An Investigator-Masked, Randomized, Parallel-Group Study of the Ocular Tolerability of Voclosporin Ophthalmic Solution versus Restasis® in Subjects with Dry Eye Disease

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DECLARATION OF SPONSOR

Title: An Investigator-Masked, Randomized, Parallel-Group Study of the Ocular Tolerability of Voclosporin Ophthalmic Solution versus Restasis® in Subjects with Dry Eye Disease

Version Number/Date: Final Version 1/12March2018

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 Conference of Harmonisation on Good Clinical Practice.

Sponsor Representatives

[redacted]

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Date (e.g., DD Month Year)

Chief Medical Officer

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13 March 2018
Date (e.g., DD Month Year)

Vice President, Quality and Regulatory Affairs

INVESTIGATOR AGREEMENT FORM

I have read the attached protocol titled: An Investigator-Masked, Randomized, Parallel-Group Study of the Ocular Tolerability of Voclosporin Ophthalmic Solution versus Restasis® in Subjects with Dry Eye Disease.

Version Number 1/12March2018:

I agree to comply with the current International Conference of 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 (e.g., DD Month Year)

SYNOPSIS

Title:	An Investigator-Masked, Randomized, Parallel-Group Study of the Ocular Tolerability of Voclosporin Ophthalmic Solution versus Restasis® in Subjects with Dry Eye Disease
Study Product:	Voclosporin ophthalmic solution (VOS)
Indication:	Dry Eye Disease (DED)
Phase:	2
Sponsor:	Aurinia Pharmaceuticals Inc.
Study Code:	AUR-VOS-2017-01
Objectives:	Primary Objective To assess the ocular tolerability of VOS compared to cyclosporine ophthalmic emulsion (Restasis®) in subjects with DED. Secondary Objective To assess the safety and efficacy of VOS in subjects with DED.
Design:	This is a Phase 2, multi-center, Investigator-masked, randomized, parallel-group study to evaluate the tolerability, efficacy and safety of VOS versus Restasis® over a 28-day treatment period in subjects with mild to moderate DED. Approximately 60 subjects will be randomized to either VOS or Restasis® at approximately 5 centers located in the US.
Treatment:	Investigational product (IP): 0.2% VOS, twice daily (BID), both eyes (OU) for 28 days. Comparator: 0.05% cyclosporine ophthalmic emulsion (Restasis®) BID, OU for 28 days. The Investigator assessing the ocular signs and subjects will be masked to study treatment.
Inclusion Criteria:	At Visit 1 and Visit 2 (as specified in the Schedule of Events), subjects may be eligible for participation if they: 1. Provide written informed consent before any study-specific procedures are performed. 2. Are male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) years, at the time of screening (Visit 1). 3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study. 4. 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.

	5. Have a documented history of DED in both eyes supported by a previous clinical diagnosis at Visit 1. 6. Have ongoing DED, as defined by at least one eye (if one eye, the same eye) meeting all the following criteria: – A symptom severity score of ≥30 for Eye Dryness on a Visual Analog Scale (VAS) (0-100) at Visit 2 – An unanesthetized Schirmer Tear Test (STT) score of ≥1 mm and ≤10 mm per 5 minutes (Note: STT Score obtained at Visit 1) – Evidence of ocular surface staining (total fluorescein staining score of at least 3 [0-15 scale]) at Visit 2. 7. Have normal lid anatomy at Visit 1.
Exclusion Criteria:	In order for subjects to be eligible, at Visit 1 and Visit 2 subjects must not: 1. Be unable or unwilling to give written informed consent and/or to comply with study procedures. 2. Have any known hypersensitivity or contraindication to study treatments (including excipients), topical anesthetics or vital dyes. 3. Be unable to demonstrate correct instillation of over the counter (OTC) ocular lubricant during Visit 1. 4. Report discomfort in both eyes from instillation of OTC ocular lubricant during Visit 2 (based on score of ≥30 on the Drop Discomfort VAS. 5. Have used Restasis® (cyclosporine ophthalmic emulsion) within 30 days prior to Visit 1. 6. Have used Restasis® for more than 1 month. (if prior use is reported.). 7. Have used Xiidra® (lifitegrast ophthalmic solution) within 14 days prior to Visit 1. 8. Have had corneal graft surgery in either eye within one year of Visit 1. 9. Have recent or current evidence of ocular infection or inflammation in either eye. 10. Have current evidence of clinically significant blepharitis (defined as requiring lid hygiene therapy), conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye. 11. Have clinically significant ocular disease in either eye (e.g., corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with study procedures or assessments. 12. Have any abnormality in either eye preventing reliable applanation tonometry. 13. Be taking or known need for any of the known treatment therapies listed in Section 7.7 at Visit 1 or during the study. This includes prohibited medications prior to Visit 1 as specified in Section 7.7. 14. Have any known hypersensitivity or contraindication to calcineurin inhibitors. 15. Have clinically significant systemic disease (e.g., uncontrolled diabetes, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study at Visit 1 and 2.

	16. Have participated in any investigational clinical study within 30 days prior to Visit 1. 17. Have altered systemic medication that could have an effect on dry eye signs or symptoms within 30 days prior to Visit 1 or anticipated during the study. 18. Be women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control.
Primary Endpoint:	Change from baseline in Drop Discomfort VAS score 1-minute post Dose 1 instillation.
Secondary Endpoints:	Key Secondary Endpoints: • Change from baseline in Drop Discomfort VAS score • Change from baseline in each of the 6 Individual Symptom Severity Assessments (VAS) scores • Change from baseline in the sum of the Individual Symptom Severity Assessments score (VAS Total Symptom Summary Score) • Change from baseline in Symptom Assessment in Dry Eye (SANDE) score • Change from baseline in unanesthetized STT score • Change from baseline in Fluorescein Corneal Staining (FCS) total score (National Eye Institute (NEI)/Industry Workshop 0-15 scale) Safety Endpoints: • Treatment-emergent adverse events (TEAEs) • Change from screening in BCVA • Changes from baseline in Slit-Lamp Biomicroscopy • Changes from screening in Dilated Ophthalmoscopy
Procedures:	At Visit 1 (screening) informed consent will be obtained from subjects and eligibility will be determined. A Schirmer Tear Test (STT) will be performed at this visit. The score will be used as the baseline and eligibility. During this visit, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, in both eyes to assess ability to self-administer study product. At Visit 2 (Randomization) continued eligibility will be confirmed. During this visit, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, in both eyes to evaluate ability to tolerate ocular drops. Individuals who are unable to successfully instill the drops or who rate OTC ocular lubricant as uncomfortable, based on a post-instillation Drop Discomfort VAS score, will not be eligible for participation in the study. (Note: For subjects meeting the Screening and Randomization Criteria, the Visit 2 Drop Discomfort VAS score will be used as the baseline value.)

	Eligible subjects will be randomly assigned in a 1:1 ratio to one of the two treatment groups: VOS BID or Restasis® BID. The first instillation of IP will be administered, at least 2-hours following administration of Refresh Plus® and by clinic personnel to both eyes (OU) during Visit 2. Investigational Product will be administered to the subject by an unmasked dedicated dosing coordinator (the subject and the Investigator will be masked to study treatment for the first post randomization instillation). Tolerability, safety and efficacy assessments will be performed at this visit. At Treatment Visits 3 and 4, tolerability, safety and efficacy evaluations will be performed. At the End of Treatment, Visit 5, tolerability, safety and efficacy evaluations will be performed. Subjects who discontinue before Visit 5 will undergo all Visit 5 evaluations (Early Termination). IP will be administered to the subject by a dedicated dosing coordinator at the clinic visits. A Drop Discomfort VAS will be administered in the clinic at 1 and 5 minutes following instillation of IP at Visits 2 through 5 (Investigator is to remain masked). With the exception of clinic day visits, subjects will self-administer IP twice a day OU over the 4-week treatment period. On the evening of Visits 2 through 4 and in the evening prior to Visit 5, the study coordinator will contact the subject by phone to prompt administration of IP followed by completion of the dosing diary and the Drop Discomfort VAS (1- minute and 5-minutes post-instillation). At Visit 6, there will be a 3-day post-treatment Follow-Up, in which safety assessments are performed and all remaining study materials are collected. The subjects will be instructed to continue to withhold all other concomitant topical medications as outlined by the protocol for the duration of their participation (through Visit 6). Serious adverse events (SAEs) ongoing as of Visit 6 will be followed until they have resolved, stabilized in the opinion of the Investigator, or returned to baseline. This study will be conducted per the schedule shown in the Schedule of Events (Table 1) and the Study Schematic (Figure 1).

Sample Size:	The study will include 60 male or female subjects.
	
	• The primary analysis will assess the difference in change from baseline in Drop Discomfort VAS scores 1-minute post-Dose 1 instillation between the two treatment groups.
	• A sample size of 26 subjects per group (52 in total) will provide at least 90% power assuming:
	  ○ a mean change from baseline Drop Discomfort VAS score of +30 mm for subjects randomized to Restasis®
	  ○ a mean change from baseline Drop Discomfort VAS score of +10 mm for those randomized to VOS
	  ○ a common standard deviation of 21
	  ○ a 2-sided alpha of 5%
	• Under the same assumptions, the study will have at least 80% power if the common standard deviation for the discomfort score were to be 25.
	• The study also provides 80% power should the treatment difference in discomfort scores be 16 (common standard deviation =20).

	• To allow for 15% dropouts, a total of 60 subjects will be randomized.
Statistical Methods:	The primary endpoint is measured on a VAS and will be summarized and analysed as continuous data. Summaries of VAS scores (absolute and change from baseline) by treatment group will be displayed for each VAS assessment (minutes 1, 5 and overall mean) at each visit. Should the data meet the necessary assumptions (normality and equal variance in both treatment groups) then the treatment groups will be compared using a t-test. If assumptions are violated, the Wilcoxon rank sum test will be used.

