STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	An Investigator-Masked, Randomized, Parallel-Group Study of the Ocular Tolerability of Voclosporin Ophthalmic Solution versus Restasis® in Subjects with Dry Eye Disease
PROTOCOL NUMBER:	AUR-VOS-2017-01
STUDY DRUG:	Voclosporin ophthalmic solution
DEVELOPMENT PHASE:	Phase 2
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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC-WHO-DD	Anatomical Therapeutic Chemical (Classification System)-World Health Organization-Drug Dictionary
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
eCRF	Electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCS	Fluorescein Corneal Staining
FDA	Food and Drug Administration
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	Investigational Product
ITT	Intent-to-treat
KCS	Keratoconjunctivitis sicca
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NFAT	Nuclear Factor of Activated T-cells
OD	Oculus dexter (Right eye)
OS	Oculus sinister (Left eye)

OSDI	Ocular Surface Disease Index
OTC	Over the counter
OU	Oculus uterque (Both eyes)
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
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

1.0 INTRODUCTION

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.

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. The common pathway for both groups is that desiccating stress leads to ocular surface inflammation.

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.

Voclosporin ophthalmic solution (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, efficacy and safety of VOS versus Restasis® in subjects with DED.

2.0 STUDY DESCRIPTION

2.1 Objectives

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

2.2 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 90 subjects will be randomized to either VOS or Restasis® at approximately 7 centers located in the US.

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 for eligibility and baseline. During this visit, all subjects will self-administer an over-the-counter (OTC) ocular lubricant, Refresh Plus®, in both eyes (OU) to assess ability to self-administer study product.

At Visit 2 (Pre-Randomization), continued eligibility will be confirmed. During this visit, all subjects will self-administer an OTC ocular lubricant, Refresh Plus®, OU 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 1-minute and 5-minute post-instillation Drop Discomfort Visual Analog Scale (VAS) score, will not be eligible for participation in the study. (Note: For subjects meeting the Screening and Randomization Criteria, the Visit 2 (pre-randomization) Drop Discomfort VAS score measured at minutes 1 and 5 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 and safety assessments will be performed at this visit.

At Treatment Visits 3, 4 and 5 (End of Treatment), tolerability, safety and efficacy evaluations will be performed. Subjects who discontinue IP 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 Visit 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,

3 and 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 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.

2.3 Inclusion Criteria

At Visit 1 and Visit 2 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.

2.4 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 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, of the protocol 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.

2.5 Randomization

A computer-generated randomization schedule will be used to assign subjects into treatment groups. The randomization will be stratified on study center.

3.0 STUDY ASSESSMENTS

3.1 Description of Study Assessments

3.1.1 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.

3.1.2 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.

3.1.3 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. FCS should take place after the Discomfort assessment at Visits 3, Visit 4 and Visit 5.

This assessment will be measured and summarized in each eye separately.

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 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

3.1.4 Unanesthetized Schirmer Tear Test

Schirmer Tear Test (without anesthesia) will be conducted at Visit 1, Visit 4 and Visit 5. At Visit 1, the STT test will be performed prior to the OTC self-instillation test and following dilated ophthalmoscopy as per the protocol. This procedure should be conducted 1 hour following administration of IP and at least 20 minutes following FCS at Visit 4 and Visit 5. 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.

This assessment will be measured and summarized in each eye separately.

3.1.5 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". This assessment is a general assessment of both eyes. There will not be a question for each individual eye.

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 $\geq$ 30 mm at 1 minute 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.

3.1.6 Best Corrected Visual Acuity (BCVA)

BCVA will be conducted at each visit per the Schedule of Events. 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. This assessment will be measured and summarized in each eye separately.

The number of letters missed or read incorrectly should be noted.

3.1.7 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. This assessment will be measured and summarized in each eye separately.

3.1.8 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. Normal or abnormal assessments will be made for each of the 11 individual criteria. This assessment will be measured and summarized in each eye separately.

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

3.2 Adverse and Serious Adverse Events

3.2.1 Adverse Event (AE)

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 adverse event (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.

3.2.2 Adverse Drug Reaction (ADR)

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.

