Sponsor:	Ocular Therapeutix, Inc.		
Protocol:	CLN-Protocol-0054		
Document Version No.:	V1.0	**Document Date:**	01-OCT-2021

A randomized, multi-center, double-masked, vehicle-controlled, Phase 1/2 study to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with dry eye disease (DED)

Protocol Number: **(Version Date)**	CLN-Protocol-0054 Version 05 – 03 June 2021
Name of Test Drug:	OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert
Phase:	1/2
Methodology:	A randomized, multi-center, double-masked, vehicle-controlled
Sponsor:	Ocular Therapeutix, Inc. 24 Crosby Drive Bedford, MA 01730 USA
Sponsor Representative:	Alet Van Beek Senior Director, Clinical Operations
Document Date:	01-OCT-2021
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Sponsor:	Ocular Therapeutix, Inc.		
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SIGNATURE PAGE

Protocol Title: A randomized, multi-center, double-masked, vehicle-controlled, Phase 1/2 study to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with dry eye disease (DED)

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Protocol Number: CLN-Protocol-0054

Document Date/Version: 01-OCT-2021 / V1.0

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Date: Oct 3, 2021

Sponsor:	Ocular Therapeutix, Inc.		
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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ABBREVIATIONS

AE	Adverse Event/Experience
AT	Artificial Tears
BCVA	Best Corrected Visual Acuity
C	Celsius
CD	Compact Disc
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
CMO	Chief Medical Officer
CRF	Case Report Form
CRO	Contract Research Organization
CsA	Cyclosporine A
CV	Curriculum Vitae
DED	Dry Eye Disease
DLT	Dose-Limiting Toxicity
e	Electronic
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
F1	Formulation 1 - OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert

F2A	Formulation 2A - OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert
F2B	Formulation 2B (F2B) - Hydrogel Vehicle Insert
F3	Formulation 3 (F3) - Hydrogel Vehicle Insert
FCS	Fluorescein Corneal Scoring
FCS MI	Fully Conditional Specification multiple imputation
FDA	Food and Drug Administration
GCB	Good Clinical Practice
GLP	Good Laboratory Practice
HED	Human Equivalent Dose
HV	Hydrogel Vehicle Insert
ICH	International Council on Harmonization
ICF	Informed Consent Form
ID	Subject Identification
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intra-Uterine Device
KCS	Keratoconjunctivitis Sicca

LogMAR	Logarithm of the Minimum Angle of Resolution
mg	Milligram
ml	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
NDA	New Drug Application
NEI	National Eye Institute
NOAEL	No Observed Adverse Event Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSR	Non-Significant Risk
PP	Per Protocol
PRN	As Needed
OD	Right Eye
OS	Left eye
OSDI	Ocular Surface Disease Index
OTX	Ocular Therapeutix
OTX-CSI	Cyclosporine Ophthalmic Insert
PK	Pharmacokinetics
SAE	Serious Adverse Event/Experience
SPEED	Standard Patient Evaluation of Eye Dryness
SRG	Safety Review Group

SUSAR	Suspected Unexpected Serious Adverse Reactions
TBUT	Tear Film Break Up Time
tCFS	Total Corneal Fluorescein Staining
µg	Microgram
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
VKC	Vernal Keratoconjunctivitis
WOCBP	Women of Child-Bearing Potential

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1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Dry Eye Disease (DED)

Dry eye disease (DED), also known as Keratoconjunctivitis Sicca (KCS), is one of the most common ophthalmic disorders presenting to the clinician (American Academy of Ophthalmology, 2018). Prevalence of dry eye is higher among women than men (Farrand et al, 2017). Prevalence also increases with age with 2.7% of Americans age 18 to 34 years and 18.6% of Americans ≥75 years diagnosed with DED (Farrand et al, 2017).

DED is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort, visual disturbances, tear film instability, and often ocular surface damage (Perry, 2008; Schultz, 2014). In humans, dry eye was found to be associated with the presence of conjunctival T-cells and elevated levels of inflammatory cytokines in the tears compared with controls (Massingale et al, 2009; Lee et al, 2013).

Investigational Product Rationale

In order to address the limitations of topical ophthalmic eye drops, Ocular Therapeutix has developed OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use. OTX-CSI combines the benefits of cyclosporine with punctal occlusion, an effective therapy for DED (McCabe, 2009). OTX-CSI contains approximately 0.36 mg of cyclosporine and is designed to deliver therapeutic levels of cyclosporine onto the ocular surface for a duration of approximately 12 weeks. Continuous release of cyclosporine from the hydrogel inserts may result in higher daily concentrations of cyclosporine delivered to the ocular surface than is found with topical Restasis.

Considering the low cyclosporine concentrations required at the ocular surface, OTX-CSI, offers promise as a potential sustained release treatment for patients with signs and symptoms of DED for approximately 12 weeks with a single insert.