Figure 1: AUR-VOS-2017-01 Study Schematic

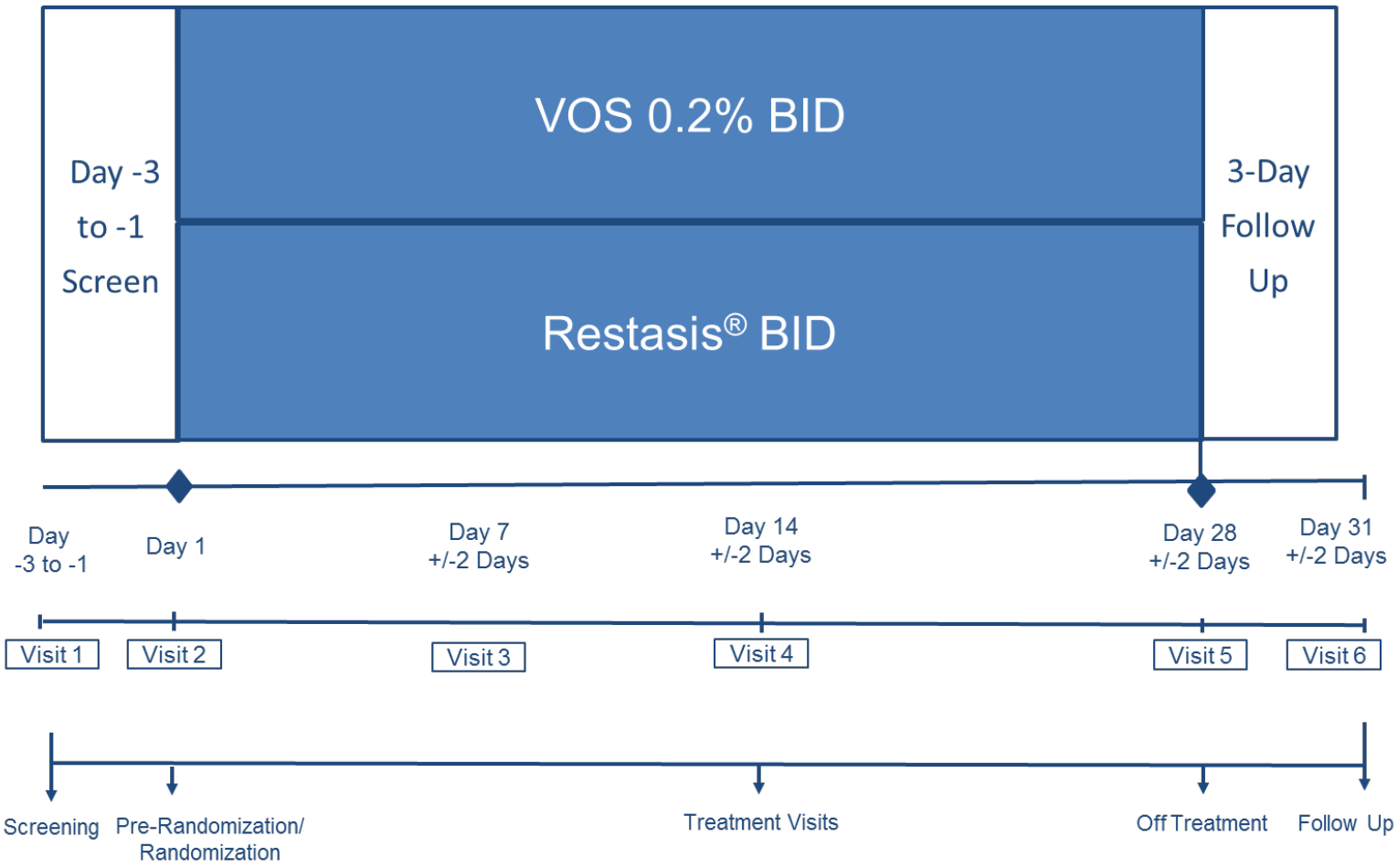

Table 1: AUR-VOS-2017-01 Schedule of Events

Visit	Visit 1 Screening	Visit 2 Pre-Randomization	Visit 2 Randomization	Visit 3 Treatment	Visit 4 Treatment	Visit 5 End of Treatment/ Early Term	Visit 6 Follow-up
Day	**Day -3 to -1**		**Day 1**	**Day 7 (±2 days)**	**Day 14 (±2 days)**	**Day 28 (±2 days)**	**Day 31 (±2 days)**
Informed Consent	✓						
Demography	✓						
Medical/Ophthalmic/ Surgical history	✓						
Eligibility Criteria Assessment	✓	✓					
Concomitant Medications Assessment	✓	✓		✓	✓	✓	✓
Urine Pregnancy Test[1]	✓						✓
SANDE[2]		✓		✓	✓	✓	
Individual Symptom Severity Assessments using VAS[3]		✓		✓	✓	✓	
BCVA[4]	✓						✓
Ophthalmoscopy (dilated)	✓						✓

Visit	Visit 1 Screening	Visit 2 Pre-Randomization	Visit 2 Randomization	Visit 3 Treatment	Visit 4 Treatment	Visit 5 End of Treatment/ Early Term	Visit 6 Follow-up
Day	**Day -3 to -1**		**Day 1**	**Day 7 (±2 days)**	**Day 14 (±2 days)**	**Day 28 (±2 days)**	**Day 31 (±2 days)**
Slit-Lamp Biomicroscopy		✓				✓	
Fluorescein Corneal Staining		✓		✓	✓	✓	
Schirmer Test	✓[5]					✓[5]	
OTC[6] Ocular Lubricant Administration at the Study Site	✓	✓					
Randomization			✓				
Investigational Product Administration at the Study Site			✓[7]	✓	✓	✓	
Drop Discomfort Assessment at the Study Site		✓[8]	✓[9]	✓	✓	✓	
AE[10] Assessment	✓	✓	✓	✓	✓	✓	✓
Investigational Product Dispensation			✓	✓	✓		
Dosing Diary and VAS[3]Scales Dispensation			✓	✓	✓		
Subject Contact for Drop Discomfort Assessment			✓	✓	✓[11]		

[1] For females of childbearing potential only; [2] Symptom Assessment and Dry Eye; [3] Visual Analog Scale;
[4] Best Corrected Visual Acuity; [5] STT should be performed at least 1 hour after IP instillation and at least 20 minutes after fluorescein corneal staining;
[6] Over the Counter; [7] Investigational Product instillation should be performed at least 2 hours after OTC ocular lubricant (Refresh Plus) instillation;
[8] Post OTC ocular lubricant instillation; [9] Post IP instillation; [10]Adverse Event;
[11] Subjects will be contacted the evening of the Visit 4 and in the evening prior to Visit 5.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
Aurinia	Aurinia Pharmaceuticals Inc.
BCVA	Best Corrected Visual Acuity
BID	Twice daily
CNI	Calcineurin inhibitor
CRA	Clinical Research Associate
CRO	Contract Research Organization
CsA	Cyclosporine A
DED	Dry Eye Disease
[redacted]	[redacted]
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
ERG	Electroretinography
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCS	Fluorescein Corneal Staining
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug

IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
KCS	Keratoconjunctivitis sicca
LogMAR	Logarithm of the Minimum Angle of Resolution
NEI	National Eye Institute
NFAT	Nuclear Factor of Activated T-cells
NOAEL	No observed adverse event level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NZW	New Zealand White
OD	Right eye
OS	Left eye
OSDI	Ocular Surface Disease Index
OTC	Over the counter
OU	Both eyes
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
STT	Schirmer Tear Test
SUSAR	Suspected unexpected serious adverse reaction

TEAE	Treatment-emergent adverse event
UPT	Urine pregnancy test
VAS	Visual Analog Scale
VOS	Voclosporin ophthalmic solution
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options

Dry Eye Disease (DED), also called keratoconjunctivitis sicca (KCS), is a common clinical problem as over 7 million people in the United States experience dry eye symptoms. Symptoms of DED include a sensation of dry eyes, foreign body sensation, irritation, burning, tearing, ocular pain, and itching, among others. DED affects quality of life and work productivity, and patients with moderate to severe DED may experience reduced visual function in addition to ocular dysfunction.

DED is a multi-factorial disease, defined by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyper-osmolarity, ocular surface inflammation and damage, and neuro-sensory abnormalities play etiological roles [1].

DED patients are classified by the overlapping etiologies of aqueous deficient and evaporative dry eye. Evaporative dry eye tends to be more prevalent than aqueous deficient; however, as the disease progresses, both components become apparent [1]. The common pathway for both groups is that desiccating stress leads to ocular surface inflammation [7,10,12]

1.1.1 Limitations of Current Treatment

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 [1]. There are currently two FDA-approved prescription medications used for DED, topical cyclosporine (Restasis®) and lifitigrast (Xiidra®). A significant number of patients using Restasis® experience the following problems: ocular irritation upon instillation, slow onset of response, and limited efficacy (Restasis® Package Insert, see Appendix 8). Problems with Xiidra® include instillation irritation, dysgeusia and reduced visual acuity which occurred in 5-25% of subjects in clinical trials (Xiidra® Package Insert). There is a clear unmet clinical need for improved therapeutic options for patients with moderate to severe DED.

1.2 Rationale for the Use of Calcineurin Inhibitors in Dry Eye Disease

In patients with DED, tear production has been shown to be increased with the use of topical immunosuppressants, including cyclosporine. It is believed T-lymphocyte infiltration and activation in the lacrimal gland represents an underlying pathogenesis for DED. Calcineurin inhibitors (CNIs) 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 [9]. Calcineurin is a calcium- and calmodulin-dependent serine-threonine phosphatase. 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 (e.g., interleukin-2, interleukin-4, tumor necrosis factor-α, granulocyte-macrophage colony stimulating factor, and interferon-γ,[11,13]).

Voclosporin is a 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 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 as compared to CsA. The combination of increased potency and decreased metabolite exposure, for voclosporin as compared to CsA, has led to better pharmacokinetic (PK)/pharmacodynamic (PD) predictability.

1.2.1 Non-Clinical Studies of Voclosporin in Dry Eye

Two Good Laboratory Practice toxicology studies [3,4] 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 evaluation, 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 Day 1 and Day 13 at pre-dose, 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 [5], 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 is >0.56 mg/eye/day.

In summary, the two repeated-dose ocular toxicology studies [3,4] 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 the S08711 study.

In addition to the three repeated dose toxicology studies, the safety and efficacy of VOS 0.2% has been evaluated in dogs with naturally occurring KCS [6], 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 twice daily (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 both safe and effective in treating KCS in dogs.

In order to determine potential melanin binding of ^{14}C-LX214, ocular tissue ^{14}C-LX214-derived radioactivity concentrations were compared between data obtained from albino NZW rabbits given a single bilateral instillation in a separate study and similarly treated pigmented Dutch-Belted rabbits. 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.