3.2.3 Serious Adverse Event

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

3.2.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any ADR that is both serious and unexpected (per the Investigator's Brochure [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).

3.2.5 Treatment-Emergent Adverse Event (TEAE)

A treatment emergent adverse event (TEAE) is defined as any AE that has an onset on or after the first dose of IP/study drug and on or before the last dose of IP/study drug plus3days.

3.2.6 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.

3.2.7 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.

3.2.8 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.

3.2.9 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.

4.0 SAMPLE SIZE AND POWER CONSIDERATIONS

The study will include approximately 90 male or female subjects.
The primary analysis will use a t-test and 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 38 subjects per group (76 in total) will provide 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 +15 mm for those randomized to VOS
- These assumed mean changes lead to a 15 mm lower change from baseline in VAS scores for VOS compared to Restasis®
- A common standard deviation of 20 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 23 mm.
The study also provides 80% power should the treatment difference in discomfort scores be 13 (common standard deviation=20 mm).

To allow for 15% dropouts, approximately 90 subjects will be randomized.

It is interesting to note that a power of 80% is achieved by this sample size when the treatment difference (VOS- Restasis®) is 12 mm in favor of VOS and alpha is 10%.

5.0 ANALYSIS POPULATIONS

Three populations will be used for analysis.

5.1 Efficacy Analysis Populations

5.1.1 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. The subjects in this group will be analyzed based on the planned treatment.

5.1.2 Per Protocol Set

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). The subjects in this group will be analyzed based on the treatment they received.

5.1.3 Safety Analysis Set

The safety analysis set 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.

6.0 HANDLING OF MISSING DATA

No specific methods for handling of missing data are proposed. Observed cases will be analyzed.

6.1 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

6.2 Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the subject's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.

- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

6.3 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed or the date of subject's last clinic visit in the study or early withdrawal or death whichever is earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier.

6.4 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.5 Missing Safety Data

A treatment-related TEAE is defined as a TEAE that is assessed by the Investigator or Sponsor as being related to study drug. If a TEAE has a missing relationship to study drug it is assumed to be related to the study drug for analysis purposes.

A disease-related TEAE is defined as a TEAE that is assessed by the Investigator or Sponsor as being related to the disease under study. If a TEAE has a missing relationship to the disease under study it is assumed to be related to the disease under study for analysis purposes unless the TEAE is assessed by the investigator as treatment-related.

Missing severity assessments will be summarised as severe.

7.0 STATISTICAL ANALYSIS

All statistical analyses and reporting will be performed using the SAS® System Version 9.4 or later.

Unless otherwise specified, continuous variables will be summarized with descriptive statistics (n, mean, median, standard deviation, standard error, minimum, and maximum), and categorical variables will be summarized with counts and percentages.

7.1 Calculation of Study Day:

Study day will be calculated as the number of days from first dose of study drug (Day 1):

- Date of event – date of first dose of study drug + 1, for events on or after first dose
- Date of event – date of first dose of study drug, for events before first dose

To this end, Day 0 remains undefined.

Definition of Baseline:

Study day will be calculated as the number of days from first dose of IP/study drug (Day 1). Baseline measurements will be the last measurement for the corresponding variable prior to the first randomized dose on Day 1.

Out of Window and Unscheduled Visits:

The protocol defined windows for scheduled visits will not be used in the analyses by visit. Data will be assigned to the scheduled visit closer in time to the actual visit. Unscheduled visit data will only be used in an analysis if there are no other available data closer in time to a scheduled visit. All unscheduled visit data will be included in data listings.

7.2 Subject Disposition

Subject disposition, including the number of subjects randomized, treated, and completing the study (and completing each study visit), will be tabulated by treatment group. The percentage of subjects treated and completing the study will be based on the total number randomized. A subject data listing will be provided.

Eligibility criteria exemptions and major protocol deviations will be summarized by treatment group and presented in a listing. Major protocol deviations may include the following: violation of inclusion or exclusion criteria, using prohibited medications, non-adherence to study treatment schedule, and unblinding of the masked assessor at day 1 study drug dosing. A guideline for classification of patients as belonging to the per protocol analysis dataset will be documented prior to database unmasking as will the masked review of patient data for purposes of classification.

