)/Industry Workshop 0-15 scale]. Note: The qualifying eye at Visit 1 must be the same eye at Visit 2. 8. Have normal lid anatomy
Exclusion Criteria:	In order for subjects to be eligible, subjects must not: 1. Be non-compliant during the run-in treatment (non-compliance defined as dosing <80% or >120% of the time, calculated by counting the number of returned and unused study drug ampules) 2. Have any known hypersensitivity or contraindication to study treatments (including excipients), topical anesthetics, or vital dyes. 3. Have had any eye surgery in either eye except for cataract surgery or laser-assisted in situ keratomileusis (LASIK). 4. Have undergone cataract or LASIK surgery within 1 year prior to Visit 1. 5. Have recent or current evidence of ocular infection or inflammation in either eye including ocular pemphigoid and Stevens Johnson Syndrome. 6. Have current evidence of clinically significant blepharitis (defined as requiring lid hygiene therapy and additional therapies such as doxycycline or Lipiflow®) or other meibomian gland dysfunction, conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye. 7. Have clinically significant ocular disease in either eye (i.e., corneal edema, uveitis, severe keratoconjunctivitis sicca) or active ocular allergies that might interfere with study procedures or assessments in the opinion of the Investigator. Severe keratoconjunctivitis sicca is defined by an FCS score of ≥13. 8. Be taking or have a known need for any of the following treatment therapies within the time frames as specified below: a) Any investigational drug or device within 30 days prior to the Screening Visit (Visit 1) and subjects may not receive any investigational drug or device during the entire study except that which is allowed by the protocol. b) Ophthalmic drugs (any topical eye medications) including prescription medication and over-the-counter (OTC) agents, from date of Visit 1 to Visit 7. c) Contact lenses 24 hours prior to the Screening Visit (Visit 1) to the end of Visit 7. d) Any prior use of amiodarone. e) Within 72 hours of Visit 1 and for the duration of the study: – Oral anti-histamines f) Within 14 days prior to Visit 1 and for the duration of the study: – Xiidra® (lifitegrast) g) Within 30 days prior to Visit 1 and for the duration of the study: – Calcineurin Inhibitors (CNIs) such as Restasis® (cyclosporin ophthalmic emulsion) or Cequa™ – Topical ocular anti-histamines – Ocular, inhaled, or intranasal corticosteroids – Topical or oral mast cell stabilizers – Topical or nasal vasoconstrictors

	– Topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs) – Topical ocular antibiotics – True Tear device h) Unstable dose within 30 days prior to the Screening Visit (Visit 1) or during the study; alteration to the dose or anticipated alterations to the dose of the following are disallowed: – Tetracyclines – Omega 3s or Omega 6s i) Unstable dose within 60 days prior to the Screening Visit (Visit 1) or during the study; alteration to the dose or anticipated alterations to the dose of the following are disallowed: – Anticholinergics – Antidepressants – Oral contraceptives – Isotretinoin – Oral systemic corticosteroids – Oral systemic immunosuppressive agents j) Within 90 days prior to the Screening Visit (Visit 1) or during the study, the subject has had cauterization of the punctum or alternations to (insertion or removal) punctal plug(s) or nasolacrimal surgery. Note: If a punctal plug is in place at the Screening Visit (Visit 1) and it is dislodged during the study, the plug should be replaced as soon as possible. 9. Have clinically significant systemic disease (i.e., uncontrolled diabetes, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study. 10. Have been randomized and treated in a previous study where VOS was the IP. 11. Be a woman of childbearing potential who is pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. All women of childbearing potential must be willing to take a urine pregnancy test at Visit 1 and Visit 6. 12. Have a condition or be in a situation that the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
Primary Endpoint:	• Proportion of subjects with a ≥10 mm increase from baseline in STT at Week 4 in the study eye. The study eye will be defined as the qualifying eye that achieves the lowest STT score at baseline. Should both eyes be qualifying eyes with identical STT scores at baseline, the eye with the worst FCS score will be used. Should these scores also be equal, the right eye will be used.
Key Secondary Endpoint:	• Mean change from baseline in Eye Dryness VAS at Week 4 in subjects with a baseline Eye Dryness VAS score ≥60mm.
Secondary Endpoints:	Secondary Endpoints: • Proportion of subjects with a ≥10 mm increase from baseline in STT at Weeks 2, 8, and 12 in the study eye. • Mean change from baseline in total FCS (NEI/Industry Workshop 0-15 scale) score to Weeks 2, 4, 8, and 12 in the study eye.

	• Mean change from baseline in FCS score in the 5 regions of the cornea (central, superior, inferior, temporal, and nasal) to Weeks 2, 4, 8, and 12 in the study eye. • Mean change from baseline in STT score to Weeks 2, 4, 8, and 12 in the study eye. • Mean change from baseline in Eye Dryness VAS (0-100 mm) score to Weeks 2, 4, 8, and 12 within treatment group. • Mean change from baseline in Ocular Discomfort VAS (0-100 mm) score to Weeks 2, 4, 8, and 12. • Mean change from baseline in Eye Dryness, Burning/Stinging, Itching, Photophobia, Eye Pain, Foreign Body Sensation, and Blurred Vision VAS (0-100 mm) score to Weeks 2, 4, 8, and 12. • Mean change from baseline of the sum of Individual Symptom Score (VAS Total Symptom Summary Score) to Weeks 2, 4, 8, and 12. • Mean change from baseline in Symptom Assessment in Dry Eye (SANDE) frequency and severity scores to Week 2, 4, 8, and 12. Safety Endpoints: • Treatment-emergent adverse events (TEAEs) • Change from baseline in BCVA over time • Changes from baseline in slit-lamp biomicroscopy over time • Changes from screening in dilated ophthalmoscopy over time
Procedures:	Subjects who have provided signed and dated informed consent will be screened for entry into this study. Subjects will be evaluated for eligibility according to the protocol inclusion/exclusion criteria. Eligible subjects will enter a 14- to 17-day run-in period during which time they will receive vehicle drops and will be instructed to instill one drop of vehicle OU BID. Subjects will be re-evaluated for eligibility after the run-in period. After the run-in period, eligible subjects will be randomly assigned in a 1:1:1:1 ratio to one of the four treatment groups: VOS 0.05% BID, VOS 0.1% BID, VOS 0.2% BID, or VOS vehicle BID. Subjects will self-instill the assigned treatment, one drop OU BID, over 12 weeks.
Sample Size:	This study is expected to enroll 480 subjects into 4 treatment arms. A two-group continuity corrected Chi square test with a 0.0166 two-sided significance level (adjusted for three treatment comparisons versus placebo) will have at least 80% power to detect the difference between a vehicle response rate of 20% (defined as the percentage of subjects with a ≥10 mm increase in STT from baseline) and a VOS response rate of 40% when the sample size in each group is 120 (total N=480). Response is defined as an increase of ≥10 mm in STT from baseline to Week 4. While the effect of withdrawals will be investigated, subjects withdrawing prior to Week 4 STT assessment for any reason will be counted as non-responders in the primary analysis and therefore no adjustment of sample size for withdrawals is necessary. Subjects providing insufficient data to determine response at Week 4 (e.g., early withdrawal) will be analysed as non-responders. An additional sensitivity analysis will analyse observed responses only. This sample size provides greater than 90% power to detect a significant change from baseline within any one of the three active treatment groups in the Eye Dryness VAS assuming the standard deviation of changes is 40 mm and the mean change from baseline is 20 mm (two-sided alpha=0.0166).

	The key secondary endpoint is analyzed within the population of subjects with an Eye Dryness VAS ≥60 mm at baseline. It is expected that this will reduce the sample size for this analysis by 25% (from 120 per group to 90 per group). Assuming a standard deviation of 30 mm for change in eye dryness score and an improvement of any active arm compared to placebo (alpha=0.0166) of 15 mm, a sample size of 90 subjects per group provides at least 80% power to detect a significant difference.
Statistical Methods:	All statistical analyses will be undertaken at study closure and will incorporate all efficacy and safety endpoints. **Analysis Populations:** The following analysis populations will be considered: • Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized. • Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations prior to their primary endpoint assessment at Week 4 and who complete the Week 4 STT. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed as randomized. • Safety Population – The safety population includes all randomized subjects who have received at least one dose of randomized study treatment. The safety population will be analyzed for all safety assessments. Subjects in the safety population will be analyzed as treated. • The run-in population will be used to describe all subjects who entered the run-in period. Baseline data will be summarized using the safety, ITT, and PP populations. Safety data will be summarized using the safety population, and efficacy analysis will use the ITT and PP populations. **Methods:** Efficacy Endpoints: Analysis of the primary endpoint, proportion of subjects with a ≥10 mm increase from baseline in STT at Week 4 in the study eye, will be conducted on the ITT and PP populations. The response rate for each VOS group compared to vehicle will be determined using a logistic regression model including terms for Investigator site, treatment group, and baseline STT. Results of this logistic regression will be displayed as odds ratios and two-sided adjusted 95% confidence intervals (CI) (VOS compared to vehicle). The proportion of subjects exhibiting a response at Week 4 will be summarized by treatment group. The key secondary endpoint of mean change from baseline in Eye Dryness VAS in the subset of subjects with baseline Eye Dryness VAS ≥60 mm will be analysed using the ITT and the PP populations. Mean change, along with an adjusted 95% CI and p-value, will be provided from a General Linear Model including terms for Investigator site, treatment group and baseline Eye Dryness VAS. Other proportional endpoints (STT response at alternative time points) will be analyzed and summarized in a similar fashion to the primary endpoint. Endpoints measured as continuous data (including VAS scores) will be summarized by visit for the ITT population only. Mean change from baseline (95% CI) will be provided for within treatment group changes and for differences between treatment groups (VOS – vehicle).