1.2.2 Clinical Studies of Voclosporin in Dry Eye

VOS 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 5 subjects with DED. In that study, both 0.02% and 0.2% concentrations were found to be safe and well tolerated following multiple instillations in healthy subjects. Adverse events (AEs) and ocular findings were mild and similar between VOS and placebo groups. Although the sample size was small, results from the 5 subjects with DED suggest VOS may be beneficial in the treatment of DED and is supported by the Ocular Surface Disease Index (OSDI) 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.

These factors form the basis for the rationale to investigate the safety and efficacy of voclosporin in subjects with DED. Study AUR-VOS-2017-01 will evaluate the tolerability and efficacy of VOS versus Restasis® in subjects with DED.

2. RATIONALE

2.1 Dose Rationale

Based on Phase 1 studies in healthy subjects and all clinical trials to date in the clinical development program in other indications, oral voclosporin is generally well tolerated at doses up to 0.8 mg/kg BID with no unexpected safety concerns compared to the profile expected for CNIs.

VOS was evaluated in a Phase 1 parallel, randomized, double-masked, placebo-controlled, dose-escalation (0.02% and 0.2%) study assessing the safety and tolerability of VOS in healthy volunteers, followed by an open-label evaluation of VOS (0.2%) BID in subjects with DED (see voclosporin Investigator's Brochure (IB)). Although the sample size was small, results from the five subjects with DED suggest VOS may be beneficial in the treatment of DED and is supported by the OSDI scores which were improved in all subjects at all timepoints while on study drug. The mean improvement in STT scores between baseline and the end of treatment provides further evidence of efficacy. It is anticipated that 0.2% VOS BID will be an effective dose in the treatment of immune-mediated ocular surface disease.

3. STUDY OBJECTIVES

3.1 Primary Objective

- To assess the ocular tolerability of VOS compared to cyclosporine ophthalmic emulsion (Restasis®) in subjects with DED.

3.2 Secondary Objective

- To assess the safety and efficacy of VOS in subjects with DED.

3.3 Endpoints

3.3.1 Primary Endpoint

- Change from baseline in Drop Discomfort Visual Analogue Scale (VAS) score 1-minute post Dose 1 instillation.

3.3.2 Secondary Endpoints

3.3.2.1 Key Secondary Endpoints

- Change from baseline in Drop Discomfort VAS score
- Change from baseline in each of the 6 Individual Symptom Severity Assessments (VAS) scores
- Change from baseline in the sum of the Individual Symptom Severity Assessments score (VAS Total Symptom Summary Score)
- Change from baseline in Symptom Assessment in Dry Eye (SANDE) score
- Change from baseline in unanesthetized STT score
- Change from baseline in Fluorescein Corneal Staining (FCS) total score (National Eye Institute (NEI)/Industry Workshop 0-15 scale)

3.3.2.2 Other Secondary Safety Endpoints

- Treatment-emergent adverse events (TEAEs)
- Change from screening in Best Corrected Visual Acuity (BCVA)

- Changes from baseline in Slit-Lamp Biomicroscopy
- Changes from screening in Dilated Ophthalmoscopy

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2, multi-center, Investigator-masked, randomized, parallel-group study to evaluate the tolerability, efficacy and safety of VOS versus Restasis® over a 28-day treatment period in subjects with mild to moderate DED. Approximately 60 subjects will be randomized to either VOS or Restasis® at approximately 5 centers located in the US.

At Visit 1 (screening), informed consent will be obtained from subjects and eligibility will be determined. A STT will be performed at this visit. The score will be used for eligibility and baseline. During this visit, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, OU to assess ability to self-administer study product.

At Visit 2 (Randomization), continued eligibility will be confirmed. During this visit, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, in both eyes to evaluate ability to tolerate ocular drops. Individuals who are unable to successfully instill the drops or who rate OTC ocular lubricant as uncomfortable, based on a post-instillation Drop Discomfort VAS score, will not be eligible for participation in the study. (Note: For subjects meeting the Screening and Randomization Criteria, the Visit 2 Drop Discomfort VAS score will be used as the baseline value.)

Eligible subjects will be randomly assigned in a 1:1 ratio to one of the two treatment groups: VOS BID or Restasis® BID. The first instillation of Investigational Product (IP) will be administered, at least 2 hours following administration of Refresh Plus® and by clinic personnel to OU during Visit 2. IP will be administered to the subject by a dedicated dosing coordinator (the subject and the Investigator will be masked to study treatment for the first post randomization instillation). Tolerability, safety and efficacy assessments will be performed at this visit.

At Treatment Visits 3 and 4, tolerability, safety and efficacy evaluations will be performed. At the End of Treatment, Visit 5, tolerability, safety and efficacy evaluations will be performed. Subjects who discontinue before Visit 5 will undergo all Visit 5 evaluations (early termination). IP will be administered to the subject by a dedicated dosing coordinator at the clinic visits (single masked: the Investigator and study staff will remain masked to study treatment). A Drop Discomfort VAS will be administered in the clinic at 1 and 5 minutes following instillation of IP at Visits 2 through 5. With the exception of clinic day visits, subjects will self-administer IP twice a day OU over the 4-week treatment period. On the

evening of Visits 2 through 4 and in the evening prior to Visit 5, site staff will contact the subject by phone to prompt administration of IP followed by completion of the dosing diary (See Appendix 9) and the Drop Discomfort VAS (1- and 5-minutes post-instillation).

At Visit 6, there will be a 3-day post-treatment Follow-Up, in which safety assessments are performed and all remaining study materials are collected. The subjects will be instructed to continue to withhold all other concomitant topical medications as outlined by the protocol for the duration of their participation (through Visit 6).

Serious adverse events (SAEs) ongoing as of Visit 6 will be followed until they have resolved, stabilized in the opinion of the Investigator, or returned to baseline.

This study will be conducted per the schedule shown in the Schedule of Events (Table 1) and the Study Schematic (Figure 1).

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is approximately 5 weeks. The treatment duration is 28 days with a follow-up visit 3 days after last dose (completion or early termination).

5. SELECTION, WITHDRAWAL OF SUBJECTS AND PERMANENT DISCONTINUATION OF DRUG

5.1 Number of Subjects

Approximately 60 subjects will be randomized to either VOS or Restasis®. Approximately 30 subjects will be assigned to each treatment group.

5.2 Inclusion Criteria

At Visit 1 and Visit 2 (as specified in the Schedule of Events), subjects may be eligible for participation if they:

1. Provide written informed consent before any study-specific procedures are performed.

2. Are male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) years, at the time of screening (Visit 1).

3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study.

4. 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.

5. Have a documented history of DED in both eyes supported by a previous clinical diagnosis at Visit 1.

6. Have ongoing DED, as defined by at least one eye (if one eye, the same eye) meeting all the following criteria:

    - A symptom severity score of ≥ 30 for Eye Dryness on a VAS (0-100) at Visit 2

    - An unanesthetized STT score of ≥ 1 mm and ≤ 10 mm per 5 minutes (Note: STT Score obtained at Visit 1)

    - Evidence of ocular surface staining (total fluorescein staining score of at least 3 [0-15 scale]) at Visit 2

7. Have normal lid anatomy at Visit 1.

5.3 Exclusion Criteria

In order for subjects to be eligible at Visit 1 and Visit 2 (as specified in the Schedule of Events), subjects must not:

1. Be unable or unwilling to give written informed consent and/or to comply with study procedures.
2. Have any known hypersensitivity or contraindication to study treatments (including excipients), topical anesthetics or vital dyes.
3. Be unable to demonstrate correct instillation of OTC ocular lubricant during Visit 1.
4. Report discomfort from instillation of OTC ocular lubricant during Visit 2 (based on score of ≥ 30 on the Drop Discomfort VAS).
5. Have used Restasis® (cyclosporine ophthalmic solution) within 30 days prior to Visit 1.
6. Have used Restasis® for more than 1 month (if prior use is reported).
7. Have used Xiidra® (lifitegrast ophthalmic solution) within 14 days prior to Visit 1.
8. Have had corneal graft surgery in either eye within 1 year of Visit 1.
9. Have recent or current evidence of ocular infection or inflammation in either eye.
10. Have current evidence of clinically significant blepharitis (defined as requiring lid hygiene therapy), conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye.
11. Have clinically significant ocular disease in either eye (e.g., corneal edema, uveitis, severe KCS) which might interfere with study procedures or assessments.
12. Have any abnormality in either eye preventing reliable applanation tonometry.
13. Be taking or known need for any of the known treatment therapies listed in Section 7.7, Prohibited Therapy and Concomitant Treatment at Visit 1 or during the study. This includes prohibited medications prior to Visit 1 as specified in Section 7.7, Prohibited Therapy and Concomitant Treatment.
14. Have any known hypersensitivity or contraindication to CNIs.

15. Have clinically significant systemic disease (e.g., uncontrolled diabetes, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study.

16. Have participated in any investigational clinical study within 30 days prior to Visit 1.

17. Have altered systemic medication that could have an effect on dry eye signs or symptoms within 30 days prior to Visit 1 or anticipated during the study.

18. Be women of childbearing potential (WOCBP) who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control.

5.4 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 WOCBP must have a negative urine pregnancy test (UPT) result at Visit 1 and must not intend to become pregnant during the study. Women of child bearing 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 (IUD) in place for at least 4 weeks prior to Visit 1 through Visit 5 or last administration of IP or until completion of the subject's first menstrual cycle following last administration of the IP, whichever period of time is longer.

2. Barrier method (condom or diaphragm) with spermicide for at least 4 weeks prior to Visit 1 through Visit 5 or last administration of the IP or until completion of the subject's first menstrual cycle following last administration of the IP, whichever period of time is longer.

3. Stable hormonal contraceptive for at least 3 months prior to Visit 1 through Visit 5 or last administration of the IP or until completion of the subject's first menstrual cycle following administration of the IP, whichever period of time is longer.

   NOTE: For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the IP is not applicable as females receiving this form of contraception will not have menses.

4. In a monogamous relationship with a surgically sterilized (i.e., vasectomized) partner at least 6 months prior to Visit 1 through Visit 5 or last administration of the IP or until completion of the subject's first menstrual cycle following administration of the IP, whichever period of time is longer.

5.5 Withdrawal of Subjects

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 5), if possible. If possible, the subject should also be advised to come for the Follow-up Visit, 3 days after last dose (Visit 6). If a subject refuses end of study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study specific electronic case report form (eCRF). It is the subject's right to withdraw from the study without providing a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent." Withdrawn subjects will not be replaced.