The total number and percentage of subjects included in each of the analysis datasets will be summarized by treatment group, with percentages based on the total number of randomized subjects. A subject data listing will be provided.

Discontinuations and the reasons for discontinuation from study medication will be summarized for all randomized subjects. Summaries will include the number and percentage of subjects within each treatment group. Reasons for Discontinuation or Early Termination/Study Withdrawal following the receipt of study drug will include the following:

- Intolerable Adverse Event
- Death
- Lost to Follow Up
- Physician Decision
- Prohibited Medication Required
- Pregnancy
- Protocol Noncompliance
- Site Terminated By Sponsor
- Study Terminated By Sponsor
- Withdrawal of Consent
- Lack of Efficacy
- OTHER: specify

A subject data listing will be provided.

7.3 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for the ITT analysis population; however, should there be a reasonable difference in the size of the ITT and safety analysis populations, demographic and baseline characteristics will be summarized for both. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual subject data listings.

Continuous variables such as age will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), and categorical variables such as gender, race, ethnicity, will be summarized using counts and percentages of subjects.

7.4 Treatment Compliance and Exposure

The duration of drug exposure and % compliance will be summarized by treatment group.

Duration of drug exposure will be calculated for each subject as the last date of dosing minus the first date of dosing + 1. The number and percentage of subjects by treatment group will be summarized according to the following duration-of-exposure categories: ‘< 1 wk’, ‘1 to < 3 wks’, 3 to < 5 wks’ and ≥ 5 wks.’

A subject data listing will be provided.

7.5 Study Endpoints

7.5.1 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.

7.5.2 Key Secondary/Efficacy Endpoints

- Change from baseline in Drop Discomfort VAS score (both eyes assessed together)
    - Summarized and analyzed for change from baseline to 1-minute and 5-minute post instillation, for the AM and PM doses on Visits 2 (randomization), 3, 4 and 5 (15 analyses in addition to the primary endpoint). An overall analysis of all discomfort scores will be undertaken
- Change from baseline in each of the 6 Individual Symptom Severity Assessments (VAS) (both eyes assessed together)
    - Summarized and analyzed for change from baseline to visit 3, 4 and 5. An overall analysis for each VAS incorporating all visits will be undertaken
- Change from baseline of the sum of the Individual Symptom Severity Assessments (VAS Total Symptom Summary Score) (both eyes assessed together)
    - Summarized and analyzed for change from baseline to visit 3, 4 and 5. An overall analysis incorporating all visits will be undertaken
- Change from baseline in SANDE score (both eyes assessed together)
    - Summarized and analyzed for change from baseline to visit 3, 4 and 5. An overall analysis incorporating all visits will be undertaken
- Change in unanesthetized STT score (each eye assessed individually)
    - Summarized and analyzed for change from baseline to visit 4 and 5
- Change from baseline in FCS total score (NEI/Industry Workshop 0-15 scale) Safety Endpoints (each eye assessed individually)
    - Summarized and analyzed for change from baseline to visit 3, 4 and 5. An overall analysis incorporating all visits will be undertaken

7.5.3 Safety Endpoints

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

7.5.4 Exploratory Endpoints

Four additional composite endpoints have been defined as exploratory endpoints. These endpoints will be assessed for each subject in their eye that achieves the worst STT score at baseline. Should a subject have identical STT scores in both eyes at baseline, the eye with the worst FCS score will be used. Should these scores also be equal, the right eye will be used.

- Proportion of patients achieving an improvement from baseline in the STT of ≥ 5mm at visits 4 and 5
- Proportion of patients achieving an improvement from baseline in the STT of ≥ 10mm at visits 4 and 5
- Proportion of patients achieving an improvement from baseline in the STT of ≥ 5mm along with any improvement in FCS total score at visits 4 and 5
- Proportion of patients achieving an improvement from baseline in the STT of ≥ 10mm along with any improvement in FCS total score at visits 4 and 5

7.6 Methods of Analysis

7.6.1 Ordinal and Continuous Variables

All endpoints, other than TEAE, slit-lamp biomicroscopy and ophthalmoscopy, are measured on a VAS or ordinal scale and will be summarized and analyzed as continuous data.