	Mixed Effect Model Repeated Measures (MMRM) will also be used to analyze all available data for a given endpoint. The MMRM model will include terms for Investigator site, treatment group, visit, treatment-by-visit interaction, and applicable baseline measure. Results will be expressed as differences between treatment arms (VOS – vehicle) along with associated 95% CIs and p-values. Safety Endpoints: Adverse events will be aggregated by System Organ Class and preferred term and presented as summary tables. BCVA will be summarized as a continuous endpoint with results displayed as mean changes from baseline for each visit. Slit-lamp biomicroscopy and dilated ophthalmoscopy will be summarized using frequency counts and shift tables from baseline.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AUDREY	AUrinia DRy EYe
Aurinia	Aurinia Pharmaceuticals Inc.
BCVA	Best Corrected Visual Acuity
BID	Twice daily
CI	Confidence interval
CNI	Calcineurin inhibitor
CPM	Clinical Project Manager
CRO	Contract Research Organization
CsA	Cyclosporine A
DED	Dry Eye Disease
DES	Dry Eye Syndrome
eCRF	Electronic case report form
EDC	Electronic data capture
ERG	Electroretinography
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCS	Fluorescein Corneal Staining
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KCS	Keratoconjunctivitis sicca
LASIK	Laser-assisted in situ keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution

MMRM	Mixed Effect Model Repeated Measures
NEI	National Eye Institute
NFAT	Nuclear Factor of Activated T-cells
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NZW	New Zealand White
OTC	Over-the-counter
OU	Both eyes
PP	Per Protocol
SAE	Serious adverse event
SANDE	Symptom Assessment in Dry Eye
STT	Schirmer Tear Test
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
VAS	Visual Analog Scale
VOS	Voclosporin ophthalmic solution

1. INTRODUCTION AND BACKGROUND

Dry eye syndrome (DES) (also known as dry eye disease (DED) and keratoconjunctivitis sicca (KCS), herein referred to as DES) is a complex disorder of the ocular surface disease (OSD) characterized by tear film instability progressing to tear hyperosmolarity, epithelial damage with inflammation, neurogenic inflammation, and eventual fibrosis of the lacrimal gland with reduced tear production [(Boboridis and Konstas 2018)]. The Tear Film and Ocular Surface Society Dry Eye Workshop group defines global DES as a multi-factorial disease of the ocular surface characterized by a loss of homeostasis of the tear film accompanied by ocular symptoms. These include tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities [(Craig, Nichols et al. 2017)]. The overall incidence of DES has significant geographic variation, with published data ranging from 5%-34% of US adults over 50 years of age. Given the heterogeneity of patients, a retrospective analysis of the US Department of Defense Medical Claims Data demonstrated an overall prevalence of 5.3% of adults have DES, impacting twice as many women as men, and increasing in prevalence with age. The 2015 US Census estimated that up to 16 million people experienced DES in the US [(Dana, Bradley et al. 2019)]. In patients with DES, tear production has been shown to be increased with the use of topical immunosuppressants, including cyclosporine. Symptoms of DES include a sensation of dry eyes, foreign body sensation, irritation, burning, tearing, ocular pain, and itching, among others. DES affects quality of life and work productivity, and patients with moderate to severe DES may experience reduced visual function in addition to ocular dysfunction. Current therapy includes a stepped approach, which starts with over-the-counter (OTC) lubricants and artificial tear replacements, and then expands to include topical anti-inflammatory therapy and punctal occlusion [(Craig, Nichols et al. 2017)]. There are currently three FDA-approved prescription medications used for DES, topical cyclosporine ophthalmic solution 0.05% (Restasis®, herein referred to as Restasis) [(Restasis® 2017)], lifitegrast ophthalmic solution 5% (Xiidra®, herein referred to as Xiidra) [(Xiidra® 2017)], and cyclosporine ophthalmic solution 0.09% (Cequa™, herein referred to as Cequa) [(CEQUA® 2018)]. A significant number of patients using Restasis experience the following adverse reactions: ocular irritation upon instillation, slow onset of response, and limited efficacy [(Restasis® 2017)]. Adverse reactions with Xiidra include instillation irritation, dysgeusia, and reduced visual acuity that occurred in 5%-25% of subjects in clinical trials [(Xiidra® 2017)]. The most common adverse reactions reported with Cequa were pain on instillation of drops (22% of subjects) and conjunctival hyperemia (6% of subjects) [(CEQUA® 2018)]. Despite these approved products, an unmet clinical need remains for improved therapeutic options for patients with moderate to severe DED.

In patients with DES, tear production has been shown to be increased with the use of topical immunosuppressants, including cyclosporine. It is believed that T-lymphocyte infiltration and activation in the lacrimal gland represents an underlying pathogenesis for DES. Calcineurin inhibitors reversibly inhibit immunocompetent lymphocytes, particularly T-lymphocytes, in the G0 or G1 phase of the cell cycle and also reversibly inhibit the production and release of lymphokines [(Granelli-Piperno 1986)]. Calcineurin is a calcium- and calmodulin-dependent

serine-threonine phosphatase. Calcineurin inhibitors (CNIs) inhibit the ability of calcineurin to dephosphorylate the nuclear factor of activated T-cells (NFAT), which is required for translocation of NFAT from the cytoplasm to the nucleus, thereby preventing activation of various transcription factors necessary for the induction of cytokine genes during T-cell activation (i.e., interleukin-2, interleukin-4, tumor necrosis factor-α, granulocyte-macrophage colony stimulating factor, and interferon-γ) [(Stepkowski 2000, Wiseman 2016)].

Voclosporin (LX214) is a novel next generation CNI that is currently being evaluated for a variety of systemic and topical indications. Voclosporin is structurally similar to cyclosporine A (CsA), except for a novel modification of a functional group on the amino acid-1 residue of the molecule. This alteration has changed how voclosporin binds to calcineurin leading to an improved potency when compared to CsA. This modification has also changed the metabolic profile of voclosporin by shifting metabolism away from amino acid-1, which is the major site of metabolism for CsA. The altered metabolic profile has led to a faster elimination of metabolites resulting in lower metabolite exposure compared to CsA. The combination of increased potency and decreased metabolite exposure, for voclosporin compared to CsA, has led to better pharmacokinetic/pharmacodynamic predictability.

1.1 Nonclinical Studies of Voclosporin in Dry Eye

Two Good Laboratory Practice (GCP) toxicology studies [(S07654 2009, S07655 2009)] have been conducted to evaluate the safety of voclosporin ophthalmic solution (VOS) in the eye of the New Zealand White (NZW) rabbit and the Beagle dog with dosing for 14 days. Test animals were euthanized on Day 15, and recovery animals were sacrificed on Day 29. Animals received two, four, or eight bilateral topical applications of 0.2% VOS within 8 hours daily, corresponding to doses of approximately 0.14, 0.28, and 0.56 mg/eye/day, respectively. Control animals received 8 doses of the vehicle within 8 hours daily. Safety was evaluated using macroscopic and microscopic ophthalmologic evaluations; tonometry; electroretinography (ERG) evaluation; gross and microscopic pathology of the eyes (including optic nerve), submandibular lymph nodes, spleen, and thymus; and hematology, blood chemistry, and coagulation parameters. Blood voclosporin concentrations were obtained on Days 1 and 13 at pre-dose and 8, 8.5, 10, and 12 hours after the first VOS instillation.

In the NZW rabbit study, no VOS ocular treatment-related changes in serum chemistry, hematology, coagulation, gross pathology, or organ weights were found at the completion of the dosing period or following a 14-day recovery (without treatment). Similarly, no treatment-related macroscopic or microscopic ophthalmological changes or effects on intraocular pressure associated with the administration of VOS were reported. There were no histologic findings in the spleen, thymus, or rostral and caudal sections of the mandibular lymph nodes. A standard battery of bilateral full-field flash ERGs was performed; sporadic statistically significant differences were seen, but as these were all limited to one eye, were not dose-dependent, and were not supported by corresponding changes in related ERG parameters (for example, a change in a-wave implicit time was not accompanied by a change in a-wave

amplitude), they were judged to have no significance. The ocular no observed adverse effect level (NOAEL) for VOS in NZW rabbits was determined to be 0.56 mg/eye/day. There was some accumulation of voclosporin in blood over the course of the study, with mean trough levels on Day 13 of 0.028, 0.154, and 0.325 ng/mL for the low, mid, and high dose groups, respectively. The mean maximum blood concentration achieved 1 hour after dosing (high dose group) was 2.29 ng/mL on Day 13.

In the Beagle dog study, similar results were reported for all safety parameters. The ocular NOAEL for VOS in Beagle dogs was determined to be 0.56 mg/eye/day. There was some accumulation of voclosporin in blood over the course of the study, with mean trough levels on Day 13 of 0.017, 0.173, and 0.297 ng/mL for the low, mid, and high dose groups, respectively. The mean maximum blood concentration achieved 1 hour after dosing (high dose group) was 1.178 ng/mL on Day 13.

In an additional 13-week NZW rabbit study [(S08661 2009)] no mortality, systemic toxicity, or effects on specific ocular indices were observed following daily bilateral topical ocular administration of placebo or VOS (0.2% voclosporin) at a frequency of up to eight times daily (hourly intervals; ~0.56 mg/eye/day) for 13 weeks or following a 4-week recovery period. The NOAEL for repeat topical ocular administration of VOS (0.2% voclosporin) to male and female NZW rabbits for 13 weeks was >0.56 mg/eye/day.

In summary, the two repeated-dose ocular toxicology studies [(S07654 2009, S07655 2009)] demonstrated that there were no specific ocular indices or histopathology, and no systemic toxicity observed in either dogs or rabbits with 14 days of dosing. In addition, there was no mortality, systemic toxicity, or effects on specific ocular indices observed following daily bilateral topical ocular administration of placebo or VOS (0.2% voclosporin) at a frequency of up to eight times daily (hourly intervals; ~0.56 mg/eye/day) for 13 weeks or following a 4-week recovery period in rabbits.

In addition to the three repeated dose toxicology studies, the efficacy and safety of VOS 0.2% has been evaluated in dogs with naturally occurring KCS [(S15389-00 2017)], diagnosed by the Schirmer Tear Test (STT) of >1 mm/min and <8 mm/min in one or both eyes (OU). Thirty-five dogs ≥6 months old were randomly assigned in a 3:1 ratio to receive either VOS (n=25) or Optimmune® Ophthalmic Ointment (n=10) for 28 days BID. Results showed that treatment with VOS resulted in a statistically significant within-group increase in mean STT from baseline of 4.6 mm/min to each post-treatment visit. Qualitatively, this increase in magnitude was higher than seen in the concurrent Optimmune control group. For the Optimmune group, the change from baseline to Visit 2, 3, and 4, respectively, was not statistically significant, whereas for the VOS-treated group, each change from baseline was statistically significant ($p<0.0001$), demonstrating that VOS was effective in treating KCS in dogs.

In order to determine potential melanin binding of ^{14}C-LX214 (pre-clinical drug product formulation), ocular tissue ^{14}C-LX214-derived radioactivity concentrations were compared

between data obtained from albino NZW rabbits [(S08661 2009)] given a single bilateral instillation in a separate study and similarly treated pigmented Dutch-Belted rabbits [(S08662 2009)]. Ocular pigments in Dutch-Belted rabbits are widely spread in multiple structures including iris (stroma and epithelium), ciliary body (stroma and one epithelial layer), choroid (stroma), retina (epithelium), eyelids, and conjunctiva. The total radioactivity in these ocular tissues of Dutch-Belted rabbits was not statistically significantly different from NZW rabbits at the six sampling time points. Therefore, there was no evidence of melanin binding of ^{14}C-LX214 after a single ocular administration. These data were confirmed in an in vitro model.