The two active formulations of OTX-CSI being studied in this clinical trial contain the same cyclosporine dose and release drug at the same daily rates but differ in their hydrogel composition. These two formulations are designed to have different breakdown periods of the hydrogel with one formulation designed to last approximately 2 to 3 months (Formulation 1 (F1)) and the other approximately 3 to 4 months (Formulation 2A (F2A)).

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The two HV insert formulations being studied contain no active drug but differ in their hydrogel formulation. These two formulations are designed to have different hydrogel breakdown periods with one formulation designed to last approximately 1 week (Formulation 3 (F3)) and the other approximately 3 to 4 months (Formulation 2B (F2B)).

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a randomized, multi-center, double-masked, vehicle-controlled, phase 1/2 clinical study designed to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with DED. Approximately 145 subjects (290 eyes) will be enrolled in this study at approximately 15 sites in the US.

Subjects will be enrolled in two cohorts. Cohort 1 will be an open-label group consisting of approximately 5 subjects. Cohort 2 will be a randomized, double-masked group consisting of approximately 140 subjects treated with 2 different hydrogel formulations of OTX-CSI and 2 different formulations of hydrogel vehicle inserts (HV). Both eyes will be treated with the same treatment/formulation.

Cohort Number	Number of Subjects	Treatment	Formulation
1 Open-label	5	OTX-CSI	2A
2 Randomized, double-masked	40	OTX-CSI	1
	40	OTX-CSI	2A
	40	HV	2B
	20	HV	3

Cohort 1

Subjects in Cohort 1 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility and eligibility will be re-confirmed at Visit 2 (Insertion/Day 1). The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 1 will be followed until Week 16 (Visit 8) whether or not an insert is visualized.

Cohort 2

Subjects in Cohort 2 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility. At Visit 2 (Insertion/Day 1) eligibility will be confirmed and subjects who are eligible will be randomly assigned to one of four treatment groups (OTX-CSI Formulation 1, OTX-CSI Formulation 2A, HV Formulation 2B or HV Formulation 3) in a 2:2:2:1 ratio. Should only a unilateral insertion be possible, Visit 2B will occur within 3 days to attempt the insertion again. The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5),

Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 2 will be followed until Week 16 (Visit 8) whether or not an insert is visualized.

For both cohorts, if an OTX-CSI or HV insert is visualized in either eye or both eyes at Week 16 (Visit 8) the subject will return to the clinic in 30 days (± 10 days; Visit 9) and will continue returning to the clinic every 30 days as needed until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity. Additionally, subjects may be exited any time at the investigator's discretion. If an OTX-CSI or HV insert cannot be visualized at Week 16 (Visit 8) and the physician has determined that there is no evidence of biological activity, the subject will exit the study.

This study will be conducted per the schedule shown in Figure 1.

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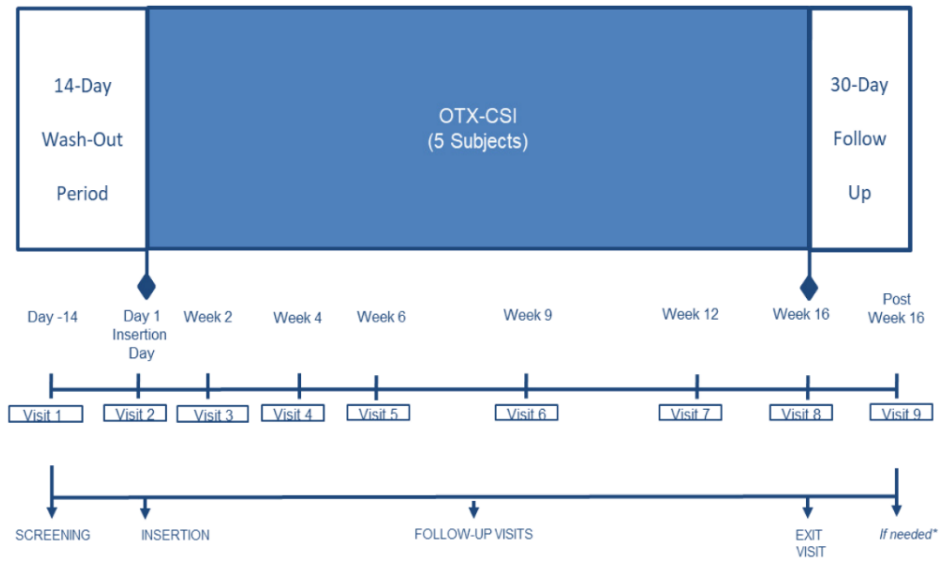
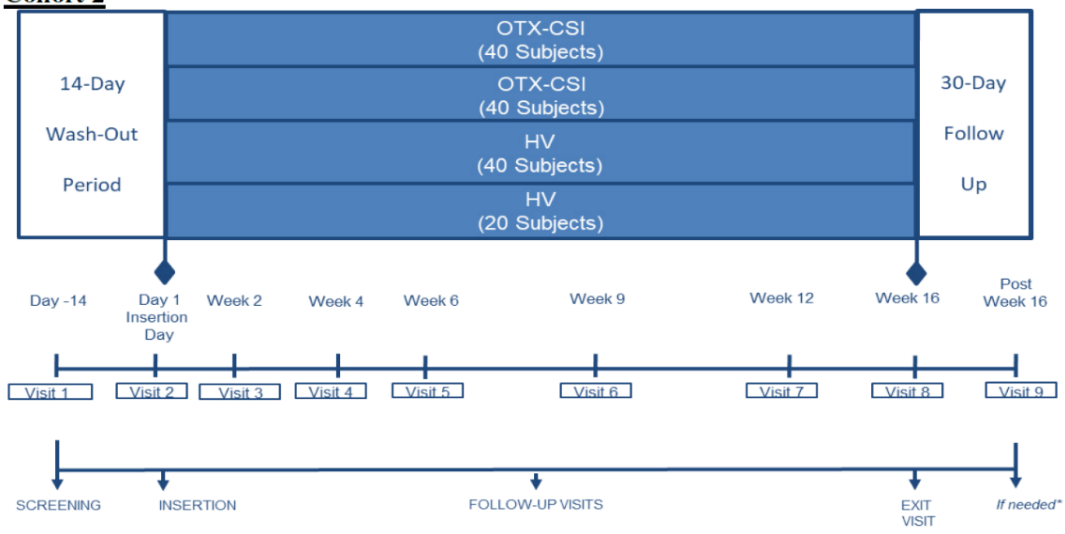
Figure 1 Cohort 1 and Cohort 2 Study Schematic