Summaries of scores (absolute and change from baseline) by treatment group will be displayed for each assessment time (where applicable) at each visit. Treatment comparisons will made using a t-test from an ANCOVA model including terms for treatment group, investigator site and baseline score. Results will be summarized by the estimate of treatment difference, a 95% CI for the treatment difference and a p-value. If assumptions are violated, the Wilcoxon rank sum test will be used. If required, transformations may be considered in order to meet the necessary assumptions.

For variables assessed at multiple time points and/or multiple visits the individual analyses will be complemented by an overall supplementary analysis incorporating all data collected for the endpoint in question. Endpoints will be analyzed using a Mixed Effect Model Repeated Measures

(MMRM) analysis with treatment group, visit, treatment-by-visit interaction, baseline score and investigator site included as covariates in the model. Results will be expressed as differences between treatment groups (along with the associated 95% CI). Least Square (LS) means and corresponding 95% CIs for the change in baseline values will be presented for each visit. Where endpoints are collected multiple times within a visit additional covariates will be added to the model. E.g. time post dose (1 minute / 5 minutes) and AM or PM assessment. The model will be fitted using an unstructured covariance matrix. Should this model fail to converge, an autoregressive covariance matrix will be used. The covariance matrix used will be referenced in table footnotes. The Kenward-Roger degree of freedom adjustment will be applied. In order to aid the modelling process it is possible that smaller centers will need to be combined. If necessary, the smallest center will be combined with the next smallest, and so on.

7.6.2 Endpoints measured as a Proportions

The proportion of subjects achieving the endpoint will be summarized at each visit. Results of the proportional endpoints will be expressed as an odds ratio and an associated 2-sided confidence interval for voclosporin compared to Restasis®. The logistic model used will include terms for treatment group, baseline STT score and investigator site. Odds ratios greater than unity will mean the odds of achieving the endpoint are greater for voclosporin than for Restasis® and therefor indicate a benefit of voclosporin. The p-value for the treatment difference will also be reported.

7.6.3 Other Variables

For TEAEs, slit-lamp biomicroscopy and ophthalmoscopy findings, see Safety Evaluations below.

8.0 SAFETY EVALUATIONS

8.1 Adverse Events

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.

For enrolled subjects, all AEs and SAEs will be recorded in the AE section of the subject's eCRF and source documentation.

A treatment emergent adverse event (TEAE) is defined as any AE that has an onset on or after the first dose of IP/study drug and on or before the last dose of IP/study drug plus 3 days. Only treatment-emergent events will be summarized. All events in the clinical database regardless of when they occurred will be provided in data listings i.e., for enrolled subjects, data listings will have screening AEs/SAEs and TEAEs/serious TEAEs. Adverse events will be presented by Medical Dictionary of Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT).

An overall summary will be presented which gives the number and percentage of subjects within each treatment group (n (%)), and the number of events (E) that experienced:

- Any TEAE
- Any Treatment-Related TEAE
- Any Disease-Related TEAE
- Any Serious TEAE
- Any Serious Treatment-Related TEAE
- Any Serious Disease-Related TEAE.
- Any TEAE Leading to Study Drug Discontinuation
- Any Treatment-Related TEAE Leading to Study Drug Discontinuation
- Any Disease-Related TEAE Leading to Study Drug Discontinuation
- Any TEAE with Outcome of Death
- Any Treatment-Related TEAE with Outcome of Death
- Any Disease-Related TEAE with Outcome of Death

In summary tables, ocular AEs recorded once for each eye separately but in the same timeframe will be summarized once at the greater intensity and relationship to study drug. The number and percentage of subjects experiencing one or more events within a MedDRA SOC and PT class without regard to intensity, relationship, or seriousness will be tabulated by treatment group. Additional tables for TEAEs and Serious TEAEs will display events by SOC, PT, and maximum intensity.