1.2 Clinical Studies of Voclosporin in Dry Eye

Voclosporin ophthalmic solution has been investigated in one Phase 1 dose-escalation study (LX214-01) in 30 healthy volunteers, followed by an open-label evaluation of VOS in five subjects with mild to moderate DES. In this study, both 0.02% and 0.2% concentrations were found to be safe and well tolerated following multiple instillations in healthy subjects. All adverse events (AEs) across study cohorts were mild or moderate in severity and all resolved completely, most without requiring treatment. Although the sample size was small, results from the five subjects with DES suggested VOS may be beneficial in the treatment of DES and is supported by the Ocular Surface Disease Index scores, which were improved in all subjects at all time points while on study drug. Overall, the results indicated VOS can be used safely when administered BID for two weeks [(LX214-01 2009)].

Additionally, one Phase 2, Investigator-masked, randomized, parallel-group study was conducted in 100 subjects with DES at 7 treatment sites to evaluate the efficacy, safety, and tolerability of VOS compared to Restasis [(AUR-VOS-2017-01 2019)]. Results of this study indicated that VOS was well tolerated at doses up to 0.2% w/v OU, BID for up to 28 days.

Clinically relevant and statistically superior treatment effects were observed in favor of VOS at most time points for the standard signs of DES, namely change from baseline in STT and fluorescein corneal staining (FCS). After 2 weeks of treatment, a benefit of treatment with VOS compared with Restasis was observed in these objective signs of DES. This potentially indicates a more rapid onset of action and beneficial anti-inflammatory effect for VOS.

Pre-specified exploratory efficacy analyses also favored VOS, which demonstrated a statistically significant difference in the number of subjects achieving a ≥10 mm improvement in STT at Week 4 in the VOS group (42.9%) compared with the Restasis group (18.4%) (OR=4.40; 95% CI: 1.55, 12.51; p=0.0055).

There were marked improvements from baseline in symptom severity at Week 1 with sustained improvements at Week 4 in both treatment groups, though there were no statistically significant differences between treatment groups.

Voclosporin ophthalmic solution was well-tolerated over a 4-week treatment period, and no new or unexpected safety signals were observed with the use of VOS in DES, though more

AEs were reported in the VOS group. The overall safety profile was consistent with the expectations for the class of drug, the patient population, and concomitant therapies. These data demonstrated the positive benefit/risk profile for VOS and support the choice of proceeding with a dose-ranging clinical study to further explore safety and efficacy over a longer duration [(AUR-VOS-2017-01 2019)].

1.3 Study Rationale

These results from the AUR-VOS-2017-01 study support the conduct of this dose-ranging clinical study (AUR-VOS-2019-01, AUrinia DRy EYe (AUDREY)) to explore safety and efficacy over a longer duration. Please refer to Section 1.2 of the Investigator's Brochure (IB) [(*VOS-Investigator's-Brochure* 2019)] for additional details supporting the safety and efficacy of VOS in subjects with DES.

2. STUDY OBJECTIVES

To assess the efficacy and safety of three different concentrations of VOS (0.05%, 0.10%, and 0.20%) when administered BID in both eyes (OU) over 12 weeks compared to vehicle in subjects with DES.

3. CLINICAL HYPOTHESIS

The clinical hypothesis for this study is that at least one of three concentrations of VOS (0.05%, 0.10%, and 0.20%) when administered OU BID over 4 weeks is significantly different compared to vehicle alone for the following DES sign improvement:

- Proportion of subjects with a ≥10 mm increase from baseline in STT at Week 4 in the study eye

4. OVERALL STUDY DESIGN

This is a Phase 2/3, multi-center, randomized, double-masked, vehicle-controlled study to assess the efficacy and safety of three different concentrations of VOS when administered OU BID over 12 weeks in subjects with mild to moderate DES. A 14- to 17-day run-in period with VOS vehicle will be included. Subjects will undergo a 2-week run-in period in which VOS vehicle will be self-administered OU, BID. Subjects will be re-assessed to confirm that all participants meet all of the inclusion criteria and none of the exclusion criteria. It is estimated the study will enroll approximately 480 subjects across approximately 9 study centers. Eligible subjects will be randomized in a 1:1:1:1 ratio to one of the following study treatment arms after the 14- to 17-day run-in period:

- 0.05% VOS BID
- 0.10% VOS BID
- 0.20% VOS BID
- VOS Vehicle BID

Subjects will be stratified by eye dryness VAS score ≥60 mm and <60 mm.

See Figure 1 for the AUDREY (AUR-VOS-2019-01) study schematic.

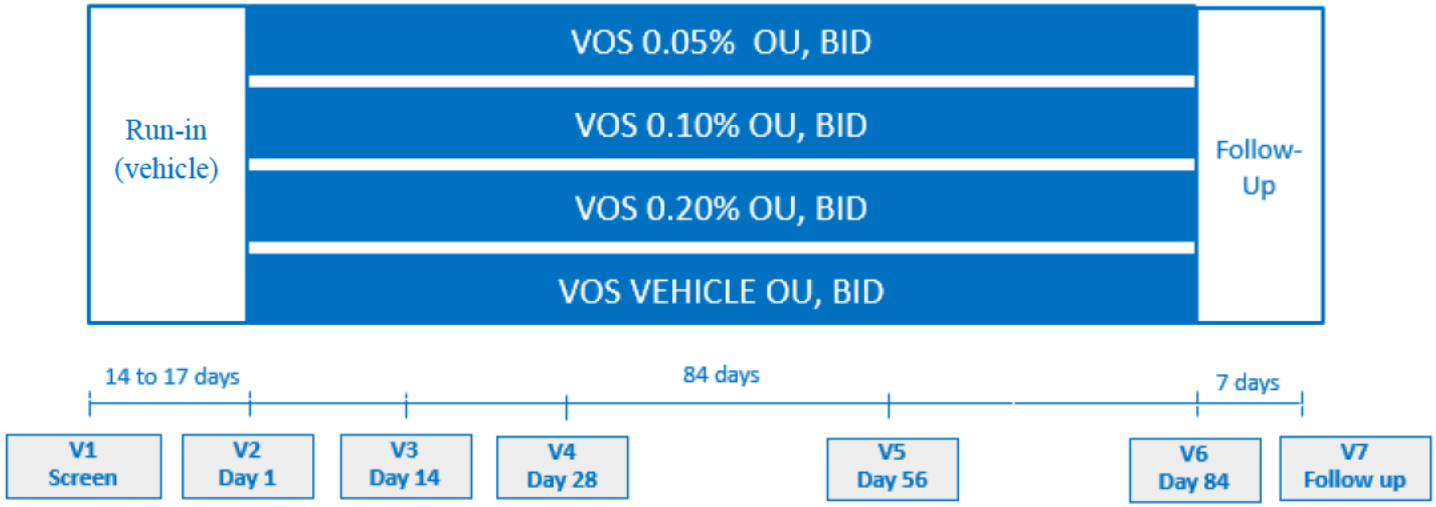


Figure 1 AUDREY (AUR-VOS-2019-01) Study Schematic

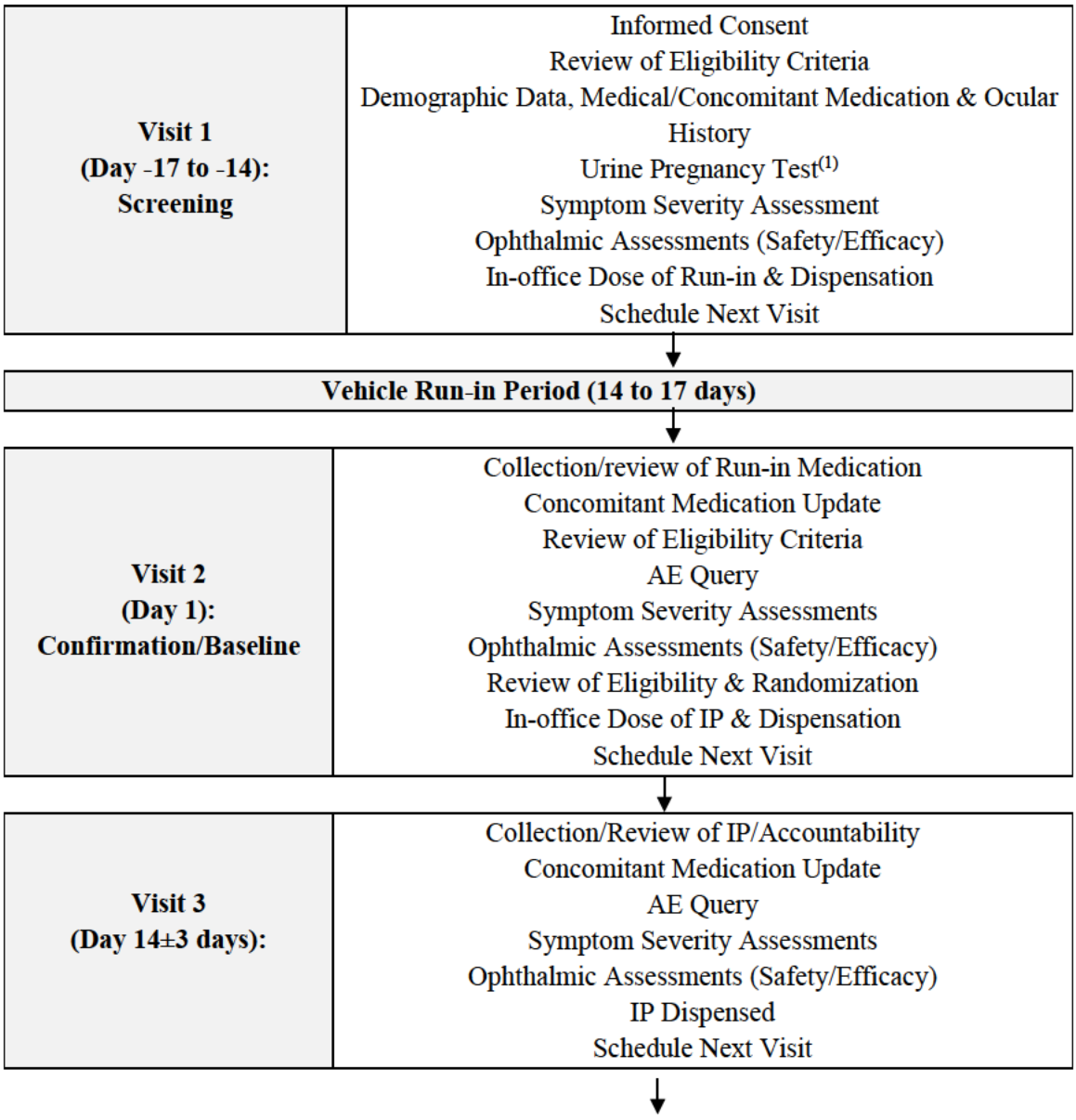
Notes: V = Visit; VOS = Voclosporin ophthalmic solution.