5.6 Discontinuation of Study Treatment

If any subject is discontinued from study treatment, the reason for discontinuation will be documented in the eCRF. If the reason for discontinuing study treatment is an AE, the specific event or test will be recorded in the eCRF. The subject should also be advised to come for the Safety Follow-up Visit, 3 days after last dose.

Subjects who are permanently discontinued from study treatment will be treated as deemed appropriate by the Investigator.

5.6.1 Discontinuation of Study Treatment Due to an Adverse Event

Subjects may be permanently discontinued from study treatment because of the appearance of an unacceptable AE. It is vital to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to evaluate protocol-specified safety follow-up procedures (see Section 9.3, Reporting Procedure for AEs, SAEs, and Pregnancy). If a subject is withdrawn due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilization has occurred. All AEs should be followed until resolution, stabilization or the subject is lost to follow-up and cannot be contacted.

6. RANDOMIZATION, MASKING AND UNMASKING PROCEDURES

6.1 Randomization

A computer-generated randomization schedule will be used to assign subjects into treatment groups. The randomization ratio will be maintained within each study center. A randomization list will be generated and provided by an unmasked statistician.

The Sponsor, the project teams at the designated Contract Research Organizations (CROs), and investigative staff responsible for assessments of study endpoints will be masked to study product assignments. There will be an unmasked dedicated dosing coordinator who will dispense the IP to the subject and who will perform drug accountability on the returned IP. This individual will be otherwise uninvolved in the study operations. Furthermore, there will be a Clinical Research Associate (CRA) dedicated to drug accountability who will be unmasked to the treatment assignment by default but will be uninvolved in review of the clinical trial data beyond the scope of IP accountability. In case of medical emergency, or occurrence of an SAE, the randomization code may be unmasked and made available to the Investigator, Sponsor, and/or other personnel involved in the monitoring or conduct of this study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject as needed. Since there is no specific antidote to VOS, immediate emergency unmasking is not necessary. If the Investigator feels it is necessary to unmask a subject's assignment after an emergency situation, the Investigator may call the Medical Monitor and notify the Sponsor. The IP assignment will be revealed on a subject-by-subject basis with the approval of the medical monitor and Sponsor, thus leaving the masking of the remaining subjects intact.

A randomization schedule will be generated by an unmasked statistician who will also be responsible for loading the schedule into the electronic data capture (EDC) system. No other [redacted] or Aurinia Pharmaceuticals Inc. (Aurinia) staff will have access to the schedule.

Randomization team members will work independently of other team members at the CRO. With the exception of the dedicated dosing coordinator and drug accountability CRA, all other study personnel, the Sponsor, and project teams at the CROs involved in the study will be masked to study product assignments.

6.2 Masking

On Day 1 Dose 1, this study is double-masked. The IP allocation (VOS versus Restasis®) will be masked to the Sponsor, the subject and the investigative staff with the exception of a dedicated dosing coordinator and unmasked CRA. The dosing coordinator will be responsible for dispensing and retrieving IP to/from subjects, instructing subjects regarding dosing of the IP, addressing study subjects' questions regarding IP, and reviewing daily dosing diaries. As a consequence of these interactions, the dosing coordinator will be unmasked to the study treatment for each subject. In order to ensure subject masking, at Visit 2, first dose, the dosing coordinator will not provide any IP related information prior to instilling the IP. The IP will be instilled in a masked manner. Instructions regarding storage and dosing will be provided after this first instillation.

On Days 2-28, subjects will not have visibility to the study product assignment; however, as VOS and Restasis® have different storage conditions and appearance, it may be possible that the subjects who have previously used Restasis®, may know that those differ from their prior experience. Therefore, the study will be considered Investigator-masked during this timeframe.

The randomization schedule will be generated by the Randomization Statistician (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study Investigator and members of the project team.

6.3 Unmasking

The treatment assignment for an individual subject may be obtained in the case of a medical emergency when knowledge of the IP identity is essential for the clinical management of the subject. The Investigator must make every effort to contact the study medical monitor or the Clinical Study Manager before unmasking the treatment assignment.

In the event of emergency unmasking, the Investigator must inform the Sponsor immediately, without revealing to the Sponsor personnel the treatment assignment.

If unmasking is required for emergency subject management, the Investigator must document the medical rationale for unmasking and forward the information to the Sponsor within 24 hours of unmasking.

If an SAE is assessed as unexpected and related to the IP, and therefore meets the requirement for expedited regulatory submission, the Sponsor's Drug Safety Surveillance department will unmask the treatment assignment for the individual subject. Expedited reports will be submitted to Regulatory Authorities in accordance with applicable regulations. Expedited

reports will be distributed to Investigators without revealing the treatment assignment and will be submitted to Institutional Review Boards (IRBs).

If emergency unmasking is required, withdrawal of the subject from the study is not mandatory unless there are other circumstances that require the subject's discontinuation. At the Sponsor's discretion, the subject may remain in the study without continued use of the IP.

In the event of accidental unmasking, the event would be reported as a protocol deviation and escalation to the Sponsor. The subject may remain in the study. If identified by the study center, a Sub-Investigator may be asked to assume clinical study assessments for a subject if the PI was inadvertently unmasked.

7. STUDY TREATMENTS

7.1 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.

7.1.1 VOS Study Treatment

Company Code: [redacted]

Chemical Name: [redacted]

Empirical Formula: [redacted]

Generic Name: Voclosporin ophthalmic solution (VOS)

Dosage Form: Voclosporin ophthalmic solution is provided as clear micellar solutions in single-use blow/fill/seal ampules for topical ocular administration. One drop (~30 µL) of the 0.2% solution contains approximately 0.06 mg of voclosporin

Strength: 0.2%

Manufacturer: Aurinia Pharmaceuticals Inc.

7.1.2 Restasis®

See Package Insert in Appendix 8.

7.2 Drug Dosage and Administration

7.2.1 Treatment Arms

Investigational Product: 0.2% VOS, BID, OU for 28 days.

Comparator: 0.05% cyclosporine ophthalmic emulsion (Restasis®) BID, OU for 28 days.

7.2.2 Dosing Guidelines

7.2.2.1 VOS/Restasis®– Study Treatment

7.3 Package and Labeling

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 Good Clinical Practice (GCP).

7.4 Study Treatment Allocation

Subjects will be randomized to receive either VOS or Restasis® in a 1:1 ratio. Subjects will be allocated a kit number for the duration of the study. Subjects will be assigned to treatment groups using the randomization module within the EDC system. As eligible subjects are enrolled and the corresponding Randomization eCRF completed, a kit number will be assigned.

7.5 Site Supply, Storage, Accountability

7.5.1 Site Supply

Once a site has been approved for study initiation, the site will be supplied with an initial stock of IP. Each site will receive one shipment of both Restasis® and VOS prior to study enrollment. Additional shipments of both Restasis® and VOS will be provided to each site as needed.

7.5.2 Storage

VOS should be stored refrigerated between 2º C and 8º C (35º F to 49º F) but may be brought to room temperature prior to use. Subjects should be consistent in their use of VOS IP.

Opened ampules must not be stored for re-use as the formulation does not contain preservatives.

STUDY DRUG SHOULD NOT BE FROZEN. DO NOT USE IF THE VIAL CONTENT DOES NOT APPEAR CLEAR.

Restasis® should be stored at room temperature (15-25°C/59-77°F).

Each site should have a thermometer 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.

7.5.3 Accountability

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 designee for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all undispensed IP will be returned to Aurinia. The decision to destroy IP at a site must be made by Aurinia. If the dispensed/returned IP is destroyed at a site, the Investigator must receive Aurinia approval of the site's standard operating procedure addressing the destruction process and forward documentation of destruction to Aurinia.

7.6 Procedures for Overdose

Preclinical findings suggest that systemic effects from an overdose are unlikely, as the peak blood levels after ocular instillation are below those achieved with oral doses of voclosporin.

Based on clinical experience with voclosporin, symptomatic treatment of AEs is indicated. In the event of overdose, discontinuation of treatment should be considered.

7.7 Prohibited Therapy and Concomitant Treatment

Any concomitant treatment given for any reason during the study must be recorded in the eCRF and in the subject's source documents, including dosage, start and stop dates, and reason for use.

Any class of medications not mentioned in Section 7.7.1, Prohibited Medications and with the potential to interfere with evaluation of the study treatment must be discussed and documented with the Medical Monitor.

7.7.1 Prohibited Medications

The following drugs/therapies shall be prohibited during the study and for the timeframes specified below: A subject should not have received

- any investigational drug or device within 30 days prior to the Screening Visit (Visit 1) and may not receive any investigational drug or device during the entire study except that which is allowed by the protocol
- Ophthalmic drugs (any topical eye medications) including prescription medication and OTC agents, except IP, from Visit 1 to Visit 6.
- Contact lenses during the period from the Screening Visit (Visit 1) to the end of the study (Visit 6)
- Prohibited Medications:
    - Any prior use of amiodarone
    - Within 14 days prior to study and for the duration of the study:
        - Xiidra® (lifitigrast)
    - Within 30 days prior to study and for the duration of the study:
        - Restasis® (cyclosporin ophthalmic emulsion); NOTE: Any prior use of Restasis® may not have exceeded 1 month of continuous use
        - Topical ocular antihistamines
        - Ocular, inhaled or intranasal corticosteroids
        - Topical or oral mast cell stabilizers
        - Oral antihistamines
        - Topical or nasal vasoconstrictors
        - Topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs)

- Topical ocular antibiotics

- 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

- 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

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

- At screening visit (Visit 1) or any time throughout the study:
  - Chronic oral anti-viral medications for ocular herpetic disease

8. STUDY PROCEDURES

8.1 Description of Study Assessments

8.1.1 Dry Eye Disease Activity Assessments

The following assessments will occur as part of the evaluation of DED (See Appendix 2).

8.1.1.1 Symptom Assessment in Dry Eye (SANDE)

Subjects will be asked to subjectively rate the frequency and severity of their dry eye symptoms at Visits 2, 3, 4 and 5 using the SANDE. The total length of the line from "rarely" to "all the time" (frequency of symptoms) and from "very mild" to "very severe" (severity of symptoms) is 100 mm. Subjects will be asked to subjectively rate the frequency and severity of their symptoms (OU) by placing an "X" on the relevant horizontal line. The length of the line between the "rarely" or "very mild" starting point and the first point where the subject's mark crosses each line will be measured and recorded 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 prior to assessing for AEs and prior to any other invasive visit assessment (See Appendix 3).