Cohort 1



*Subject remains in study until insert is no longer visible and no evidence of biological activity.

Cohort 2



*Subject remains in study until insert is no longer visible and no evidence of biological activity.

2.2. Objectives of Statistical Analysis

The objectives of the trial with respect to Cohort 1 are to assess the safety and tolerability of OTX-CSI in subjects with DED. The objectives of the trial with respect to Cohort 2 are to assess the safety, tolerability, and efficacy of OTX-CSI in subjects with DED.

2.3. Randomization Methodology and Masking

Cohort 1 will be open-label and treatment assignment will be known to the sponsor, investigator and subjects. All 5 enrolled subjects in Cohort 1 will receive OTX-CSI Formulation 2A.

Cohort 2 will be randomized to treatment assignment and double-masked.

A randomization schedule will be computer-generated by a qualified biostatistician independent of the study conduct or project team and uploaded into the EDC system. The EDC/IRT system will be used for randomization and unmasking. At Visit 2 (Insertion/Day 1) eligibility will be confirmed and subjects who are eligible will be randomly assigned to one of four treatment groups (OTX-CSI Formulation 1, OTX-CSI Formulation 2A, HV Formulation 2B or HV Formulation 3) in a 2:2:2:1 ratio.

The HV and OTX-CSI inserts administered to subjects at randomization in the double-masked treatment phase will be comparable in appearance. Study subjects and investigators and their staff will be masked to the identity of treatment until the final database is locked. The Sponsor's personnel involved with the conduct and monitoring of the study will remain masked until completion of the study and database lock.

2.4. Stopping Rules and Unmasking

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor.

If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data to the two individuals in the Safety Review Group (Sponsor Medical Monitor and Sponsor Statistician) who are not involved in the study conduct or directly by the investigator if required in an emergency.

2.5. Study Procedures

The Time and Events Schedule, as outlined in the study protocol, is provided in Table 1.

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Table 1 Time and Events Schedule

Study Parameter*	Screening/ Baseline Visit Day -14	Insertion Day Day 1	Follow-up Week 2 ±2 days	Follow-up Week 4 ±2 days	Follow-up Week 6 ±3 days	Follow-up Week 9 ±3 days	Follow-up Week 12 ±3 days	Final Visit Week 16[8] ±3 days	30-Day Follow-Up Visit[9] (± 10 days)
Visit	1	2	3	4	5	6	7	8	9
Informed Consent	X								
Determine Eligibility	X	X							
Demographic Information	X								
Medical/Ophthalmic History	X								
Record Medications	X	X	X	X	X	X	X	X	X
Record Adverse Events[10]		X	X	X	X	X	X	X	X
Urine Pregnancy Test[1]	X							X	
OSDI	X	X	X	X	X	X	X	X	X
VAS for Eye Dryness	X	X	X	X	X	X	X	X	X
SPEED	X	X	X	X	X	X	X	X	X
Corneal Fluorescein Staining Using the NEI Scale	X	X	X	X	X	X	X	X	X
Conjunctival Lissamine Green Staining Using the NEI Scale	X	X	X	X	X	X	X	X	X
Assessment of BCVA	X	X	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy (including punctum assessment)	X	X[4]	X	X	X	X	X	X	X
OTX-CSI or HV Insert Presence by Visual Assessment			X	X	X	X	X	X	X
Ease of Visualization as assessed by Investigator			X	X	X	X	X	X	X
Systemic PK sample collection[2] (at selected sites)		X[5]	X						
Tear Film PK sample collection[7] (at all sites)		X[6]	X	X	X	X	X	X	X
Measurement of TBUT	X	X			X		X		
Schirmer Test (without anesthesia)	X	X	X	X	X	X	X	X	X
IOP Measurement	X	X						X	
Fundus Exam[3]	X							X	
Punctum Size Assessment		X						X	