This study is double-masked. The investigational product (IP) allocation will be masked to Aurinia, the subject, and the investigative staff with the exception of the Clinical Research Organization (CRO)'s unmasked statistician and CRO and Aurinia clinical supplies personnel.

Subjects who have provided signed and dated informed consent will be screened for entry into this study. Subjects will be evaluated for eligibility according to the protocol inclusion/exclusion criteria.

Efficacy will be assessed through the evaluation of signs and symptoms of DES. A detailed visit-by-visit flow chart is provided in Figure 2.

Figure 2 Visit-by-Visit Study Flow Chart



Visit 4 **(Day 28±3 days):**	Collection/Review of IP/Accountability Concomitant Medication Update AE Query Symptom Severity Assessments Ophthalmic Assessments (Safety/Efficacy) IP Dispensed Schedule Next Visit
Visit 5 **(Day 56±3 days):**	Collection/Review of IP/Accountability Concomitant Medication Update AE Query Symptom Severity Assessments Ophthalmic Assessments (Safety/Efficacy) IP Study Drug Dispensed Schedule Next Visit
Visit 6 **(Day 84±3 days):** **End of Treatment**	Collection/Review of IP/Accountability Concomitant Medication Update AE Query Symptom Severity Assessments Ophthalmic Assessments (Safety/Efficacy) Urine Pregnancy Test(1) Schedule Follow-Up Visit
Visit 7 **(+7 days from Visit 6 ± 3 days):** **Post-Treatment Follow-Up**	Concomitant Medication Update AE Query BCVA Study Exit

1 = required for women of childbearing potential

Notes: AE = Adverse event; BCVA = Best Corrected Visual Acuity; IP = Investigational product.

5. STUDY POPULATION

5.1 Number of Subjects

It is estimated that 480 subjects across 9 study centers will be enrolled and randomized in a 1:1:1:1 ratio to one of the following study treatment arms:

- 0.05% VOS BID
- 0.10% VOS BID
- 0.20% VOS BID
- VOS Vehicle BID

5.2 Study Population Characteristics

All subjects must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects are eligible for participation if they:

1. Provide written informed consent before any study-specific procedures are performed.
2. Are male or female, with a minimum age of 18 years (or legal age of consent if >18 years), at the time of screening.
3. Have a documented history of DES in both eyes supported by a previous clinical diagnosis prior to Visit 1.
4. Are willing and able to follow protocol procedures and instructions and can be present for the required study visits for the duration of the study.
5. Have a symptom severity score of ≥30 mm for Eye Dryness on the Individual Symptom Severity Assessment Visual Analog Scale (VAS) (0-100 mm) at both Visit 1 and 2.
6. Have a BCVA in both eyes of +0.7 logarithm of the Minimum Angle of Resolution (logMAR) or better as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at Visit 1.
7. Have ongoing DES, as defined by at least one eye (if one eye, the same eye) meeting both of the following criteria at both Visit 1 and Visit 2:
    a) Have an unanesthetized Schirmer Tear Test (STT) score of ≥1 mm and ≤10 mm per 5 minutes.

b) Have a total fluorescein corneal staining (FCS) score of at least 3 [National Eye Institute (NEI)/Industry Workshop 0-15 scale].

Note: The qualifying eye at Visit 1 must be the same eye at Visit 2.

8. Have normal lid anatomy

5.4 Exclusion Criteria

In order for subjects to be eligible, (as specified in the Schedule of Events) subjects must not:

1. Be non-compliant during the run-in treatment (non-compliance defined as dosing <80% or >120% of the time, calculated by counting the number of returned and unused study drug ampules).

2. Have any known hypersensitivity or contraindication to study treatments (including excipients), topical anesthetics, or vital dyes.

3. Have had any eye surgery in either eye except for cataract surgery or laser-assisted in situ keratomileusis (LASIK).

4. Have undergone cataract or LASIK surgery within 1 year prior to Visit 1.

5. Have recent or current evidence of ocular infection or inflammation in either eye including ocular pemphigoid and Stevens Johnson Syndrome.

6. Have current evidence of clinically significant blepharitis (defined as requiring lid hygiene therapy and additional therapies such as doxycycline or Lipiflow®) or other meibomian gland dysfunction, conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye.

7. Have clinically significant ocular disease in either eye (i.e., corneal edema, uveitis, severe KCS) or active ocular allergies that might interfere with study procedures or assessments in the opinion of the Investigator. Severe KCS is defined by an FCS score of ≥13.

8. Be taking or have a known need for any of the following treatment therapies within the time frames as specified below:

    a) Any investigational drug or device within 30 days prior to the Screening Visit (Visit 1) and subjects may not receive any investigational drug or device during the entire study except that which is allowed by the protocol.

    b) Ophthalmic drugs (any topical eye medications) including prescription medication and OTC agents, from date of Visit 1 to Visit 7.

c) Contact lenses 24 hours prior to the Screening Visit (Visit 1) to the end of Visit 7.

d) Any prior use of amiodarone.

e) Within 72 hours of Visit 1 and for the duration of the study:

- Oral antihistamines

f) Within 14 days prior to Visit 1 and for the duration of the study:

- Xiidra® (lifitegrast)

g) Within 30 days prior to Visit 1 and for the duration of the study:

- Calcineurin Inhibitor such as Restasis® (cyclosporin ophthalmic emulsion) or Cequa™
- Topical ocular anti-histamines
- Ocular, inhaled, or intranasal corticosteroids
- Topical or oral mast cell stabilizers
- Topical or nasal vasoconstrictors
- Topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs)
- Topical ocular antibiotics
- True Tear device

h) Unstable dose within 30 days prior to the Screening Visit (Visit 1) or during the study; alteration to the dose or anticipated alterations to the dose of the following are disallowed:

- Tetracyclines
- Omega 3s or Omega 6s

i) Unstable dose within 60 days prior to the Screening Visit (Visit 1) or during the study; alteration to the dose or anticipated alterations to the dose of the following are disallowed:

- Anticholinergics

- Antidepressants
- Oral contraceptives
- Isotretinoin
- Oral systemic corticosteroids
- Oral systemic immunosuppressive agents

j) Within 90 days prior to the Screening Visit (Visit 1) or during the study, the subject has had cauterization of the punctum or alternations to (insertion or removal) punctal plug(s) or nasolacrimal surgery. Note: If a punctal plug is in place at the Screening Visit (Visit 1) and it is dislodged during the study, the plug should be replaced as soon as possible.

9. Have clinically significant systemic disease (i.e., uncontrolled diabetes, hepatic, renal, endocrine or cardiovascular disorders) that might interfere with the study.

10. Have been randomized and treated in a previous study where VOS was the IP.

11. Be a woman of childbearing potential who is pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. All women of childbearing potential must be willing to take a urine pregnancy test at Visit 1 and Visit 6. Details surrounding adequate forms of contraception are outlined in Section 5.6.

12. Have a condition or be in a situation that the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

5.5 Withdrawal Criteria

Subjects may voluntarily withdraw from study participation at any time for any reason. Alternatively, subjects may be withdrawn at the Investigator's discretion if it is in the subject's best interest.

Every effort should be made for subjects who withdraw from the study (either voluntarily or at the Investigator's discretion) to undergo end-of-study assessments (Visit 6). If possible, the subject should also be advised to come into the site for the Follow-Up Visit (Visit 7), 7 days (±3 days) after self-instilling the final dose. If a subject refuses end-of-study procedures, the reason for refusal should be fully documented in the subject's source document. It is the subject's right to withdraw from the study without providing a reason. In this case, the source documents and the electronic case report form (eCRF) should document the reason for discontinuation as "withdrawal of consent." Withdrawn subjects will not be replaced.

5.6 Aurinia Adequate/Effective Contraception

An adult woman is considered to be of childbearing potential unless she is at least 1 year post-menopausal or 3 months post-surgical sterilization. All women of childbearing potential must have a negative urine pregnancy test result at Visit 1 and must not intend to become pregnant during the study. Women of childbearing potential who are not abstinent must have been using one of the following acceptable methods of birth control for the times specified:

1. Intrauterine device in place for at least 4 weeks prior to Visit 1 through Visit 7
2. Barrier method (condom or diaphragm) with spermicide from Visit 1 through Visit 7.
3. Stable hormonal contraceptive for at least 60 days prior to Visit 1 through Visit 7.
4. In a monogamous relationship with a surgically sterilized (i.e., vasectomized) partner at least 6 months prior to Visit 1 through Visit 7.

6. STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Endpoint

Proportion of subjects with a ≥10 mm increase from baseline in STT at Week 4 in the study eye. The study eye will be defined as the qualifying eye that achieves the lowest STT score at baseline. Should both eyes be qualifying eyes with identical STT scores at baseline, the eye with the worst FCS score will be used. Should these scores also be equal, the right eye will be used.

6.1.2 Key Secondary Endpoint

Mean change from baseline in Eye Dryness VAS at Week 4 in subjects with a baseline Eye Dryness VAS score ≥60 mm.

6.1.3 Secondary Endpoints

- Proportion of subjects with a ≥10 mm increase from baseline in STT at Weeks 2, 8, and 12 in the study eye.
- Mean change from baseline in total FCS (NEI/Industry Workshop 0-15 scale) score to Weeks 2, 4, 8, and 12 in the study eye.
- Mean change from baseline in FCS score in the 5 regions of the cornea (central, superior, inferior, temporal, and nasal) to Weeks 2, 4, 8, and 12 in the study eye.
- Mean change from baseline in STT score to Weeks 2, 4, 8, and 12 in the study eye.
- Mean change from baseline in Eye Dryness VAS (0-100 mm) score to Weeks 2, 4, 8, and 12 within treatment group.
- Mean change from baseline in Ocular Discomfort VAS (0-100 mm) score to Weeks 2, 4, 8, and 12.
- Mean change from baseline in Eye Dryness, Burning/Stinging, Itching, Photophobia, Eye Pain, Foreign Body Sensation, and Blurred Vision VAS (0-100 mm) score to Weeks 2, 4, 8, and 12.
- Mean change from baseline of the sum of Individual Symptom Score (VAS Total Symptom Summary Score) to Weeks 2, 4, 8, and 12.
- Mean change from baseline in Symptom Assessment in Dry Eye (SANDE) frequency and severity scores to Week 2, 4, 8, and 12.