The following Adverse Event listings will be provided:

- Listing of TEAEs by treatment group ordered by subject, SOC, PT, and date (study day)
- Listing of serious TEAEs by treatment group ordered by subject, SOC, PT, and onset date (study day)
- Listing of TEAEs leading to study drug interruption or discontinuation
- Listing of TEAEs resulting in death
- Listing of all AEs not classified as Treatment Emergent

8.2 Concomitant Medications

All concomitant medications listed on the case report form will be provided in data listings in the clinical study report. Each medication will be mapped to their corresponding Preferred Term from the ATC-WHO-DD. A frequency distribution of all concomitant medications used during the study will be provided for each treatment group. Medications used prior to randomization but stopped prior to randomization will be summarized separately from those used concomitantly. A subject data listing will be provided.

8.3 Dry Eye History and Medical History

History terms will be classified according to the MedDRA system to the levels of SOC and primary PT.

An overall summary will be presented which gives the number and percentage of subjects within each treatment group that experienced each condition or procedure. A subject data listing will be provided.

8.4 Slit-Lamp Biomicroscopy

The observations from the Slit-Lamp Biomicroscopy will be summarized in frequency tables based on the Normal / Abnormal assessment at each visit for each measure. Shift tables (From: Normal/Abnormal To: Normal/Abnormal) will be provided for each individual assessment as a measure of change from baseline for each visit. A subject data listing will be provided.

8.5 Ophthalmoscopy/Dilated Fundoscopy

The observations from the Dilated Ophthalmoscopy exam will be summarized in frequency tables based on the Normal / Abnormal assessment at each visit for each measure separately. Shift tables (From: Normal/Abnormal To: Normal/Abnormal) will be provided for each individual assessment as a measure of change from baseline for each visit. A subject data listing will be provided.

8.6 Urine Pregnancy Test

A listing of urine pregnancy test results will be provided.