Table 1 Time and Events Schedule – continued

Study Parameter*	Screening/ Baseline Visit Day -14	Insertion Day Day 1	Follow-up Week 2 ±2 days	Follow-up Week 4 ±2 days	Follow-up Week 6 ±3 days	Follow-up Week 9 ±3 days	Follow-up Week 12 ±3 days	Final Visit Week 16[8] ±3 days	30-Day Follow-Up Visit[9] (± 10 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Randomization (Cohort 2)		X							
OTX-CSI or HV Insert Placement		X[11 & 12]							
Ease of Insertion as assessed by the Investigator		X							
Dispense Artificial Tears (as needed)	X	X	X	X	X	X	X		
Dispense Daily Subject Diary for Artificial Tear Use (as needed)	X	X	X	X	X	X	X		
Collect/review Daily Subject Diary for Artificial Tear Use (as needed)		X	X	X	X	X	X	X	

*All examinations need to be performed on both eyes. See Section 8.4 to confirm the order that the assessments should be performed.

1 A negative UPT is required for women of childbearing potential to be included in the study.
2 Select sites will collect Systemic PK. All sites will collect Tear Film PK.
3 Dilated fundus examination at screening; undilated fundus examination at Week 16.
4 Prior to insertion, a clinical determination of the absence of infection will be made based on the lack of erythema or discharge at the punctum.
5 Systemic PK sample on Day 1 will be collected after successful insertion at 2 hours (±30 minutes) **or** 4 hours (±30 minutes) post-insertion.
6 Tear Film PK will be collected at 1 hour (±30 minutes), 2 hours (±30 minutes), and 4 hours (±30 minutes) post insertion on Day1. Tear Film PK should be collected using Schirmer strips.
7 Tear Film PK will be collected using Schirmer Tests strips. These will be collected and sent to the central lab for analysis. See lab manual.
8 Early termination subjects should complete assessments based on the final visit (Visit 8) schedule of assessments.
9 Post week 16 visit will be conducted every 30 days (± 10 days) until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity. Additionally, subjects may be exited at the investigator's discretion
10 Signs, symptoms, conditions occurring prior to insertion on Day 1 should be captured as medical history.
11 For Cohort 1 subjects only, within the first six weeks post treatment, if an insert is not visualized in one or both eyes by the Investigator, the Investigator should place a new insert in the respective eye(s) after confirming patency. Refer to Appendix 13 for placement instructions. Replacement of inserts for Cohort 2 subjects is not permitted.
12 If placement is only successful in one eye, subjects should be asked to return within 1-3 days to attempt insertion in the other eye. The following items should be repeated at the return visit, Insert Placement, Ease of Insertion, Tear Film PK and AEs.

2.6. Efficacy and Safety Variables

2.6.1. Efficacy Variables

2.6.1.1. Primary Efficacy Variable

1- Schirmer Test (mm) and its change from baseline (CFB) at Week 12

2.6.1.2. Secondary Efficacy Variables

1- Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline at Week 12
2- Eye Dryness Severity and Frequency Scores (VAS) and their CFB to each post-baseline visit.
3- Schirmer Test (mm) and its change from baseline (CFB) to each post-baseline visit.
4- Total Corneal Fluorescein Staining (tCFS) using National Eye Institute (NEI) scale and its CFB to each post-baseline visit.
5- CFS sub-regions using NEI scale and its CFB to each post-baseline visit.
6- Conjunctival Lissamine Green Staining using NEI scale and its CFB to each post-baseline visit.
7- Ocular Surface Disease Index questionnaire (OSDI©) (total score, each of the three domains and the individual questions) and its CFB to each post-baseline visit.
   - OSDI total score will be calculated using below OSDI© formula:

$$Overall\ OSDI\ score\ = \frac{(Sum\ of\ scores\ for\ all\ questions\ answered)\ \times\ 25}{number\ of\ questions\ answered}$$

   - OSDI score for each section (ABC) will be calculated using below formula:

$$OSDI\ score\ for\ each\ section\ (A,B,C) = \frac{(Sum\ of\ scores\ for\ all\ questions\ answered\ for\ the\ section)\ \times\ 25}{number\ of\ questions\ answered\ in\ that\ section}$$

   The OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability.
8- SPEED measures (overall score and individual questions) and its CFB to each post-baseline visit.
   - SPEED overall score will be calculated as Sum of the questions in frequency and severity of symptoms.