6.2 Safety Measures

- Treatment-emergent adverse events (TEAEs)
- Change from baseline in BCVA over time
- Changes from baseline in slit-lamp biomicroscopy over time
- Changes from screening in dilated ophthalmoscopy over time

7. RANDOMIZATION, MASKING AND UNMASKING PROCEDURES

7.1 Randomization

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later stage. Subjects will be allocated a subject number at screening visit (Visit 1) and registered with an interactive web randomization system (IWRS). Subjects meeting the required eligibility criteria will be randomized to treatment at Visit 2 (baseline). The randomization will be stratified by Eye Dryness score (<60 mm and ≥60 mm). The subjects will be randomized in a ratio 1:1:1:1 to receive either VOS vehicle, VOS 0.05%, VOS 0.10%, or VOS 0.20%. The randomization ratio will be maintained within each study center. A randomization list will be generated and provided by an unmasked statistician.

7.2 Masking

All study personnel and subjects will be masked to the study treatment administered during the study. VOS vehicle, 0.05% VOS, 0.10% VOS, and 0.20% VOS will be identical in appearance. The treatment group allocated will not be available to the study monitor, project statistician, or the project team at Aurinia Pharmaceuticals or the CRO. The site staff, monitors, and study subjects will remain masked until the end of the study. In case of emergency, the unmasking process below should be followed.

7.3 Unmasking

In the rare event that an AE or pregnancy occurs for which knowledge of the identity of the study treatment administered is necessary to manage the subject's condition, the IWRS code for that subject may be broken and the test substance identified. Procedures for unmasking will be provided in a separate manual.

Should unmasking be required, the Investigator should call the Medical Monitor before unmasking whenever possible; however, the Investigator is responsible for the medical care of the individual study subject and does not require the agreement of the Medical Monitor before unmasking. In the event that the Medical Monitor cannot be reached, the Investigator should contact the Project Manager at the CRO. The reason for unmasking must be documented. The information on study treatment should only be used for decision making in the subject's further treatment. Details on unmasked treatment assignments should not be shared with the Study Monitor and project team. Unmasked subjects will be discontinued from the study.

8. STUDY MATERIALS

8.1 Dosage Forms/Formulation

All study treatment to be used in this study will be manufactured in accordance with current Good Manufacturing Practice (GMP). Study treatment will be supplied by Aurinia.

8.1.1 Study Treatments

Company Code: [redacted]

Chemical Name: [redacted]

Empirical Formula: [redacted]

Generic Name: VOS

Dosage Form: Voclosporin Ophthalmic Solution is provided as a clear micellar solution in single-use blow fill seal ampules for topical ocular administration.

Strength: 0.05% VOS, 0.10% VOS, or 0.20% VOS

Manufacturer: Aurinia Pharmaceuticals Inc.

Study drug will be supplied as a sterile, clear, micellar solution containing 0.05%, 0.10%, or 0.20% Active Pharmaceutical Ingredient (voclosporin), in single-use blow fill seal ampules for topical ocular administration. [redacted]

The vehicle solution contains all components of the drug product solution with the exception of voclosporin.

8.1.2 Description and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen were selected based on nonclinical studies described in Section 1.1 and clinical studies described in Section 1.2. The proposed treatment period of 12 weeks is

also based on nonclinical and clinical studies and on the immunosuppressive mechanism of action of the drug.

8.1.3 Instructions for Use and Administration

- At the end of Visit 1, qualified subjects will receive a kit with run-in (vehicle ophthalmic solution) for OU, BID dosing until Visit 2. Subjects will be instructed to dose in the morning and evening. One drop of the IP will be instilled in each eye BID. Subjects will be instructed to bring all used and unused IP to every clinic visit to conduct accountability.

- At Visit 2, the run-in kit will be collected from subjects for drug accountability. At the end of Visit 2, qualified subjects will be randomized using the IWRS and dispensed a kit containing either VOS 0.05%, VOS 0.10%, VOS 0.20%, or vehicle for BID dosing until Visit 3. Subjects will be instructed not to take the morning dose of run-in on the day of study randomization (Visit 2). Instructions regarding timing between doses will remain identical to instructions given for the run-in period at Visit 1.

- At Visit 3, the study drug kit will be collected from subjects for drug accountability. Subjects will receive a new kit of study drug assigned via the IWRS (with the same treatment assignment that they were randomized to at Visit 2) for BID dosing until Visit 4.

- At Visit 4, the study drug kit will be collected from subjects for drug accountability. Subjects will be dispensed two new kits of study drug assigned via the IWRS (with the same treatment assignment that they were randomized to at Visit 2) for BID dosing until Visit 5.

- At Visit 5, the study drug kits will be collected from subjects for drug accountability. Subjects will be dispensed two new kits of study drug assigned via the IWRS (with the same treatment assignment that they were randomized to at Visit 2) for BID dosing until Visit 6.

- At Visits 6, the study drug kits and any leftover IP not previously returned to clinic will be collected from subjects for drug accountability.

- Subjects will be instructed not to take their morning dose of run-in or study drug on the day of follow-up visits (Visits 2, 3, 4, 5, and 6) prior to the visit. Subjects will be instructed to store study drug at home under refrigeration at 2°C-8°C (36-46°F) in the kit box.

- If needed, replacement kits are also available to be dispensed to a subject.

8.2 Other Study Supplies

Urine pregnancy tests, Schirmer test strips, sodium fluorescein and tropicamide ophthalmic solution will be provided by Sponsor.

9. STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the inclusion and exclusion criteria outlined Sections 5.3 and 5.4.

9.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., prior to changes in a subject's medical treatment and/or prior to study-related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB).

9.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in Exclusion Criteria Number 8.

9.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion and none of the exclusion criteria at both Visit 1 and Visit 2. No re-screening is permitted.

9.1.5 Methods for Assignment to Treatment Groups

Prior to initiation of study run-in (at Visit 1), each subject who qualifies for entry will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site, and no numbers will be skipped or omitted. If all inclusion and none of the exclusion criteria are met at Visits 1 and 2, each qualifying subject will then be assigned a randomization number at the end of Visit 2 using an IWRS.

The randomization number will be recorded on the patient's source document and eCRF. Aurinia, Investigators, and study staff will be masked during the randomization process and throughout the study.

9.2 Concurrent Therapies

The use of any concurrent medication, prescription, or OTC is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted.

9.2.1 Prohibited Medications

Disallowed medications/treatments during the study are outlined in Exclusion Criteria 8.

9.2.2 Rescue Medications

No rescue medications are required for this study.

9.2.3 Special Diets or Activities

No special diets or activities are required for this study.

9.3 Examination Procedures

An ICF must be signed and dated by the subject and witness before any study–related procedures are performed. Procedures listed below should be performed in the given order. A detailed Schedule of Events can be found in Appendix 1: Schedule of Visits and Measurements.

Procedures listed below can be reviewed in detail in Appendix 2: Examination Procedures, Tests, Equipment, and Techniques.

9.3.1 Visit 1: Day -17 to -14 Screening and Run-In Period

All subjects will undergo the following screening assessments:

- Informed Consent/HIPAA: Prior to any changes in a subject's medical treatment and/or invasive procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.

- Demographic Data and Medical/Medication/Ocular History: Collect and record all demographic data, medical history, any medications, and any underlying condition(s). Significant non-ocular medical history only within the past year and medications within the past 30 days will be captured. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 30 days prior to screening. (Any clinically significant findings will be recorded in the Medical Ocular History section of the eCRF).

- Urine Pregnancy Test (for women of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study.

- SANDE

- VAS

- BCVA- Subjects must have a score of ≥0.7 logMAR (Snellen equivalent score of ≥20/100 or better) in each eye at Visit 1.

- Initial review of Inclusion/Exclusion Criteria

- Slit-lamp biomicroscopy

- FCS as assessed by the NEI scale for Grading of Fluorescein Staining

- STT (performed at least 20 minutes after FCS is performed)
- Dilated ophthalmoscopy
- Final review of Inclusion/Exclusion Criteria
- Dispensation of run-in kit and instructions for BID dosing until Visit 2
    - Subjects will be instructed to dose in each eye BID (once in the morning and once in the evening)
    - Subjects will be instructed to not dose with run-in on the morning of their next visit (Visit 2)
- Subject self-administers the first dose of run-in, OU, under the supervision of a trained technician
- Dosing diary will be provided and subjects will be instructed on how to record date and time of dosing
- Qualified subjects will be scheduled for Visit 2

9.3.2 Visit 2: Day 1-Baseline

- Collection and review of returned run-in kit for compliance
- Subject will be asked if he/she dosed with run-in on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Concomitant medication updates
- AE query (since last visit)
- SANDE
- VAS
- BCVA
- Slit-lamp biomicroscopy
- FCS
- STT (performed at least 20 minutes after FCS is performed)

- Review of eligibility criteria
- Randomization
- Dispensation of study drug kit according to randomization for BID dosing until Visit 3
    - Subjects will be instructed to dose in each eye two times daily (once in the morning and once in the evening).
    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 3)
- Subject self-administers the first dose of study drug, OU, under the supervision of a trained technician
- AE query post-instillation
- Dosing diary will be provided and subjects will be instructed on how to record date and time of dosing
- Schedule subjects for Visit 3

9.3.3 Visit 3: Day 14 (±3 days)

- Collection and review of study drug accountability (including dosing diaries)
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Concomitant medication updates
- AE query (since last visit)
- SANDE
- VAS
- BCVA
- Slit-lamp biomicroscopy
- FCS
- STT (performed at least 20 minutes after FCS is performed)

- Dispensation of study drug kit according to randomization for BID dosing until Visit 4
    - Subjects will be instructed to dose in each eye two times daily (once in the morning and once in the evening)
    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 4)
- Subject self-administers the study drug, OU, under the supervision of a trained technician
- AE query post-instillation
- Dosing diary will be provided and subjects will be instructed on how to record date and time of dosing
- Schedule subjects for Visit 4