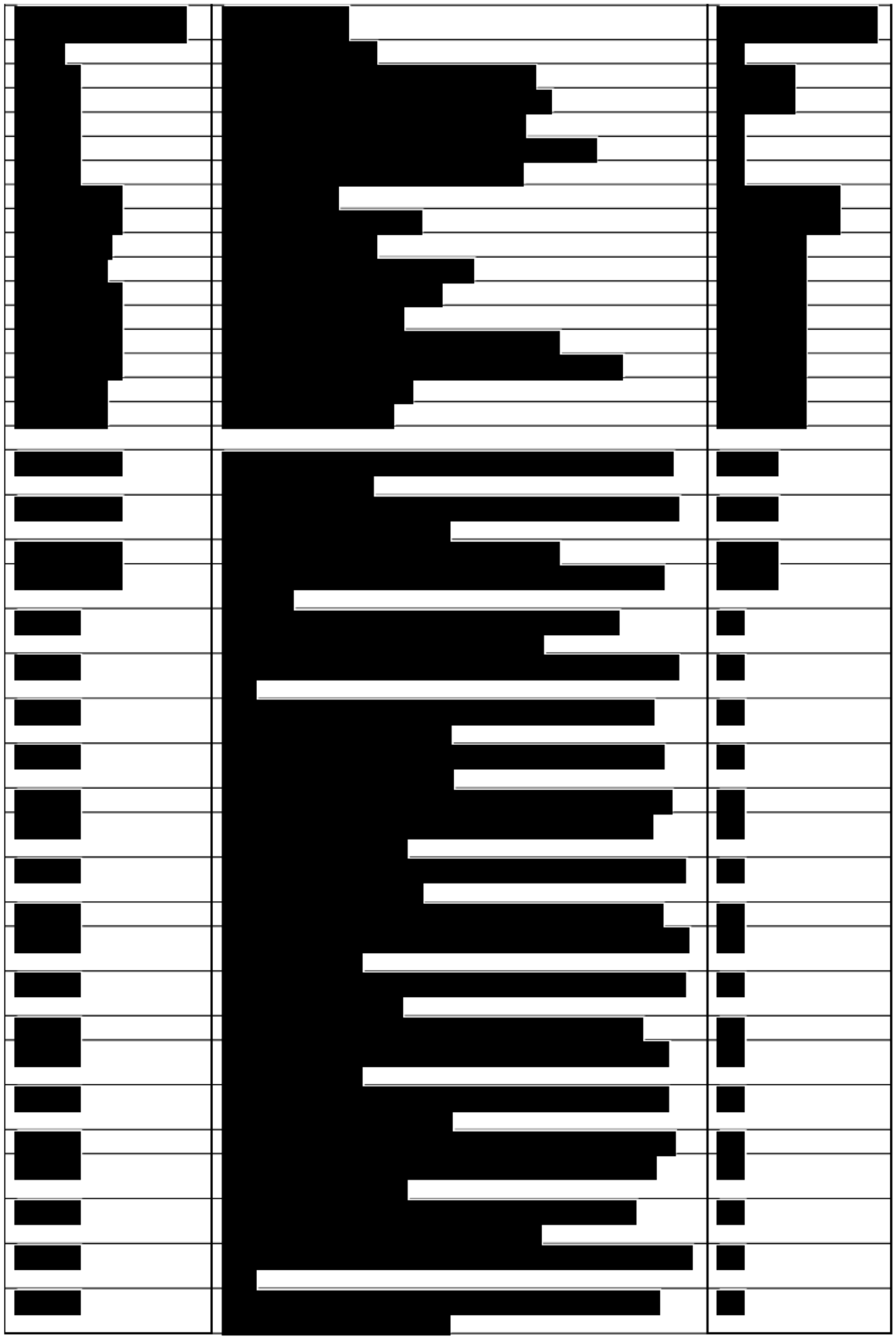
9. CHANGES FROM THE PROTOCOL

Four additional composite endpoints have been defined for analysis that were not defined in the protocol. These composite endpoint use both the STT and the FCS assessments and full details are set out in sections 7.5.4 and 7.6.2.

10. INTERIM ANALYSIS

No interim analyses are planned.