The final score ranges from 0 to 28, with higher scores representing the severe dryness.

2.6.2. Safety Variables

The safety variables are as follows:

1- Ocular and non-ocular adverse events
2- Best Corrected Visual Acuity (BCVA): LogMAR Visual Acuity (VA) score at each visit and its CFB at each post-baseline visit
3- Slit-Lamp biomicroscopy parameters by location (Eyelid Vascularity (vascular engorgement), Vascular, Engorgement of Eyelid Margin of upper and lower lid, Punctal Appearance, Lid Apposition, Lashes, Conjunctiva, Sclera, Cornea, Anterior Chamber, Iris, Pupil, Lens) by visit
4- Intraocular Pressure (IOP) measurement (mmHg) and its CFB by visit
5- Fundus Examination: Vitreous, Retina, Macula, Choroid, Optic nerve by visit
6- Artificial tears use during the study: the use of Artificial tears since last visit at each post-baseline visit.

3. SUBJECT POPULATIONS

3.1. Population Definitions

1. **Intent-to-Treat (ITT):** The ITT population will include all randomized subjects.

2. **Modified Intent-to-Treat (mITT)**: the Modified ITT population is defined as all subjects in ITT who received the insert, investigational product (IP) (OTX-CSI or HV). The mITT population will be used as the primary efficacy analysis population and will be performed for all efficacy endpoints.

3. **Per Protocol (PP):** includes all mITT subjects who do not have any major protocol deviation which is likely to seriously affect the safety and efficacy outcomes of the study and who do not report excessive artificial tear use defined as greater or equal to 60 drops between Week 9 (Visit 6) and Week 12 (Visit 7). Analysis on the PP population will be used as secondary efficacy analysis and will be performed for select efficacy endpoints, analyzing subjects under the treatment actually received. Important protocol deviations will be identified prior to locking the study database.

4. **Safety Set (SAF):** includes all subjects who received investigational product (IP) (OTX-CSI or HV) from Cohort 1 and Cohort 2. Analyses performed on the Safety population will be according to the treatment the subject actually received.

5. **Cohort 1 population:** Cohort 1 population will include all subjects who received IP. Demographic and baseline characteristics, other ocular examination data, and safety data will be summarized.

3.2. Protocol Deviations

At the discretion of the sponsor, major protocol deviations as determined by a review of the data prior to unmasking of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the PP Population. This file will include a description of the protocol deviations, and classification of major or minor protocol deviations. It will be finalized prior to hard database lock and unmasking. Major protocol deviations will be summarized by treatment groups and overall. The data listing for all protocol violations will be also presented.

4. STATISTICAL METHODS

4.1. Sample Size Justification

No formal sample size calculations were performed. The proposed sample size will allow for initial estimates of efficacy as well as provide for sufficient safety information to be obtained, while still limiting the number of subjects exposed to the IP.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted, and labeled according to the International Council on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters. For categorical variables, summary tabulations of the number of missing, and number and percentage of each category of the parameter will be presented by treatment groups and visits (as applicable). For continuous variables, the n, mean, standard deviation, median, minimum, and maximum values will be presented.

The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. Differences between treatment groups will be calculated as OTX-CSI minus HV, and change from baseline will be calculated as follow-up visit minus baseline visit values.

All statistical testing will be done at the two-sided alpha level of 0.05.

4.2.2. Unit of Analysis

Both eyes will be treated with the same treatment/formulation. If both eyes qualify, the eye having the higher total corneal fluorescein staining score will be designated as the study eye and the other eye designated as the non-study eye. If both eyes have the same total corneal fluorescein staining score, the study eye will be designated randomly, and the other eye designated as the non-study eye. If only one eye qualifies, that eye will be the study eye, but both eyes will still receive the same treatment/formulation.

The unit of analysis in this study will be the study eye (primary study eye) for all efficacy summaries. Efficacy summaries will be presented for both study and non-study eyes for Cohort 1 and Cohort 2. Cohort 1 will be included for all safety summaries and will include summaries of both study and non-study eyes. All primary, sensitivity, secondary, and exploratory endpoints will be analyzed for both study and non-study eyes, separately. All summaries will be presented by treatment groups and visits, where appropriate. In addition to summarizing the individual formulations, the two formulations of OTX CSI will be combined and summarized.