8.1.1.2 Visual Analogue Scale (VAS) Symptom Assessments

Individual Symptom Severity Assessments using VAS:

Subjects will be asked to rate their current symptoms (unrelated to study drug instillation) at Visits 2, 3, 4 and 5. The following six symptoms will be evaluated: Burning/Stinging, Foreign Body Sensation, Photophobia, Eye Pain, Eye Dryness, and Itching.

The subject will be asked to subjectively rate each of six ocular symptom (OU) by placing a vertical mark on the horizontal line to indicate their level of discomfort. 0 corresponds to "No Symptoms" and 100 corresponds to "Severe Symptoms." 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 (See Appendix 4).

8.1.1.3 Fluorescein Corneal Staining

Corneal staining will be performed at Visit 2, 3, 4 and 5. Corneal staining assessment will be performed using methods developed by the NEI Dry Eye Workshop (See Appendix 7).

Evaluation Technique

NOTE: All steps in this procedure should be completed for the right eye (OD) prior to repeating the procedure for the left eye (OS).

- Place Slit-Lamp magnification at 10x (it is acceptable to use 16x if no reticle is used)
- Use a yellow barrier filter (Wratten or Tiffen #11 or #12)
- Place 5 µL of non-preserved, 2% fluorescein into eye, gently touching the drop at the tip to the lower palpebral conjunctiva of the eye
- In order to thoroughly mix the fluorescein with the tear film, ask the subject to blink several times and move his/her eye around
- Wait 2.5 minutes to assess cornea
- Measure staining under Cobalt blue light (465 nm to 490 nm)
- Compare staining with the standard with scoring in each of 5 areas of the 5 corneal sections

Scoring system

- Grade each of 5 sections of cornea (superior, inferior, nasal, temporal, central)
- Provide grades for each of the 5 sections:
  - Grade by NEI scale (definition in Appendix 7) as 0, 1 (mild), 2 (moderate), or 3 (severe)
- Total score is obtained by summing each of the 5 sections of the cornea
  - NEI score will be from 0-15

(See Appendix 7).

8.1.1.4 Unanesthetized Schirmer Test (STT)

Schirmer Tear Test (without anesthesia) will be conducted at Visit 1 and Visit 5. This procedure should be conducted 1 hour following administration of IP and at least 20 minutes following FCS at Visit 5:

Identical Schirmer strips will be supplied to each site. When conducting assessments room temperature and humidity should be relatively consistent throughout each visit and throughout the study.

- While still in the plastic sheath, fold the notched end of the Schirmer strip at the apex of the "v." Additionally, make a partial second fold at the halfway point of the strip so that the strip does not lie directly in the subject's line of sight
- Remove the right eye strip from the sheath
- Ask the subject to look up and gently draw the right lower lid in a downward and temporal direction
- Place the rounded end of the strip toward the temporal one-third of the lower eyelid
- Repeat this procedure in the left eye
- Darken the room but ensure that the largest letter(s) of a Snellen or ETDRS chart is visible
- Instruct the subject to relax and look at the chart while blinking normally or have patients gently close eyes
- Remove the strips after 5 minutes
- After removing the strips, with a sharp pencil draw a horizontal line across the leading edge of moisture and a second horizontal line across the lowest point of moisture
- Using a ruler and/or the millimeters recorded on the strips, measure a point halfway between the two lines and record this as the amount of wetting

8.1.2 Post-Instillation Tolerability Assessments

8.1.2.1 Drop Discomfort Assessment

Drop discomfort will be assessed by the subject through a Drop Discomfort VAS (0-100 mm) where 0 corresponds to "no discomfort" and 100 corresponds to "maximal discomfort." (See Appendix 1).

At Visit 2, prior to randomization, in order to evaluate the subject's ability to tolerate ocular drops, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, in both eyes. Upon instillation of the ocular lubricant in both eyes, subjects will be instructed by the site staff to rate their eye discomfort at 1- and 5- minutes post-instillation by placing a mark on the

Discomfort VAS. Subjects who rate OTC ocular lubricant as uncomfortable, defined as a VAS score ≥ 30 mm, will not be eligible for participation in the study. These Drop Discomfort VAS scores will be used as the baseline values.

At Visit 2, after randomization, a dosing coordinator will instill the IP in both eyes. Subjects will be instructed by a masked site staff to rate their eye discomfort at 1- and 5-minutes post-instillation of IP as described above.

Subjects will complete this assessment in the clinic following the AM dose of IP at Visits 2, 3, 4 and 5 and again at home following the PM dose on the evenings of Visits 2, 3, 4 and the evening prior to Visit 5.

8.1.3 Safety Assessments

The following assessments will occur as part of the safety evaluation of the subjects:

8.1.3.1 Best Corrected Visual Acuity (BCVA)

BCVA will be conducted at Visit 1 and Visit 6. Visual acuity testing should precede any examination requiring contact with the eye or instillation of study dyes. LogMAR visual acuity must be assessed using an ETDRS or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

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

The subject should be positioned per the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked

to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart encouraging the subject to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted. (See Appendix 6).

8.1.3.2 Ophthalmoscopy

Dilated ophthalmoscopy exam will be performed per the Investigator's standard procedure at Visit 1 and Visit 6.

The Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Visit 1, the Investigator will determine whether the abnormality would exclude subject from study participation. A clinically significant change from baseline may indicate an AE.

8.1.3.3 Slit-Lamp Biomicroscopy

The biomicroscopy exam will be performed at Visit 2 and Visit 5. It should be performed with the Slit-Lamp using a beam of width and intensity to provide optimal evaluation of anterior segment.

This procedure will be performed in the same manner for all subjects observed at the Investigator's site (See Appendix 5).

8.2 Schedule of Assessments

A detailed schedule of assessments (including all protocol-required assessments, visits, and visit windows) is located on the Schedule of Events (Table 1). No study-related assessments will be performed (including changes to current medications to meet study eligibility) until the subject has provided signed and dated informed consent. Every effort will be made to keep the subject within the requested visit schedule. If a subject is seen outside of the visit window listed on the Schedule of Events, the reason must be clearly documented in the source notes.

8.2.1 Screening Procedures

8.2.1.1 Visit 1

The screening visit will take place within 3 days prior to Visit 2. After obtaining informed consent, site staff will perform/assess the following procedures in the order below. There will be a collection of information including:

- Demographics
- Prior documented DED diagnosis
- Ocular, general medical and surgical history
- Concomitant medication history
- UPT for all eligible WOCBP
- BCVA assessment
- Dilated ophthalmoscopy
- Unanesthetized STT
- Assessment of ocular lubricant self-instillation
- Inclusion and exclusion criteria assessment: Subjects who do not meet the evaluated criteria will not continue participation in the study. Any subject who does not meet eligibility requirements will be considered a Screen Failure.

Subjects should be reminded not to use artificial tears or any other OTC or prescription or any other topical eye medication except for the IP for the duration of their participation in the study.

Subject will be scheduled to return for Visit 2 in one to three days.

8.2.2 Treatment Procedures

8.2.2.1 Visit 2

Pre-Randomization

The site staff will perform/assess the following procedures:

- SANDE
- Individual Symptom Severity Assessments (VAS)
- Concomitant medication review
- AE assessment since last visit
- Self-instillation of ocular lubricant and Drop Discomfort assessment (VAS)
- Slit-Lamp biomicroscopy
- FCS
- Inclusion and exclusion criteria assessment. Any subject who does not meet eligibility requirements will be designated as Visit 2 Screen Failure and discontinued from the study

Upon verification of study eligibility, subjects will be randomized to receive either VOS or Restasis®.

Post-Randomization

The following procedures will be performed after randomization:

- IP administration: the unmasked dedicated dosing coordinator will administer the first dose of IP to the subject in both eyes

Note: IP administration should not take place until at least 2 hours after administration of ocular lubricant.

- Drop Discomfort assessment: A masked site staff will administer the Drop Discomfort VAS to the subject and instruct the subject to complete the Drop Discomfort VAS at 1-minute and 5-minutes post-dose
- Assess for occurrence of any AEs
- IP dispensation: The **dedicated Dosing Coordinator** will dispense the IP, provide instructions for IP administration and storage conditions
- Dosing Diary and VAS scales dispensation: Train the subjects on the completion of the daily dosing diary and VAS scales

- Evening contact scheduling: **Masked site staff** will schedule and contact the subject in the evening of the clinic visit to prompt administration of the next dose and completion the Drop Discomfort VAS
- Subjects should be reminded to withhold AM dose of IP on morning of next clinic visit and to return all used and unused IP

Subject will be scheduled to return for Visit 3 on Day 7 ±2 days.

PM Contact with Patient:

- **Masked site staff** will call subject to prompt IP administration and will remain on call to facilitate completion of the Drop Discomfort VAS at 1-minute and 5-minutes post-dose

8.2.2.2 VISIT 3 (Treatment Day 7 ±2)

The site staff will perform/assess the following procedures:

- SANDE
- Individual Symptom Severity Assessments (VAS)
- Query the subject regarding AEs
- Update concomitant medication use
- AE assessment since last visit
- **Dedicated dosing coordinator** will collect returned carton containing used and unused IP ampules
- **Dedicated dosing coordinator** will collect Dosing Diary, Drop Comfort VAS and dispense new Dosing Diary and Drop Comfort VAS
- **Masked site staff** will query the subject regarding compliance with dosing and the protocol. If the subject has not been compliant with the dosing regimen, record this in the source document and eCRF and discuss proper compliance with the subject
- FCS
- IP Administration:
    - The **dedicated dosing coordinator** will administer the AM dose of IP in the clinic
- Drop Discomfort VAS:

    - The **masked site staff** will administer the Drop Discomfort VAS at 1-minute and 5-minutes post-dose
- Assess for occurrence of any AEs following instillation
- **Dedicated dosing coordinator** will dispense IP to the subject
- Evening contact scheduling: **Masked site staff** will schedule and contact the subject in the evening of the clinic visit to prompt administration of the next dose and completion the Drop Discomfort VAS
- Remind subject to withhold AM dose of IP on morning of next clinic visit and to return all used and unused IP

Schedule the subject to return in 1 week for Visit 4 on Day 14 ±2 days.