11. TABLES, LISTINGS AND FIGURES



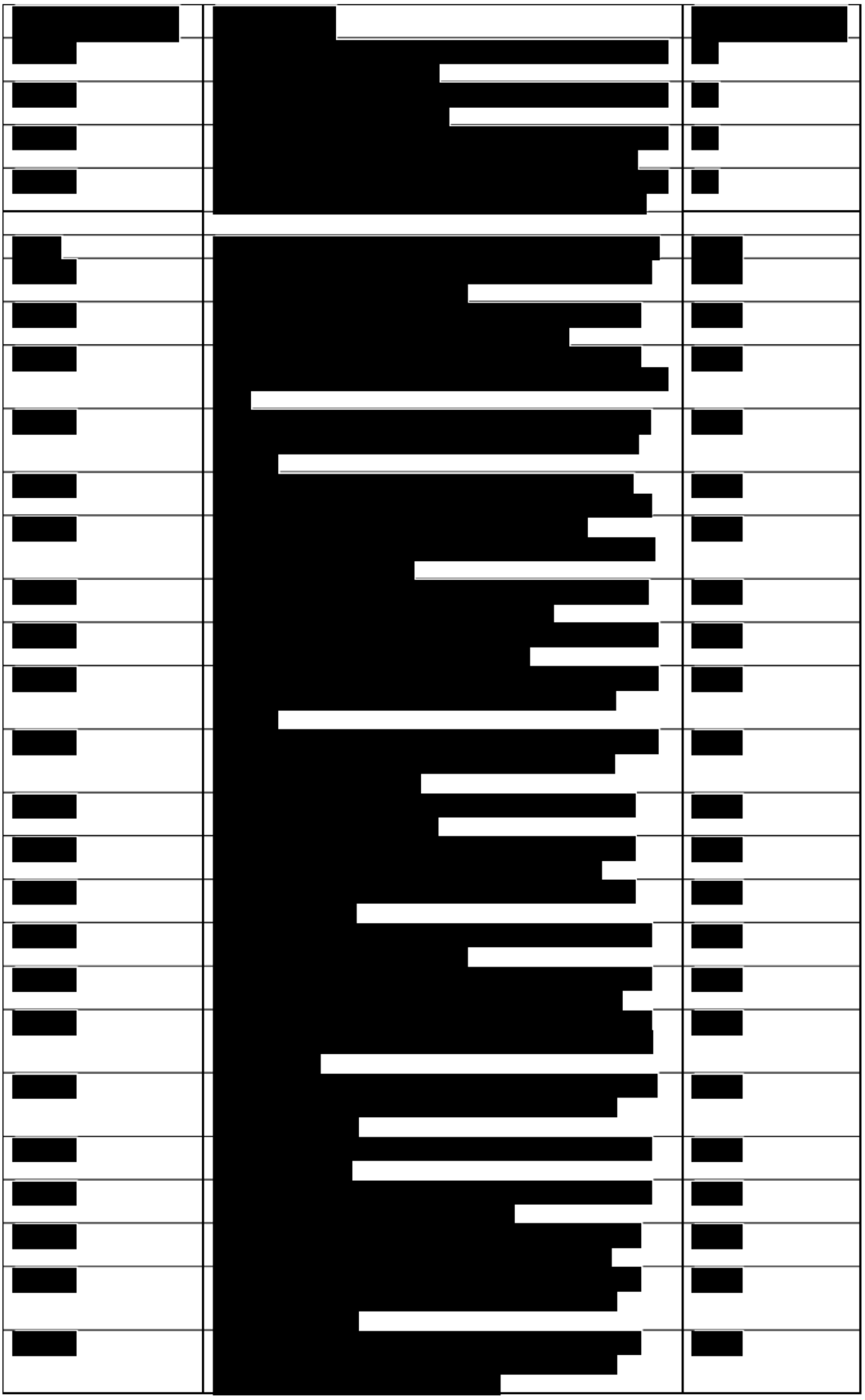


Table Number	Table Title	Population(s)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

List of Listings

Listing Number	Listing Title
[redacted]	[redacted]

APPENDIX 1: 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[1]	Visit 6 Follow-up[2]
Day	**Day -3 to -1**		**Day 1**	**Day 7 (±2 days)**	**Day 14 (±2 days)**	**Day 28 (±2 days)**	**Post-treatment FU (+3 days)**
Informed Consent	✓						
Demography	✓						
Medical/Ophthalmic/ Surgical history	✓						
Eligibility Criteria Assessment	✓	✓					
Concomitant Medications Assessment	✓	✓		✓	✓	✓	✓
Urine Pregnancy Test[3]	✓					✓	
SANDE		✓		✓	✓	✓	
Individual Symptom Severity Assessments using VAS		✓		✓	✓	✓	
BCVA	✓	✓		✓	✓	✓	✓
STT	✓				✓[4]	✓[4]	
Slit-Lamp Biomicroscopy		✓				✓	
FCS		✓		✓[9]	✓[9]	✓[9]	
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[1]	Visit 6 Follow-up[2]
Day	**Day -3 to -1**		**Day 1**	**Day 7 (±2 days)**	**Day 14 (±2 days)**	**Day 28 (±2 days)**	**Post-treatment FU (+3 days)**
OTC Ocular Lubricant Administration at the Study Site	✓	✓					
Randomization			✓				
IP Administration at the Study Site			✓[5]	✓	✓	✓	
Drop Discomfort Assessment at the Study Site		✓[6]	✓[7]	✓	✓	✓	
AE Assessment	✓	✓	✓	✓	✓	✓	✓
IP Dispensation			✓	✓	✓		
Dosing Diary and VAS Scales Dispensation			✓	✓	✓		
Subject Contact for Drop Discomfort Assessment			✓	✓	✓[8]		

Abbreviations: AE=Adverse event; BCVA= Best Corrected Visual Acuity; FCS= Fluorescein Corneal Staining; IP=Investigation Product; OTC=Over-the-counter; SANDE= Symptom Assessment and Dry Eye; STT=Schirmer Tear Test; VAS=Visual Analog Scale.

[1] 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).

[2] Visit 6 should be conducted 3 days after End of Treatment (+3 Day window).

[3] For women of childbearing potential only.

[4] STT should be performed at least 1 hour after IP instillation and at least 20 minutes after FCS.

[5] IP instillation should be performed at least 2 hours after OTC ocular lubricant (Refresh Plus) instillation.

[6] Post OTC ocular lubricant instillation.

[7] Post IP instillation.

[8] Subjects will be contacted by masked site staff the evening of the Visit 4 and in the evening prior to Visit 5.

[9] FCS should be performed after the Drop Discomfort Assessment.