4.2.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coding using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 - Mar 2021. Concomitant medications will be coded using World Health Organization (WHO) DD B3 WHO Drug DDE – Sep 2019.

4.2.4. Methods of Pooling Data

The two OTX formulations will be combined and summarized as well as individual formulations.

4.2.5. Adjustments for Covariates

The statistical modeling of change from baseline for each variable will be adjusted for its baseline value.

4.2.6. Multiple Comparisons/Multiplicity

As this is a Phase 1/2 study, no adjustments to alpha will be made for testing of multiple endpoints.

4.2.7. Subpopulations

No analyses of subgroups of subjects are planned.

4.2.8. Withdrawals, Dropouts, Loss to Follow-up, replacement

Any subject who wishes to voluntarily discontinue study drug or withdraw from participation in the study for any reason is entitled to do so without obligation.

IP may be discontinued (insert removed) and any subject may be discontinued from study participation at any time during the study at the discretion of the Investigator or the Sponsor for any reason.

In the event that study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have the subject complete Visit 8 assessments as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

Subjects who withdraw from Cohort 1 will be replaced. Subjects who withdraw from Cohort 2 will not be replaced.

4.2.9. Missing, Unused, and Spurious Data

If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The imputed dates will only be used to classify events as treatment emergent and will only be used in the table analyses. Listings will display the available date data.

The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will only be excluded as being treatment-emergent if the start month/year is before the month/year of study drug administration or if the date of resolution is before study drug administration.
- If the start day and month are missing but the start year is complete, an AE will only be excluded as being treatment-emergent if start year is before the year of study drug administration or if the date of resolution is before study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the date of resolution is before study drug administration.

4.2.9.1. Imputation Method for Efficacy Endpoints

To impute missing, Markov Chain Monte Carlo (MCMC) multiple imputation (MI), Fully Conditional Specification multiple imputation (FCS MI) and last observation carried forward (LOCF) methods will be used.

For MI, we will have below phases:

1. Imputation Phase: in this phase, the missing data will be imputed using SAS PROC MI and a complete data set will be created. This process of imputation will be repeated 25 times. Therefore, 25 compete datasets will be created. In this phase, treatment group, baseline value, and post-baseline visits from visit 3 to visit 8, respectively, will be included in multiple imputation model.

2. Analysis Phase: each of the 25 complete data sets will be analyzed independently using desired statistical method (e.g. ANCOVA for primary efficacy analysis).

3. Pooling Phase: in this phase the estimates obtained from each analyzed complete dataset from phase 2, will be combined using PROC MIANALYZE.

The analysis of efficacy variables Schirmer Test, Eye Dryness Severity Score and Eye Dryness Frequency Score on mITT and PP populations will be performed by imputing missing data using MCMC MI methodology with repeated 25 times of imputation under the assumption of missingness at random. Last observation carried forward (LOCF) method and Fully Conditional Specification multiple imputation (FCS MI) with 200 burn-in iterations and 25 times of imputation under the assumption of missingness at random will be used for sensitivity analyses (Section 4.7.2). LOCF method will be used for sensitivity analyses.

4.2.10. Visit Windows

Visit windows will be calculated based on the schedule of assessments in Table 1. Any visits or procedures performed outside the scheduled visits must be documented in the Unscheduled Visit page of the eCRF. Although there is a visit window around the expected visit date, nominal visits will be used for the per-visit analyses.

4.3. Interim Analyses

An interim analysis was not planned for this study.

4.4. Subject Disposition

A summary of subject disposition will be tabulated, including the number screened and screened failure, and procedural screen failures will be presented. Subjects are considered procedural screen failures if the investigator is unsuccessful at placing the OTX-CSI or HV intracanalicular ophthalmic insert in both eyes (i.e. neither eye has an insert). The number and percentage of subjects included in each of the analysis populations (ITT, mITT, PP, SAFETY) will be presented by treatment groups and overall. Subject disposition events including randomization, treated, completed study, withdrawal prior to completing the study, and reasons for withdrawal will be summarized by treatment groups and overall.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized for the mITT and Cohort 1 populations, separately, using descriptive statistics. Demographic characteristic information will include Gender (Male, Female), Age (year), Ethnicity (Hispanic or Latino, Not Hispanic or Latino), and Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown, Other).

Demographic and Baseline data will be provided in data listings.

4.5.1. Baseline Ocular Assessments

The following baseline assessments will be presented using descriptive statistics for mITT and Cohort 1 populations, separately, by treatment group and overall.