PM Contact with Patient:

- **Masked site staff** will call subject to prompt IP administration and will remain on call to facilitate completion of the Drop Discomfort VAS at 1-minute and 5-minutes post-dose

8.2.2.3 VISIT 4 (Treatment Day 14 ±2)

The site staff will perform/assess the following procedures:

- SANDE
- Individual Symptom Severity Assessments (VAS)
- Query the subject regarding AEs
- Update concomitant medication use
- **Dedicated dosing coordinator** will collect returned carton containing used and unused IP ampules
- **Dedicated dosing coordinator** will collect Dosing Diary, Drop Comfort VAS and dispense new Dosing Diary and Drop Comfort VAS.
- **Masked site staff** will query the subject regarding compliance with dosing and the protocol. If the subject has not been compliant with the dosing regimen, record this in the source document and eCRF and discuss proper compliance with the subject

- FCS
- IP Administration:
    - The **dedicated dosing coordinator** will administer the AM dose of IP in the clinic.
- Drop Discomfort VAS:
    - The **masked site staff** will administer the Drop Discomfort VAS at 1-minute and 5-minutes post-dose
- Assess for occurrence of any AEs following instillation
- **Dedicated dosing coordinator** will dispense IP to the subject
- Evening contact scheduling: **Masked site staff** will schedule and contact the subject in the evening of the clinic visit to prompt administration of the next dose and completion the Drop Discomfort VAS
- Remind subject to withhold AM dose of IP on morning of next clinic visit and to return all used and unused IP

Schedule the subject to return in 1 week for Visit 5 on Day 28 ±2 days.

PM Contact with Patient:

- **Masked site staff** will call subject to prompt IP administration and will remain on call to facilitate completion of the Drop Discomfort VAS at 1-minute and 5-minutes post-dose.

8.2.2.4 VISIT 5 (End of Treatment Day 28 ± 2)

PM Contact with Patient: (Evening Prior to Visit 5)

- **Masked site staff** will call subject to prompt IP administration and will remain on call to facilitate completion of the Drop Discomfort VAS at 1-minute and 5-minutes post-dose

During the visit the site staff will perform/assess the following procedures:

- SANDE

- Individual Symptom Severity Assessments (VAS)
- Query the subject regarding AEs
- Update concomitant medication use
- **Dedicated dosing coordinator** will collect returned carton containing used and unused IP ampules
- **Dedicated dosing coordinator** will collect Dosing Diary and Drop Comfort VAS.
- **Masked site staff** will query the subject regarding compliance with dosing and the protocol. If the subject has not been compliant with the dosing regimen, record this in the source document and eCRF and discuss proper compliance with the subject
- Slit-Lamp biomicroscopy
- FCS
- IP Administration:
    - The **dedicated dosing coordinator** will administer the AM dose of IP in the clinic
- Drop Discomfort VAS:
    - The **masked site staff** will administer the Drop Discomfort VAS at 1-minute and 5-minutes post-dose
- Unanesthetized STT. This should be performed no less than 1-hour following the administration of IP and at least 20 minutes following FCS

Schedule the subject to return in 3 days for the post-treatment follow-up visit.

8.2.3 End of Study (or Early Discontinuation) Procedures

On completion of treatment at Day 28 or earlier if subject is discontinued/withdrawn early, all assessments for Visit 5 (end of study or early termination) will be completed per the Schedule of Events. See also Section 5.5, Withdrawal of Subjects, for further information on withdrawal procedures and criteria.

8.2.4 Follow-up Procedures

8.2.4.1 VISIT 6 (Post-Treatment Follow-Up Day 31 ±2)

During the visit, the site staff will perform/assess the following procedures:

- Query the subject regarding AEs
- Update concomitant medication use
- UPT for WOCBP
- BCVA
- Dilated ophthalmoscopy

Subjects are discharged from the study and instructed to resume their normal prior ocular therapy.

9. EVALUATION, RECORDING AND REPORTING OF AEs AND SAEs

9.1 Definitions

9.1.1 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.

9.1.2 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.

9.1.3 Suspected Adverse Reaction (SAR)

A Suspect Adverse Reaction (SAR) is any AE for which there is reasonable possibility that the drug caused the AE. For purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest causal relationship between the drug and the AE.

9.1.4 Unexpected

An AE or SAR is considered "unexpected" if it is not listed in the **IB or is not listed at the specificity or severity that has been observed.**

9.1.5 Life-threatening

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

9.1.6 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 which 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 informed consent form (ICF).

9.1.7 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 suspected unexpected serious adverse reaction (SUSAR).

9.2 Adverse Event Descriptors

9.2.1 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.

9.2.2 Causal Relationship Categorization

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment 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.

9.2.3 Outcome Categorization

Outcome may be classified as recovered without sequelae; recovered with sequelae; improved; worsened; ongoing; ongoing at end of study; 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 SAE reporting form. SAEs that are ongoing at the time of death will have an outcome of "unknown" recorded. SAEs resulting in a fatal outcome will have an outcome of "fatal" recorded.

9.2.4 Symptoms of the Disease Under Study

Symptoms and fluctuations in laboratory parameters related to the disease under study will not be classed 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 or laboratory parameters, however, will be recorded as an AE and clearly marked as worsening or by the subject's worst observed intensity. The Investigator will be required to assess the relationship to disease under study for each AE as related or not related. An AE will not be able to be assessed as related to both disease under study and related to study treatment.

9.2.5 Abuse, Misuse, Overdose and Medication Error

All AEs of special interest such as study treatment abuse, misuse, overdose, and medication error must be documented in the subject's eCRF and source documentation. If any occurrence

of abuse, misuse, overdose, or medication errors leads to any event that fulfils any seriousness criteria, the event has to be reported as an SAE.

9.3 Reporting Procedure for AEs, SAEs, and Pregnancy

9.3.1 Adverse Events

All AEs observed from time of signing of the ICF will be recorded in the subject's source documentation. This applies to all AEs regardless of presumed relationship to the study drug. For screen failure subjects, any AEs and SAEs occurring during the screening period (after informed consent) will be recorded in the subject's source documentation only and will not be collected on the eCRF. Adverse events leading to discontinuation of study drug must be collected.

If any AE is reported, the date of onset, relationship to disease under study, relationship to study treatment, 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.

The AE reporting period begins at the time the ICF is signed by the subject. For screen failure subjects, any AEs and SAEs occurring during the screening period will be recorded in the subject's source documentation only. For enrolled subjects (i.e., those who successfully complete screening), the AE reporting period ends at the Follow-Up visit (Visit 6). 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 documents. 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. This information should be collected prior to completion of assessments at all study visits (with the exception of the SANDE and Individual Symptom Assessment VAS). In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be considered AEs.

9.3.2 Serious Adverse Events

For screen failure subjects, any SAEs occurring during the screening period (after informed consent) will be recorded in the subject's source documentation only and will not be collected on the eCRF.

For enrolled subjects (i.e., those who successfully complete screening), all SAEs occurring after the signing of the ICF will be reported to [redacted] within 24 hours of the Investigator, designee, or site staff's knowledge of the event regardless of relationship to study drug or relationship to disease under study. For enrolled subjects, all SAEs will be recorded in the AE section of the subject's eCRF and source documentation.

In the event that the site experiences a temporary disruption of the EDC system a back-up 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:

- Site staff will complete the paper SAE report form and e-mail it within 24 hours to the following address, Email: [redacted]
- Only in cases where the email system is unavailable, site staff will send the SAE form by fax to [redacted]

If notification is made via email or fax, site staff must enter the SAE information into the EDC system as soon as the system becomes available.

All initial and follow-up SAE must be reported by the Investigator to [redacted] within 24 hours of becoming aware of the event.

All SAEs, regardless of causality, will be reported from the time the ICF is signed until 30 days following the last study visit or 30 days after last study treatment administration in subjects who withdraw or discontinue prior to study completion. No formal study visit is required but Investigators must report any SAEs that occur during this 30-day period on the eCRF. 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.

All recorded SAEs, regardless of relationship to disease under study or relationship to study treatment, 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.

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. A rationale for the assessment of a causal relationship must be provided by the Investigator. The Investigator will also be required to assess the relationship to 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. Any safety information that is obtained after the follow-up visit (Visit 6) will be documented in the safety database only.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study visit (including the follow-up visit) or until 30 days after the last study treatment administration, whichever is longer, whether considered treatment related or not, must be reported to Aurinia. If the subject died, the SAE report should include the cause of death as the event term and whether or not the death was related to study treatment, 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.

Additional follow-up information must be reported in the eCRF 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 [redacted] by the reporting procedures described above.

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

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

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

9.3.3 Pregnancy

Pregnancy occurring in a female subject or in the partner of a male subject should be reported to [redacted] within 24 hours of becoming aware of the event using the pregnancy eCRF. The Investigator should counsel the subject, and in the case of a male subject, the subject's partner, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. A female subject must immediately inform the Investigator if she becomes pregnant during the study. Monitoring of the pregnancy in a female subject should continue until conclusion of the pregnancy. In case of a pregnancy in the partner of a male subject, the Investigator should obtain informed consent of the pregnant partner prior to monitoring of the pregnancy.

Women 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).

All pregnancies, subject or partner of a subject, that occur during the study or come to the attention of the Investigator within 30 days after the last study visit (including the Follow-up Visit) or until 30 days after last study treatment administration, whichever is longer, must be reported to [redacted] by the reporting procedures described above.

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 9.3.2, Serious Adverse Events.

In the event that the site experiences a temporary disruption of the EDC system, a back-up paper Pregnancy Reporting Form will be available for site staff to complete. The Investigator must complete, sign and date the Pregnancy form and verify the accuracy of the information recorded on the form with the corresponding source documents.

- Site staff will complete the paper Pregnancy report form and e-mail it within 24 hours to the following address, Email: [redacted]
- Only in cases where the email system is unavailable, site staff will send the Pregnancy form by fax to: [redacted]

If notification is made via email or fax, site staff must enter the Pregnancy information into the EDC system as soon as the system becomes available.

10. STATISTICAL ANALYSIS

10.1 Statistical Methods

Complete details of the statistical and analytical methods will be provided in a formal Statistical Analysis Plan (SAP) which will be finalized prior to the database lock. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the Clinical Study Report.

All statistical analyses will be undertaken at study closure and will incorporate all endpoints.

10.2 Sample Size and Power Calculations

The study will include approximately 60 male or female subjects.

The primary analysis will assess the difference in change from baseline in Drop Discomfort VAS scores (range 0 to 100 mm) 1-minute post-Dose 1 instillation between the two treatment groups.