9.3.4 Visit 4: Day 28 (±3 days)

- Collection and review of study drug accountability
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Concomitant medication updates
- AE query (since last visit)
- SANDE
- VAS
- BCVA
- Slit-lamp biomicroscopy
- FCS
- STT (performed at least 20 minutes after FCS is performed)
- Dispensation of two study drug kits according to randomization for BID dosing until Visit 5
    - Subjects will be instructed to dose in each eye BID (once in the morning and once in the evening)

- Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 5)

- Subject self-administers the study drug, OU, under the supervision of a trained technician
- AE query post-instillation
- Dosing diary will be provided and subjects will be instructed on how to record date and time of dosing
- Schedule subjects for Visit 5

9.3.5 Visit 5: Day 56 (±3 days)

- Collection and review of study drug accountability
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Concomitant medication updates
- AE (since last visit)
- SANDE
- VAS
- BCVA
- Slit-lamp biomicroscopy
- FCS
- STT (performed at least 20 minutes after FCS is performed)
- Dispensation of two study drug kits according to randomization for BID dosing until Visit 6

    - Subjects will be instructed to dose in each eye BID (once in the morning and once in the evening)

    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 6)

- Subject self-administers the study drug, OU, under the supervision of a trained technician

- AE query post-dose
- Dosing diary will be provided and subjects will be instructed on how to record date and time of dosing
- Schedule subjects for Visit 6

9.3.6 Visit 6: Day 84 (±3 days)/Early Termination Visit

- Collection and review of study drug accountability
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Concomitant medication updates
- AE query (since last visit)
- SANDE
- VAS
- BCVA
- Slit-lamp biomicroscopy
- FCS
- STT (performed at least 20 minutes after FCS is performed)
- Dilated ophthalmoscopy
- Urine pregnancy test
- AE query post-assessments
- Schedule subjects for Visit 7

9.3.7 Visit 7: Post-Treatment Safety Follow-Up (+7 days from Visit 6, ±3 days)

- Concomitant medication updates
- AE query
- BCVA

- Study Exit

9.3.8 Unscheduled Visits

Unscheduled visits may also be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp biomicroscopy
- BCVA
- Urine pregnancy test
- Dilated ophthalmoscopy
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the Investigator

9.4 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1 through 5 and given written instructions. The subject's used and unused study drug ampules will be collected at each visit from Visit 2 up to and including Visit 6 to assess dosing compliance. Dosing compliance will be based on the unused ampule count. If the subject is <80% or >120% compliant with dosing based on the expected number of unused ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded at each visit.

These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

9.5 Subject Disposition

9.5.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

9.5.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- AEs
- unmasking when medically necessary
- protocol violations
- administrative reasons (i.e., inability to continue, schedule change)
- lost to follow-up
- sponsor termination of study
- subject choice (i.e., withdrawal of consent)
- other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the Investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to the CRO and/or Aurinia and will be clearly documented on the eCRF. Discontinued subjects will not be replaced.

9.6 Study Termination

The study may be stopped at any time by the Investigator, Aurinia, and/or the CRO with appropriate notification.

9.7 Study Duration

An individual subject's participation will involve 7 visits over approximately 15 weeks (approximately 105 days) from first day of screening phase, the run-in period, treatment phase, and follow-up period.

9.8 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the protocol and pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, quality assurance and/or their designees may carry out on-site inspections and/or audits, which may include source data checks. Therefore, direct access to the original source data will be required for inspections

and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

10. EVALUATION, RECORDING AND REPORTING OF AEs AND SAEs

10.1 Definitions

10.1.1 Adverse Event

Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment is an AE. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.2 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established, all unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

10.1.3 Unexpected ADR

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product).

10.1.4 Serious Adverse Event (SAE)

An SAE is an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Results in death (Note: death is an outcome, not an event)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused a death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event or reaction

The definitions and reporting requirements of International Council for Harmonisation (ICH) Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2 will be adhered to.

Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

Hospitalizations for elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, will not be classed as SAEs. Previously scheduled hospitalizations must be documented in the subject's source documents before the subject signed the ICF.

10.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any ADR that is both serious and unexpected (per the IB) that, based on the opinion of the Investigator or Aurinia, is felt to have a reasonable suspected causal relationship to a medicinal product is a SUSAR.

10.1.6 Treatment-Emergent Adverse Event (TEAE)

Any AE with an onset date between the first dose of randomized study treatment and the last study visit (Post-Treatment Safety Follow-Up Visit 7 or last visit attended by the subject).

10.2 Adverse Event Descriptors

10.2.1 Intensity/Severity Categorization

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event. The medical assessment of intensity will be determined by using the following definitions:

- Mild: The AE is easily tolerated and does not interfere with usual activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.

- Severe: The AE is incapacitating, and the subject is unable to work or complete usual activity.

10.2.2 Causal Relationship Categorization

The Investigator will be required to assess the relationship to study treatment (defined as vehicle for run-in period and active drug/vehicle for randomized subjects) for each AE as related or not related, in addition to the relationship to disease under study (see Section 10.2.4). An AE will not be able to be assessed as related to both disease under study and related to study treatment.

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment and disease under study for each AE and SAE. The Investigator must decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment. If there is no valid reason for suggesting a relationship, then the AE/SAE must be classified as not related. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause and effect relationship between the study treatment and the occurrence of the AE/SAE, then the AE/SAE will be considered related. For SAEs, the Investigator must provide a brief comment explaining the rationale of his/her assessment of causal relationship on the SAE reporting form.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship of the clinical event to study drug administration indicates a causal relationship, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Not related	No	The temporal relationship of the clinical event to study drug administration does not indicate a causal relationship, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

If the causal relationship between an AE/SAE and the study treatment is determined to be "related", the event will be considered to be related to study treatment for the purposes of expedited regulatory reporting. In circumstances where the Investigator has not yet provided his/her assessment about the relationship, the event will be considered as "related" and qualify for expedited regulatory reporting.

10.2.3 Outcome Categorization

Outcome may be classified as recovered without sequelae; recovered with sequelae; improved; worsened; ongoing; fatal; or unknown. If the outcome is reported as recovered with sequelae for an SAE, the Investigator should specify the kind of sequelae on the paper SAE Reporting Form.

10.2.4 Symptoms of the Disease Under Study

Symptoms related to DES will not be classified as AEs as long as they are within the normal day-to-day fluctuation of the disease. An explanation of these circumstances must be written in the source documents.

Worsening of the symptoms, however, will be recorded as an AE and clearly marked as worsening or by the subject's worst observed intensity.

10.2.5 Adverse Events of Special Interest including Abuse, Misuse, Overdose and Medication Errors

A clinically significant decrease in visual acuity (defined as an increase of ≥0.22 in logMAR score) from baseline (Visit 1) will be considered an AE of special interest and must be documented in the AE section of the subject's eCRF and source documentation. If the AE fulfils any seriousness criteria, the event must be reported on a paper SAE Reporting Form and documented as serious in the AE section of the subject's eCRF and source documentation.

Special situations including treatment abuse, misuse, overdose and medication errors causing or with the potential to cause harm should be reported as an AE. An event that fulfills the seriousness criteria should be reported as a SAE.

10.3 Reporting Procedure for AEs, SAEs, and Pregnancy

10.3.1 Adverse Events

All AEs, regardless of causality, will be reported from time of signing the ICF until Post-Treatment Safety Follow-Up Visit 7 and recorded in the subject's source documentation. This applies to all AEs regardless of presumed relationship to the study drug.

For screen failure subjects prior to run-in period, any AEs occurring during the screening period will be recorded from the time of signing the ICF in the subject's source documentation only and will not be collected on the eCRF.

For subjects qualifying for the run-in period all AEs will be recorded in the AE section of the subject's eCRF and source documentation. This applies to all run-in period events between Visit 1 and Visit 2 whether the subject is subsequently randomized or not.

For enrolled/randomized subjects, any AEs occurring following first dose of randomized study treatment and up to Post-Treatment Safety Follow-Up Visit 7 will be recorded in the AE section of the subject's eCRF and source documentation.

If any AE is reported, the date of onset, relationship to study treatment, relationship to disease under study, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, and whether the AE is serious or not, will be recorded. Use of colloquialisms and abbreviations should be avoided. Only one AE term should be recorded in

the event field on the AE eCRF. Where possible, the Investigator should report a diagnosis rather than signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified by the Investigator and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse events leading to discontinuation of study drug must be collected.

Any AEs with an onset date during the study with follow-up/updated outcomes after the last study visit (or last study treatment administration) will be recorded as "ongoing" in the eCRF at the time of study completion. Adverse events persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilization has occurred (or the subject is lost to follow-up and cannot be contacted) and recorded in the source documentation only. If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc. In circumstances where the Investigator is unable to contact with the subject, the Investigator must provide a written statement to Aurinia confirming that the subject is lost to follow-up.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be considered AEs.

10.3.2 Serious Adverse Events

For screen failure subjects prior to run-in period, any SAEs occurring during the screening period (after informed consent) will be recorded on a paper SAE Reporting Form and in the subject's source documentation only and will not be collected on the eCRF.

For subjects qualifying for the run-in period, all SAEs will be recorded on the paper SAE Reporting Form, in the AE section of the subject's eCRF and source documentation. This applies to all run-in period events whether the subject is subsequently randomized or not.

For enrolled/randomized subjects, any SAEs occurring following first dose of randomized study treatment and up to Post-Treatment Safety Follow-Up Visit 7 will be recorded on the paper SAE Reporting Form, in the AE section of the subject's eCRF and source documentation. All SAEs, regardless of causality, will be reported to the Clinical Project Manager and Medical Monitor on a paper SAE Reporting Form within 24 hours of the Investigator, designee, or site staff's knowledge of the event.

Note that data collection within the electronic data capture (EDC) system (Subject eCRF) is considered complete at the time of the last study visit according to the protocol schedule of assessments. Any SAEs with an onset date during the study with follow-up/updated outcomes post the last study visit (or last study treatment administration) will be recorded as "ongoing" in the eCRF at the time of study completion. For SAEs, the follow-up/resolution will be recorded on a paper SAE Reporting Form, and source documentation. If the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must make reasonable efforts to contact the subject to inquire about SAEs.

A paper SAE Reporting Form will be available for site staff to complete. The Investigator must complete, sign, and date the SAE form and verify the accuracy of the information recorded on the form with the corresponding source documents. The required contact information for reporting SAEs will be provided in the safety manual:

- Site Staff will contact the Clinical Project Manager (CPM) at the CRO to notify them of an SAE via phone or email as soon as the site becomes aware of the event.

- Site staff will complete a paper SAE Reporting Form and email to the CPM at the CRO and the Medical Monitor within 24 hours.

- If email is unavailable, site staff will call the CPM at the CRO and Medical Monitor within 24 hours.