The assessments below will be presented at the eye level (study eye and non-study eye):

1. Unanesthetized Schirmer's Test
2. Corneal Fluorescein Staining (tCFS)
3. CFS sub-regions using NEI scale
4. Conjunctival Lissamine Green Staining (CLGS)
5. CLGS sub-regions
6. Tear Film Break Up Time (TFBUT)
7. Best Corrected Visual Acuity (BCVA) LogMAR Score
8. IOP Measurement (mmHg)

The assessments below will be presented at the subject level:

1. Eye Dryness Severity (VAS) Score
2. Eye Dryness Frequency (VAS) Score
3. OSDI total score (0-100) and the scores of three domains
4. SPEED Total Score (0-28)

4.5.2. Ocular and Non-Ocular Medical History

Medical history, including ocular medical history, will be coded using the MedDRA Version 24.0 - Mar 2021. Non-ocular medical history will be summarized in the mITT and Cohort 1 populations, separately, by system organ class (SOC) and preferred term (PT) by treatment group and overall. SOC will be sorted alphabetically. PT will be sorted by descending frequency overall within each SOC. Subjects with a particular medical history event or medical history class will be counted once at the PT level and once at the SOC level. Ocular medical history will be summarized at the eye and subject levels by treatment group and overall, for the mITT and Cohort 1 populations, separately, with separate summaries for the study eye and non-study eye.

Data listings will be provided for medical history as well.

4.6. Treatment Exposure

Details of study drug administration, including duration of treatment will be tabulated and presented in the Safety population. The duration of exposure will be calculated in days as latest date investigator confirms insert is not present in either eye minus date of the earliest insertion in either eye plus 1 and summarized using descriptive statistics by treatment group and overall. Treatment exposure for subjects who discontinue the study prior to the insert no longer being present in both eyes, will be calculated in days as date of last insert visualization in either eye minus date of the earliest insertion in either eye plus 1. In addition, treatment exposure for subjects who discontinue the study prior to the insert no longer being present in both eyes will be set to the longest observed insert exposure in the applicable cohort as an additional analysis.

All dosing information will be presented in a data listing.

4.7. Efficacy Evaluation

The efficacy summaries and analyses will be presented for both study and non-study eyes for Cohort 2 only.

The Primary efficacy analysis of the Schirmer test will be conducted using the mITT and PP populations. All the efficacy parameters, with the exception of categorical Schirmer test evaluation (i.e., ≥10 mm increase in Schirmer) and the categorical BCVA evaluation (i.e. Loss of 3 lines of vision), will be analyzed as continuous variables. Their absolute values at each timepoint (Visit 1, Visit 2, Baseline, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, and 30-Day Follow-Up), and change from baseline to each post-baseline visit will be summarized using descriptive statistics (the number of subjects, mean, SD, median, minimum and maximum) by treatment group and overall. The number and percentage of subjects with ≥10 mm increase from baseline in Schirmer test and loss of 3 lines of vision based on BCVA at each post-baseline visit will be tabulated by treatment group and overall. The results for 30-Day Follow-Up visits will be reported only for observed data.

4.7.1. Primary Analyses

For the primary efficacy endpoint analyses of Schirmer Test change from baseline, the following modeling and analyses will be performed on MCMC MI of mITT population:

A linear model with fixed effects of treatment (four individual formulations) and baseline Schirmer test value as covariate will be used to compare different formulations in terms of Schirmer Test change from baseline at Visit 7 (Week 12) and all other post-baseline visits (Visit 3, Visit 4, Visit 5, Visit 6, and Visit 8). In the linear model, least square means treatment group comparison of CSI Formulation 1 to HV Formulation 2B, CSI Formulation 2A to HV Formulation 2B, CSI Formulation 1 to HV Formulation 3, CSI Formulation 2A to HV Formulation 3, will be reported. This model will also be used to compare overall OTX-CSI (combined Formulation 1 and Formulation 2A using sample size weights of Formulation 1 and Formulation 2A as coefficients for the parameters in least square means treatment group comparison) to each HV Formulation (2B and 3). Unadjusted treatment group analyses using two-sample t-test will be run on these treatment group combinations.

These analyses will also be performed on the PP population.

4.7.2. Sensitivity Analyses

To determine robustness of results, the sensitivity analyses will be performed for the primary efficacy endpoint, Schirmer test at visit 7 (week 12) and all other post-baseline visits (Visit 3, Visit 4, Visit 5, Visit 6, and Visit 8), on the mITT and PP populations by using:

1. last observation carried forward (LOCF)
2. observed data only
3. FCS MI.

As sensitivity analyses, LOCF, observed data, and FCI MI will be analyzed in a manner similar to the primary efficacy variable (details in section 4.7.1). For the unadjusted treatment group comparisons analyses using LOCF and observed data, in addition to t-test, Wilcoxon rank sum test will be run on the treatment group combinations.