A sample size of 26 subjects per group (52 in total) will provide at least 90% power assuming:

- A mean change from baseline Drop Discomfort VAS score of +30 mm for subjects randomized to Restasis®
- A mean change from baseline Drop Discomfort VAS score of +10 mm for those randomized to VOS
- A common standard deviation of 21 mm
- A 2-sided alpha of 5%

Under the same assumptions, the study will have at least 80% power if the common standard deviation for the discomfort score were to be 25.

The study also provides 80% power should the treatment difference in discomfort scores be 16 (common standard deviation=20).

To allow for 15% dropouts, approximately 60 subjects will be randomized.

10.3 Populations

10.3.1 Intent-to-Treat Set

The tolerability and efficacy analysis will be based on the intent-to-treat (ITT) principles and will consist of all randomized subjects who receive at least 1 dose of study treatment.

10.3.2 Per Protocol

The per-protocol set will be a subset of subjects in the ITT population who do not have any major protocol violations (to be defined prior to unmasking).

10.3.3 Safety Set

The safety analysis will consist of all randomized subjects who receive at least 1 dose of study treatment. The subjects in this group will be analyzed based on the treatment they received.

10.4 Concomitant Therapy

All concomitant medications will be coded by the World Health Organization (WHO) Anatomical Therapeutic Chemical Drug Reference List classification. The version used will be provided in the Clinical Study Report.

10.5 Endpoint Evaluations

10.5.1 Primary Endpoint

The primary endpoint is the change from baseline to 1-minute post-instillation of IP in Drop Discomfort VAS score at Visit 2. The baseline measure will be taken 1-minute following Refresh Plus® administration at least 2 hours prior to IP administration.

10.5.2 Secondary Endpoints

10.5.2.1 Key Secondary/Efficacy Endpoints

- Change from baseline in Drop Discomfort VAS score
- Change from baseline in each of the 6 Individual Symptom Severity Assessments (VAS)
- Change from baseline of the sum of the Individual Symptom Severity Assessments (VAS Total Symptom Summary Score)
- Change from baseline in SANDE score
- Change in unanesthetized STT score
- Change from baseline in FCS total score (NEI/Industry Workshop 0-15 scale) Safety Endpoints

10.5.2.2 Safety Endpoints

- Treatment-emergent adverse events (TEAEs)
- Change from screening in BCVA
- Changes from baseline in Slit-Lamp Biomicroscopy
- Changes from screening in Dilated Ophthalmoscopy

10.6 Statistical and Analytical Methods

10.6.1 Primary Analysis

The primary endpoint is measured on a VAS and will be summarized and analyzed as continuous data. Summaries of VAS scores (absolute and change from baseline) by treatment group will be displayed for each VAS assessment (minutes 1, 5 and overall mean) at each visit. Should the data meet the necessary assumptions (normality and equal variance in both treatment groups), then the treatment groups will be compared using a t-test. If assumptions are violated, the Wilcoxon rank sum test will be used. If needed, transformations will be considered in order to meet the necessary assumptions.

10.6.2 Secondary Efficacy Analysis

Descriptive statistical summary (sample size, mean, standard deviation, median, minimum and maximum) will be presented by treatment group for each endpoint. Changes from randomization/baseline will be compared between VOS and Restasis® using a two-sample t-test or the Wilcoxon rank sum test. Further details will be addressed in the SAP.

10.6.3 Safety Analysis

Adverse events will be aggregated by System Organ Class and preferred term and presented as summary tables. Other safety endpoints will be summarized by visit as absolute values and changes from baseline (as appropriate). Endpoints with specific ranges will have counts of values falling outside of the range summarized by visit and overall.

10.7 Safety Evaluations

Safety evaluations include:

- Treatment-emergent adverse events (TEAEs)
- BCVA
- Slit-Lamp Biomicroscopy
- Dilated Ophthalmoscopy

10.8 Interim Analyses

No interim analyses are planned for this study.

10.9 Other Evaluations

N/A

11. ETHICAL CONDUCT OF THE STUDY

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki and the ICH guidelines for GCP. Aurinia will ensure that the study complies with all local, federal, and country regulatory requirements.

The Investigator must ensure the confidentiality of all subjects participating in the study.

All anonymous data remains the property of Aurinia.

11.1 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the IRB/Ethics Committee (EC)/IEC prior to use. The Investigator or an authorized associate must explain the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. After signing the ICF, subjects will be enrolled into the study and assigned a subject identification number that will be used on all subject documentation.

11.2 Institutional Review Board or EC/IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The Investigator must also ensure that the IRB/EC/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study per local requirements.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all study-related site source data, study-related documents, and reports will be available, and that the provision of direct access for monitoring and auditing by Aurinia or its designees will be permitted. In addition, the Investigator must ensure that all study-related site source data, study-related documents, and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

The Investigator is responsible for notifying Aurinia in advance of an impending regulatory inspection. He/she may request that Aurinia provide support for preparation, if necessary. The Investigator is required to provide updates to Aurinia on the ongoing activities during the inspection, respond to any citations/objectionable findings (i.e., U.S. Food and Drug Administration Form 483) and to share any follow-up responses from the Regulatory Authority.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Study Monitor (source document verification). An unmasked Monitor will also review the Investigator's drug accountability records to ensure that the drug supplies are stored and dispensed appropriately. A comprehensive validation program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Aurinia or its designee may review data as deemed necessary.

13. ADMINISTRATIVE PROCEDURES

13.1 Sponsor's Responsibilities

13.1.1 Study Supplies

Sites will be provided with all supplies required to manage this study. This will include but not be limited to the following:

- Investigator file(s) (for filing of all study-related documentation)
- Contact list of all relevant study personnel
- eCRF and completion guidelines (or equivalent EDC system)
- Study reference manual
- All study forms (e.g., SAE, Pregnancy, Drug Accountability, etc.)

13.1.2 Insurance

Aurinia confirms that it carries liability insurance which protects nonemployee physicians or Investigators/study staff against claims for which they may become liable as a result of damages caused by Aurinia products used in clinical studies. Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators or third parties and that are not in accordance with accepted common medical practices (*lege artis* procedures). Aurinia will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the IP or failure to follow the Investigator's instructions.

13.1.3 Study Monitoring

The study will be monitored by representatives of Aurinia (or designee, which may include a CRO). If not monitored by Aurinia, documentation of delegation will be described in the Clinical Trial Agreement. It is understood that the responsible Monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs at regular intervals throughout the study (frequency outlined in a separate procedural document), to verify the adherence to the

protocol and the completeness, consistency, and accuracy of the data being entered on them. The Monitor must have access to subject records needed to verify the entries on the eCRF. The Investigator (or his/her deputy) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Investigator's Responsibilities

13.2.1 Reporting and Recording of Data

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures, and electronic signatures. Only individuals who are identified on the authorized signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

13.2.2 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures, study treatments, and GCP/regulations specific to the conduct of clinical studies. This training will take place prior to enrollment of the first subject at the study site and must be documented and filed in the Investigator's Study Site File.

13.2.3 Source Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, signed ICFs, consultant letters, and subject enrollment logs. These are to be separate and distinct from eCRFs. All data for the study must be available in source documentation, including oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.

The Investigator must arrange for the retention of all study documentation (such as eCRFs, research files, and master files) for the duration specified in their respective site contract. The Investigator must keep these documents on file after completion or discontinuation of the study

according to local governing guidelines. Archived data may be held electronically, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform Aurinia immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

14. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

14.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted.

The Investigator should not implement any deviation from, or changes of the protocol without written agreement from Aurinia and prior documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when change(s) involves only logistical or administrative aspects of the study. If the Investigator must implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior written approval, the implemented deviation or change and the reasons for it should be submitted in a timely manner to Aurinia and to the IRB/IEC as required by applicable local requirements.

The Investigator, or person designated by the Investigator, will document and record the preventative and/or corrective measures for any deviation from the approved protocol.

Accidental deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented in the SAP.

Any amendment to the protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation unless there are overriding safety reasons.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the reviewed document prior to administering to study subjects.

14.2 Study Termination

Aurinia reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include but are not limited to the following: unsatisfactory subject enrollment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, Aurinia and the Investigator will assure that adequate consideration is given to the protection of the subjects. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

15. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Aurinia is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles (The Pharmaceutical Research and Manufacturers of America (PhrMa), Principals on Conduct of Clinical Trials/Communication of Clinical Trials; December 2014). Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Aurinia before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria (International Committee of Medical Journal Editors criteria; ICMJE.org) for authorship. If studies are multicenter, it may be appropriate to assign group authorship.

In addition, certain Aurinia employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee.

16. REFERENCES

1. TFOS DEWS II Definition and Classification Report; The Ocular Surface. 2017: 276-281. Available at http://sx.doi.org.

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3. S07654 – 14-Day ocular tolerability and toxicity of LX214 in New Zealand whit rabbits with 14-Day recovery period. Lux Biosciences, Inc.; 2009 Apr 3. Report No.: S07654.

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5. S08661 – Ocular tissue distribution of ^{14}C-LX214 following a single or multiple ophthalmic administration to New Zealand White Rabbit. Lux Biosciences, Inc 23 Mar 2009. Report No.: S08661.

6. S15389-00 – To evaluate the efficacy of Voclosporin Ophthalmic Solution (0.2% voclosporin) in naturally occurring keratoconjunctivitis sicca in client owned dogs with twice-daily administration. Intervet Inc (d/b/a Merck Animal Health), 28 Apr 2017. Report No.: S15389-00.

7. Chauhan S, Dana R. Role of Th17 Cells in the Immunopathogenesis of Dry Eye Disease. *Mucosal Immunol* (2009) 2(4): 375–376.

8. DEWS Report. The definition and classification of dry eye disease.; Ocular Surface. 2007:75-92. Available at: http://www.sciencedirect.com/science/article/pii/S1542012412700812.

9. Granelli-Piperno A, Andrus L, Steinman RM. Lymphokine and nonlymphokine mRNA levels in stimulated human cells: kinetics, mitogen requirements, and effects of cyclosporine A. J Exp Med. 1986 Apr;163:922-37

10. Pflugfelder et al., 2008: The diagnosis and management of dry eye: a twenty-five-year review

11. Stepkowski S.M. Molecular targets for existing and novel immunosuppressive drugs. Expert Rev Mol Med. 2000. p. 1-6.

12. Stevenson W, Chauhan SK, Dana R. Dry eye disease: An immune-mediated ocular surface disorder. *Arch Ophthalmol*. 2012;130(1):90-100. doi:10.1001/archophthalmol.2011.364.