The Investigator is encouraged to discuss with the study Medical Monitor when the issue of seriousness is unclear or questionable.

In addition to assessing the relationship to study treatment, the Investigator will also be required to assess the relationship to the disease under study for each SAE as related or not related. An SAE will not be able to be assessed as related to both disease under study and related to study treatment.

All recorded SAEs, regardless of relationship to study treatment or relationship to disease under study, will be followed up until resolution, stabilization, or the subject is lost to follow up and cannot be contacted. In circumstances where the Investigator is unable to make contact with the subject, the Investigator must provide a written statement to Aurinia confirming that the subject is lost to follow-up.

If the subject died, the paper SAE Reporting Form should include the cause of death as the event term and whether or not the death was related or unrelated to study treatment or disease under study, as well as the autopsy findings, if available. Preliminary reports will be followed by detailed descriptions, which will include copies of hospital case reports, autopsy reports/certificates, and other documents when requested and applicable.

Any SAE considered to have a causal relationship (i.e., "related") to the study treatment and discovered by the Investigator at any time after the study will be reported on a paper SAE Reporting Form and documented in the safety database only. A rationale for the assessment of a causal relationship must be provided by the Investigator.

Additional follow-up information must be reported to the CRO on a paper SAE Reporting Form, and the AE section of the subject's eCRF updated (until last study visit, see procedures described above), within 24 hours of awareness following Investigator (or site) awareness of the information. The Investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported to the CRO by the reporting procedures described above.

An Investigator who receives an Investigational New Drug (IND) Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from Aurinia will file it along with the IB and will notify the IRB/Independent Ethics Committee (IEC) if appropriate, according to local requirements.

Aurinia or its representative will be responsible for determining and, in turn, reporting SAEs to Regulatory Authorities according to the applicable regulatory requirements.

10.3.3 Pregnancy

All pregnancies will be reported from time of signing the ICF until Post-Treatment Safety Follow-Up Visit 7. Pregnancies will be recorded in the subject's source documentation and must be reported to the CRO by the reporting procedures described below.

Pregnancy occurring in a female subject should be reported to the CRO Pharmacovigilance within 24 hours of becoming aware of the event using a paper Pregnancy Reporting Form. Site staff must also enter the available pregnancy in the AE section of the subject's eCRF within 24 hours of becoming aware of the event.

The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The subject must immediately inform the Investigator if she becomes pregnant during the study. Monitoring of the pregnancy in the subject should continue until conclusion of the pregnancy.

Female subjects who have a positive pregnancy test during the study will be withdrawn from the study treatment and the procedures for withdrawal will be completed. The Medical Monitor must be contacted immediately to break the blind (if applicable).

The outcome of all such pregnancies (including normal births) should be followed up and documented, even if the subject was withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 90 days (or otherwise as appropriate) post-partum. It will be the responsibility of Aurinia, together with the appropriate support of the Investigator, to obtain this information.

Complications of pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality are considered SAEs and should be reported following the reporting procedures as outlined in Section 10.3.2, Serious Adverse Events.

A paper Pregnancy Reporting Form will be available for site staff to complete. The Investigator must complete, sign, and date the SAE form and verify the accuracy of the information recorded on the form with the corresponding source documents:

- Site Staff will contact the Clinical Project Manager (CPM) at the CRO to notify them of a Pregnancy via phone or email as soon as the site becomes aware of the event.
- Site staff will complete a paper Pregnancy Reporting Form and email to the CPM at the CRO and the Medical Monitor within 24 hours.
- If email is unavailable, site staff will call the CPM at the CRO and Medical Monitor within 24 hours.

11. STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.

- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations prior to their primary endpoint assessment at Week 4 and who complete the Week 4 STT. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed as randomized.

- Safety Population – The safety population includes all randomized subjects who have received at least one dose of randomized study treatment. The safety population will be analyzed for all safety assessments. Subjects in the safety population will be analyzed as treated.

- The run-in population will be used to describe all subjects who entered the run-in period.

Baseline data will be summarized using the safety, ITT, and PP populations. Safety data will be summarized using the safety population, and efficacy analysis will use the ITT and PP populations.

11.2 Statistical Hypothesis

The primary endpoint will be tested under the following hypotheses with statistical significance declared for any of the three comparisons versus vehicle where a p-value <0.0166 is observed:

H_{01}: There is no difference between the proportion of subjects with a ≥10 mm change from baseline in STT to Week 4 in the study eye for those receiving VOS (0.05%, 0.10%, or 0.20%) versus vehicle.

H_{11}: There is a difference between the proportion of subjects with a ≥10 mm change from baseline in STT to Week 4 in the study eye in for those receiving VOS (0.05%, 0.1%, or 0.2%) versus vehicle.

Following a significant result in the primary analysis the three pairwise comparisons for the key secondary endpoint will be tested using alpha=0.0166. The hypotheses to be tested are:

H_{02}: In subjects with baseline eye dryness VAS ≥60 mm, there is no difference between the mean change from baseline to Week 4 in the Eye Dryness VAS for those receiving VOS (0.05%, 0.10%, or 0.20%) versus vehicle.

H_{12}: In subjects with baseline eye dryness VAS ≥60 mm, there is a difference between the mean change from baseline to Week 4 in the eye dryness VAS for those receiving VOS (0.05%, 0.10%, or 0.20%) versus vehicle.

For significance to be declared in the key secondary endpoint analysis, the same treatment group should show improvement over vehicle in both the primary analysis and the key secondary analysis.

11.3 Sample Size

This study is expected to enroll 480 subjects into 4 treatment arms. A two-group continuity corrected Chi square test with a 0.0166 two-sided significance level (adjusted for three treatment comparisons versus placebo) will have at least 80% power to detect the difference between a vehicle response rate of 20% (defined as the percentage of subjects with a ≥10 mm increase in STT from baseline) and a VOS response rate of 40% when the sample size in each group is 120 (total N=480). Response is defined as an increase of ≥10 mm in STT from baseline to Week 4.

While the effect of withdrawals will be investigated, subjects withdrawing prior to Week 4 STT assessment for any reason will be counted as non-responders in the primary analysis and therefore no adjustment of sample size for withdrawals is necessary.

This sample size provides greater than 90% power to detect a significant change from baseline within any one of the three active treatment groups in the Eye Dryness VAS assuming the standard deviation of changes is 40 mm and the mean change from baseline is 20 mm (two-sided alpha=0.0166).

The key secondary endpoint is analyzed within the population of subjects with an Eye Dryness VAS ≥60 mm at baseline. It is expected that this will reduce the sample size for this analysis by 25% (from 120 per group to 90 per group). Assuming a standard deviation of 30 mm for change in eye dryness score and an improvement of any active arm compared to placebo (alpha=0.0166) of 15 mm, a sample size of 90 subjects per group provides at least 80% power to detect a significant difference.

11.4 Statistical Analysis

11.4.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes using study eye and fellow eye (non-study eye) if appropriate. For efficacy symptom-related endpoints, the unit of analysis is both eyes. For efficacy sign-related endpoints, the unit of analysis will be the study eye as defined by the following:

Study Eye: The study eye will be defined as the qualifying eye that achieves the lowest STT score at baseline (Visit 2). Should both eyes be qualifying eyes with identical STT scores at

baseline, the eye with the worst FCS score will be used. Should these scores also be equal, the right eye will be used.

11.4.2 Multiplicity Considerations

To maintain an overall alpha of 0.05, statistical significance of the pairwise treatment comparisons will be declared at the 0.05/3=0.0166 level.

11.4.3 Primary Efficacy Analyses

Analysis of the primary endpoint, proportion of subjects with ≥10 mm increase from baseline in STT at Week 4 in the study eye, will be conducted on the ITT and PP populations. The response rate for each VOS group compared to vehicle will be determined using a logistic regression model including terms for Investigator site, treatment group, and baseline STT. Results of this logistic regression will be displayed as odds ratios and two-sided adjusted 95% confidence intervals (CIs) (VOS compared to vehicle). The proportion of subjects exhibiting a response at Week 4 will be summarized by treatment group.

Subjects providing insufficient data to determine response at Week 4 (e.g. early withdrawal) will be analysed as non-responders.

An additional sensitivity analysis will analyse observed responses only.

11.4.4 Key Secondary Endpoint Analysis

The key secondary endpoint of mean change from baseline in Eye Dryness VAS in the subset of subjects with baseline Eye Dryness VAS ≥60 mm will be analysed using the ITT and the PP populations. Mean change, along with an adjusted 95% CI and p-value, will be provided from a General Linear Model including terms for Investigator site, treatment group and baseline Eye Dryness VAS.

Subjects not providing an Eye Dryness VAS at week 4 will not contribute to this analysis.

11.4.5 Secondary Efficacy Analyses

STT response at Weeks 2, 8 and 12 will be analysed in a similar fashion to the primary endpoint using the ITT population only.

Other secondary efficacy endpoints are measured as continuous data and will be summarized by visit using observed scores and change from baseline using the ITT population. Mean changes along with 95% CIs and p-values will be provided both within treatment group and for all pairwise comparisons to vehicle.

Mixed Effect Model Repeated Measures (MMRM) will also be used to analyze all available data for each endpoint. The MMRM model will include terms for Investigator site, treatment, visit, treatment by visit interaction and applicable baseline measure. Overall and by-visit

results will be expressed as differences between treatment arms (VOS – vehicle) along with associated 95% CIs and p-values.

11.4.6 Safety Variables

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs after the first dose of randomized study treatment and up to last study visit. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class, preferred term for treatment-related AEs; by system organ class and preferred term for SAEs; and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit lamp biomicroscopy, dilated ophthalmoscopy (fundoscopy), will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. Mean changes from baseline along with 95% CIs for changes and pairwise comparisons to vehicle will be calculated for visual acuity. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

11.4.7 Interim Analyses

No interim analyses are planned for this study

12. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current GCPs, including the ICH Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IPs in the United States will be adhered to.

12.1 Protection of Human Subjects

12.1.1 Subject Informed Consent

Informed consent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject.

All informed consent/assent forms must be approved for use by Aurinia and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (i.e., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the CRO prior to submission to the governing IRB and that it is read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

12.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/ERC approved version of the ICF will be used.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

12.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of the CRO, Aurinia, the IRB/IEC approving this study, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

12.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the eCRFs serves as the Investigator's record of a subject's study-related data.

12.4.1 Retention of Documentation

All study related correspondence, subject records, ICFs, records of the distribution and use of all IPs, and copies of eCRFs should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Aurinia. It is the responsibility of Aurinia to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. Aurinia must be notified in writing of the name and address of the new custodian.