13. Wiseman AC. Immunosuppressive medications. Clin J Am Soc Nephrol. 2016 Feb;11:332-43.

14. Xiidra® Package Insert

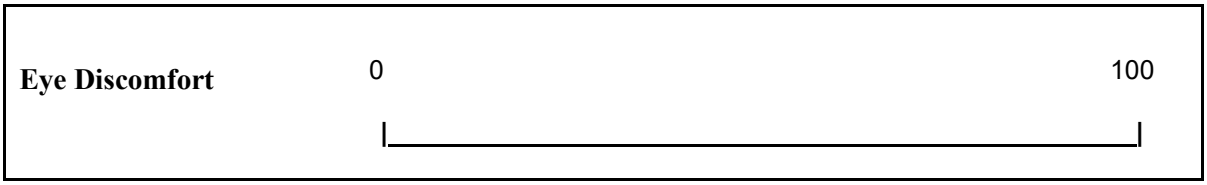
17. APPENDICES

Appendix 1 Tolerability Assessment

Drop Discomfort Assessment (Tolerability Assessment):

Subject will rate Drop Discomfort using a VAS. Subject will complete this assessment in the clinic following dosing of OTC ocular lubricant at Visit 2 and in the clinic following the AM dose of IP at Visits 2, 3, 4 and 5 and again at home following the PM dose of IP on the evenings of Visits 2, 3, 4 and the evening prior to Visit 5. The assessment will be completed at 1- and 5-minutes post-instillation of OTC ocular lubricant or IP.

Subject Instructions: Please rate how your eyes feel following instillation of the study drug by placing a vertical mark on the horizontal line. 0 corresponds to "no discomfort" and 100 corresponds to "maximal discomfort" You will rate your Drop Discomfort at 1 and 5 minutes following instillation of the study drug.



Appendix 2 EYE DRYNESS ASSESSMENTS

The following assessments are included as a part of the overall assessment of the presence and severity of DED:

- Fluorescein Corneal Staining (FCS)
- Unanaesthetized STT
- SANDE
- Individual Symptom Severity Assessments
    - VAS assessments of six symptoms: Burning/Stinging, Foreign Body Sensation, Photophobia, Eye Pain, Eye Dryness, Itching

Appendix 3 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 4 Individual Symptom Severity Assessments using VAS

<u>Subject Instructions</u>: 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**
Foreign Body Sensation (grain of sand/grittiness)	**0**	**100**
Photophobia	**0**	**100**
Eye Pain	**0**	**100**
Eye Dryness	**0**	**100**
Itching	**0**	**100**

Appendix 5 Slit-Lamp Biomicroscopy

This procedure will be the performed in the same manner for all subjects observed at the Investigator's site.

Lashes

0 = Normal

1 = Abnormal

Eyelid Erythema

0 = Normal, without any redness

1 = Abnormal

Edema

0 = Normal, no swelling of the lid tissue

1 = Abnormal

Conjunctiva Edema

0 = Normal, no swelling of the conjunctiva

1 = Abnormal

Cornea Infiltrates

0 = Absent

1 = Present

Endothelial Changes

0 = Normal, None

1 = Abnormal, pigment, keratoprecipitates, guttata

Edema

0 = Normal None, transparent and clear

1 = Abnormal

Anterior Chamber Cells

0 = Normal, No cells seen

1 = Abnormal (+ to +++ cells)

Flare

0 = Normal, No Tyndall effect

1 = Abnormal, Tyndall beam in the anterior chamber

Lens Pathology

0 = Normal; no opacity in the lens

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

Sclera Injection

0 = Normal, without any redness

1 = Abnormal

Appendix 6 Best Corrected Visual Acuity

BCVA will be conducted at Visit 1 and Visit 6 using ETDRS.

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

Appendix 7 Fluorescein Corneal Staining (FCS) National Eye Institute/Industry Workshop Scale

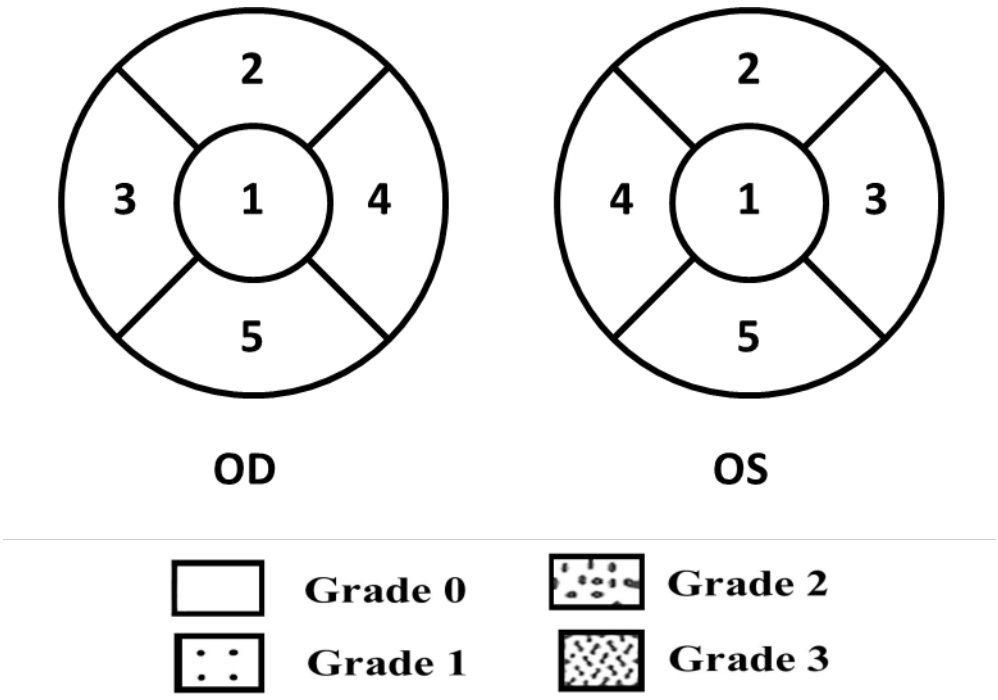


Diagram of the division of the corneal surface for FCS total score. A standardized grading System of 0-3 is used for each of the five areas on each cornea. The maximum score is 15. Grade 0 will be specified when no staining is present.

Appendix 8 Restasis® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RESTASIS® 0.05% safely and effectively. See full prescribing information for RESTASIS®.

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05%
For topical ophthalmic use
Initial U.S. Approval: 1983

INDICATIONS AND USAGE

RESTASIS® is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs. (1)

DOSAGE AND ADMINISTRATION

Instill one drop of **RESTASIS®** ophthalmic emulsion twice a day in each eye approximately 12 hours apart. (2)

DOSAGE FORMS AND STRENGTHS

Cyclosporine ophthalmic emulsion 0.5 mg/mL (3)

CONTRAINDICATIONS

- Hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces. (5.1)

ADVERSE REACTIONS

The most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

2 DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of **RESTASIS®** ophthalmic emulsion twice a day in each eye approximately 12 hours apart. **RESTASIS®** can be used concomitantly with lubricant eye drops, allowing a 15-minute interval between products. Discard vial immediately after use.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic emulsion containing cyclosporine 0.5 mg/mL

4 CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

Be careful not to touch the vial tip to your eye or other surfaces to avoid potential for eye injury and contamination.

5.2 Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potential for Eye Injury and Contamination [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of **RESTASIS®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration [*see Clinical Pharmacology (12.3)*], and maternal use is not expected to result in fetal exposure to the drug. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [*see Data*].

Data

Animal Data

At maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), cyclosporine oral solution (USP) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are 5,000 and 32,000 times greater, respectively, than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater, respectively, than the daily recommended human dose.

An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is 7,000 times greater than the daily recommended human dose. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily recommended human dose).

8.2 Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but its presence in human milk following topical treatment has not been investigated. Although blood concentrations are undetectable following topical administration of **RESTASIS®** ophthalmic emulsion *[see Clinical Pharmacology (12.3)]*, caution should be exercised when **RESTASIS®** is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **RESTASIS®** and any potential adverse effects on the breast-fed child from cyclosporine.

8.4 Pediatric Use

Safety and efficacy have not been established in pediatric patients below the age of 16.

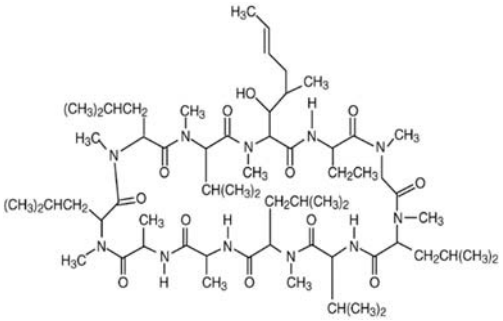
8.5 Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% contains a topical calcineurin inhibitor immunosuppressant with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] and it has the following structure:

Structural Formula



Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.: 1202.6

Cyclosporine is a fine white powder. **RESTASIS®** appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230 to 320 mOsmol/kg and a pH of 6.5-8.0. Each mL of **RESTASIS®** ophthalmic emulsion contains: **Active:** cyclosporine 0.05%. **Inactives:** glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclosporine is an immunosuppressive agent when administered systemically.

In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

12.3 Pharmacokinetics

Blood cyclosporine A concentrations were measured using a specific high pressure liquid chromatography-mass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of **RESTASIS®** 0.05%, twice daily, in humans for up to 12 months, were below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with **RESTASIS®** ophthalmic emulsion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Systemic carcinogenicity studies were conducted in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily recommended human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis

Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

14 CLINICAL STUDIES

Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1,200 patients with moderate to severe keratoconjunctivitis sicca. **RESTASIS®** demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of **RESTASIS®** ophthalmic emulsion-treated patients versus approximately 5% of vehicle-treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

No increase in bacterial or fungal ocular infections was reported following administration of **RESTASIS®**.

16 HOW SUPPLIED/STORAGE AND HANDLING

RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact.

30 Vials 0.4 mL each - NDC 0023-9163-30
60 Vials 0.4 mL each - NDC 0023-9163-60

Storage: Store at 15°-25 °C (59°-77 °F).

17 PATIENT COUNSELING INFORMATION

Handling the Container
Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. Advise patients to not touch the vial tip to their eye to avoid the potential for injury to the eye [*see Warnings and Precautions (5.1)*].

Use with Contact Lenses
RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion [*see Warnings and Precautions (5.2)*].

Administration
Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Irvine, CA 92612
Made in the U.S.A.

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Appendix 9 Daily Dosing Diary

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

- Date
- Time of Administration