12.5 Labelling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

12.5.1 Labelling/Packaging

All study treatments provided by Aurinia will be packaged and labeled for Aurinia by appropriately qualified vendors according to all applicable local and country regulatory requirements. All packaging and labeling operations will be performed according to GMP and GCP.

Run-in and investigational drug will be packaged and labeled into clinical kits.

[redacted]

12.5.2 Storage of Investigational Product

The study drugs must be stored in a secure area accessible only to the Investigator and his/her designees. Study drug(s) must be refrigerated (2-8°C (36-46 °F) – do not freeze), protected from light, and secured at the investigational site in a locked container.

Each site should have a thermometer in each storage location that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated by site personnel during normal working hours. This log must be available for review by the Site Monitor during on-site monitoring visits.

12.5.3 Accountability of Investigational Product

The Investigator at each site is responsible for IP supplies. The Investigator will ensure that adequate records of the receipt, dispensing, and return of the IP are kept and that the IP is used only for subjects enrolled in the study. All data regarding the IP must be recorded on the relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all IP dispensed and returned. At the end of the study, one copy of the drug inventory/dispensing record should be sent to Aurinia or their designee for the central study file. The original will be kept in the site files.

12.5.4 Return or Disposal of Investigational Product

After completion of the study, or if it is prematurely terminated, all IP will be returned to Aurinia or their designee. The return or disposal of IP will be specified in writing.

12.6 Aurinia Recording of Data on Source Documents and Case Reports Forms (CRFs)

All subject data will be captured in the subject source documents, which will be transcribed in the eCRFs. The Investigator is responsible for ensuring that study data are completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, original, accurate, and complete. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (i.e., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for Visit 1 screen failures with the exception of demographics and reason for screen failure. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the

end of the study and database lock, compact discs containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

12.7 Handling of Biological Specimens

N/A.

12.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. The CRO and Aurinia will have the final decision regarding the manuscript and publication.

13. REFERENCES

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14. APPENDICES

Appendix 1: Schedule of Visits and Measurements

AUR-VOS-2019-01 SCHEDULE OF EVENTS

Visit	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6/ ETV	Visit 7
Day/Week	**Day -17 to -14**	**Day 1**	**Day 14/ Week 2 (±3 days)**	**Day 28/ Week 4 (±3 days)**	**Day 56/ Week 8 (±3 days)**	**Day 84/ Week 12 (±3 days)**	**Post-Treatment Safety FU (+7 days from Visit 6 (±3 days))**
Informed consent	✓						
Eligibility criteria	✓	✓(1)					
Randomization		✓					
Ocular and non-ocular Medical history (including Ocular Surgical History, Ocular and Non-Ocular Concomitant Medications)	✓						
Demography	✓						
Concomitant medication updates		✓	✓	✓	✓	✓	✓
AE Query(2)		✓	✓	✓	✓	✓	✓
SANDE(3)	✓	✓	✓	✓	✓	✓	
Visual Analog Scale (VAS)(3)	✓	✓	✓	✓	✓	✓	
BCVA(4)	✓	✓	✓	✓	✓	✓	✓
FCS(5)	✓	✓	✓	✓	✓	✓	
STT(5)	✓	✓	✓	✓	✓	✓	
Slit-Lamp Biomicroscopy	✓	✓	✓	✓	✓	✓	

Visit	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6/ ETV	Visit 7
Day/Week	**Day -17 to -14**	**Day 1**	**Day 14/ Week 2 (±3 days)**	**Day 28/ Week 4 (±3 days)**	**Day 56/ Week 8 (±3 days)**	**Day 84/ Week 12 (±3 days)**	**Post-Treatment Safety FU (+7 days from Visit 6 (±3 days))**
Dilated Ophthalmoscopy (Fundoscopy)	✓					✓	
Run-In dispensation	✓						
Study Treatment Dispensation(6)		✓	✓	✓	✓		
Dosing Diary and Instruction provided	✓	✓	✓	✓	✓		
Study Treatment Accountability(7)		✓	✓	✓	✓	✓	
Urine pregnancy test(8)	✓					✓	
Schedule Next Visit		✓	✓	✓	✓	✓	
Study Exit							✓

1 Eligibility criteria will be re-checked after subjects have completed the run-in period.
2 Adverse event query will be conducted at pre-examination and post-instillation at Visit 2. 3, 4, 5, and 6.
3 Symptom assessments VAS/SANDE should be performed first prior to or any invasive procedure. SANDE will be performed prior to the Individual Symptom Severity Assessments VAS. Symptom Assessment VAS includes Ocular Discomfort, Eye Dryness, Burning/Stinging, Photophobia, Foreign Body Sensation, Eye Pain, Itching and Blurred Vision.
4 BCVA should be performed prior to any dyes.
5 STT should be performed at least 20 minutes after FCS is performed.
6 Study treatment instillations on the date of the visits will be performed after all study procedures have taken place. A new refrigerated IP pack will be administered to subjects at each visit with the appropriate number of ampules.
7 Accountability will be assessed by counting the number of used and unused ampules returned at each visit, beginning at Visit 2.
8 Urine pregnancy test for women of childbearing potential only.
Notes: AE = Adverse event; BCVA = Best Corrected Visual Acuity; ETV = Early Termination Visit; FCS = Fluorescein Corneal Staining; FU = Follow up; SANDE = Symptom Assessment and Dry Eye; STT = Schirmer Tear Test; VAS = Visual Analog Scale.

Appendix 2 : Examination Procedures, Tests, Equipment, and Techniques

Visual Acuity Procedures (ETDRS Chart)

LogMAR visual acuity (VA) must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. VA should be evaluated at the beginning of each visit in the study (i.e., prior to slit-lamp examination). VA testing should be done with most recent correction.

Equipment

The VA chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", i.e., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only the Series 2000 Chart 1, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be 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 in lieu of the number. The subject should be asked to read slowly, so as 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 (i.e., 'that was a "C" not an "O"') before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as 1 of 2 letters, he or she should be asked to choose 1 letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR VA for that eye.

For Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of VA during the study, all VA assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a subject forgets his glasses), the reason for the change in correction should be documented.

Best Corrected Visual Acuity (BCVA)

To provide standardized and well-controlled assessments of visual acuity during the study, consistently use the same lighting conditions during the entire 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

Slit Lamp Biomicroscopy Procedures

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the Investigator) or not clinically significant (NCS). The following will be examined:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Eyelid

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

Dilated Ophthalmoscopy (Fundoscopy)

Dilated fundoscopy will be performed using indirect ophthalmoscopy. The Investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the Investigator that may interfere with study parameters or otherwise confound the data) and those that are not clinically significant will be described. A dilated fundoscopy examination should be performed if retinal disease is detected.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes should be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects. The use of cyclopentolate 1% ophthalmic solution is recommended as secondary dilating medication, should the need arise.

Visual Analogue Scale (VAS)

Subjects will be asked the following questions regarding ocular discomfort (unrelated to study drug instillation) at all visits.

The subject will be asked to rate each ocular symptom due to dry eye syndrome by placing a vertical mark on the horizontal line to indicate the current level of discomfort. 0% corresponds to “no discomfort” and 100% corresponds to “maximal discomfort.” The linear dimension of the scale is measured in millimeters. This assessment is a general assessment of both eyes. There will not be a question for each individual eye. This assessment should be performed

following SANDE, and prior to assessing for AEs and prior to any other invasive visit assessment.

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

Burning/ Stinging	0%	100%
Itching	0%	100%
Foreign Body Sensation	0%	100%
Blurred Vision	0%	100%
Eye Dryness	0%	100%
Photophobia	0%	100%
Pain	0%	100%
Ocular Discomfort	0%	100%

Fluorescein Corneal Staining (FCS) National Eye Institute/Industry Workshop Scale

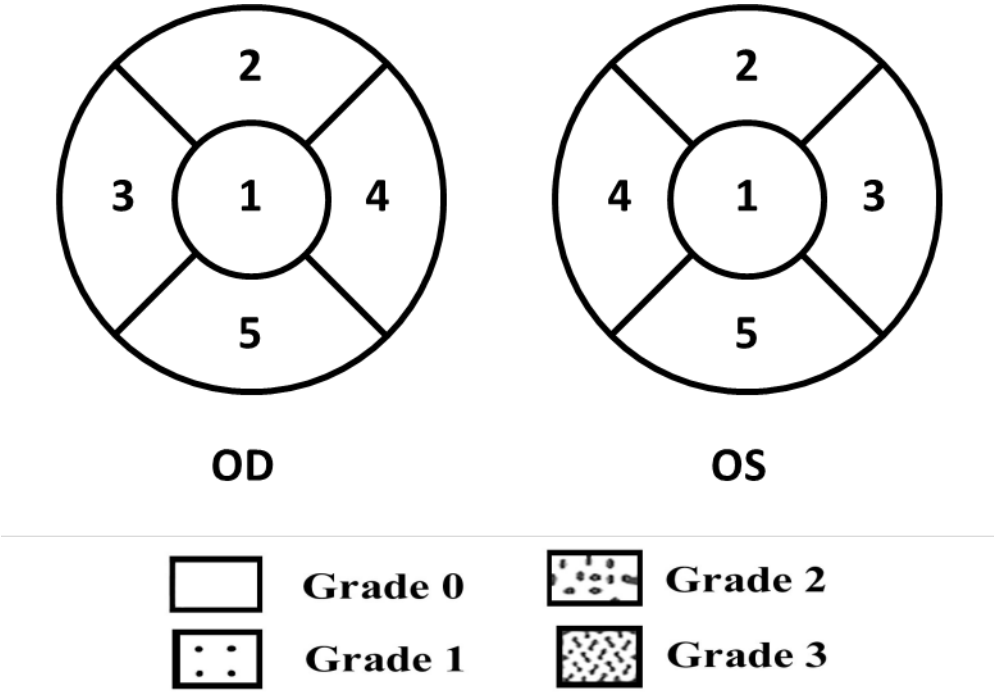

Diagram of the division of the corneal surface for FCS total score. A standardized grading System of 0-3 is used for each of the five areas on each cornea. The maximum score is 15. Grade 0 will be specified when no staining is present.

Unanesthetized Schirmer's Test

Schirmer Tear Test will be performed according to the following procedure:

- Using a sterile Tear Flo Schirmer test strip (Rose Enterprises), a bend in the strip will be made in line with the notch in the strip
- The subject will be instructed to gaze up and in
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye

Symptom Assessment in Dry Eye (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 3: Daily Dosing Diary