4.7.3. Secondary Analyses

1. To analyze the efficacy endpoint of percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline at Visit 7 (Week 12) and other Post-Baseline Visits, the logistic regression or Fisher's exact test will be used as described below:

   The two groups of Schirmer test (≥10 mm vs <10 mm) will be compared between treatment groups as CSI Formulation 1 to HV Formulation 2B, CSI Formulation 2A to HV Formulation 2B, CSI Formulation 1 to HV Formulation 3, CSI Formulation 2A to HV Formulation 3, will be reported. This model will also be used to compare overall OTX-CSI (combined Formulation 1 and Formulation 2A) to each HV Formulation (2B and 3) using the logistic regression.

   The above analyses will be performed on the change from baseline in Schirmer test (≥10 mm vs <10 mm) derived based on the imputed Schirmer data using FCS MI (details in section 4.2.9.1) at visit 7 on the mITT and PP populations using the logistic regression and Odds Ratio (OR), 95% confidence interval for OR, and P-value for OR will be reported. In addition, sensitivity analyses will be done using LOCF and observed data and the two groups of Schirmer test (≥10 mm vs <10 mm) will be compared between treatment groups using the Fisher's exact test on this endpoint. These analyses will also be performed on all post-baseline visits.

2. To analyze the efficacy endpoints of Eye Dryness Severity and Eye Dryness Frequency, statistical modeling similar to the primary efficacy endpoint analysis (4.7.1) will be performed for each post-baseline visit (Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8)

using the MCMC MI imputed data on the mITT and PP populations. In addition, sensitivity analyses done for the primary efficacy endpoint will also be performed on this endpoint.

3. To analyze the efficacy endpoints of total Corneal Fluorescein Staining (tCFS) and its sub-region, statistical modeling similar to the primary efficacy endpoint analysis (4.7.1) will be performed for each post-baseline visit (Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8) using the MCMC MI imputed data on the mITT and PP populations. In addition, sensitivity analyses done for the primary efficacy endpoint will also be performed on this endpoint.

The rest of secondary efficacy endpoint analysis of below parameters will be done similar to analysis of Schirmer test using observed data, for each post-baseline visit (Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, and30-Day Follow-Up) on mITT and PP populations using observed data:

1. Conjunctival Lissamine Green Staining using NEI scale

2. Ocular Surface Disease Index questionnaire (OSDI©) (total score, each of the three domains and the individual questions)

3. SPEED measures (overall score and individual questions) and its CFB

4.7.4. Exploratory Analyses

The exploratory analyses will be done on mITT populations for both study and non-study eye.

The Tear Film Break Up Time at Week 12 and its CFB will be summarized using descriptive statistics (the number of subjects, mean, SD, median, minimum and maximum) by treatment group and overall. Tear Film Break Up Time at Week 12 will be analyzed similar to analysis of Schirmer test using observed data.

Ease of insertion as assessed by the Investigator at Visit 2 or Visit 2B, presence of insert and ease of visualization as assessed by the Investigator at all post-baseline visits will be summarized using discrete statistics (number and percentage) and will be tested between treatment groups (CSI Formulation 1 to HV Formulation 2B, CSI Formulation 2A to HV Formulation 2B, CSI Formulation 1 to HV Formulation 3, CSI Formulation 2A to HV Formulation 3, will be reported. This model will also be used to compare overall OTX-CSI (combined Formulation 1 and Formulation 2A) to each HV Formulation (2B and 3). To analyze ease of insertion as assessed by the Investigator and ease of visualization as assessed by the Investigator, Pearson Chi-squared test will be used. To analyze presence of insert, Fisher's exact Test will be used.

4.8. Pharmacokinetic Evaluations

PK analysis will be described separately.

4.9. Safety Analyses

All safety analyses will be conducted on the Safety Population.

Adverse Events

Adverse events will be coded using the MedDRA Version 24.0 - Mar 2021 and displayed in tables and listings using System Organ Class (SOC) and Preferred Term (PT).

Analyses of adverse events will be performed for those events that are considered treatment emergent adverse events (TEAE), where treatment emergent is defined as any adverse event with onset on or after the first dose of study medication through the end of the study or any event that was present at baseline but worsened in intensity or was considered drug-related by the investigator through the end of the study.

The safety will be assessed by incidence of TEAEs, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term). An overall summary of TEAEs will be presented including the number of events and the number of the subjects with events along with percentages by treatment group and overall. The overall summary will include subjects with AE leading to death, subjects with TEAEs leading to insert removal and subjects with TEAEs leading to subject withdrawal. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count based on the total column.

The frequency and percentage of subjects with any TEAEs and separately for ocular and non-ocular TEAEs, with any ocular TEAEs by relationship to treatment (unrelated, related), with any ocular serious TEAEs by relationship to treatment (unrelated, related), with any TEAE by severity (mild, moderate, or severe), and with any serious adverse event (SAE) and separately for ocular and non-ocular events will be summarized by treatment group and overall.

All adverse events will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to withdrawal.

Non-AE Safety Analyses

The following safety assessments will be summarized using descriptive statistics for Safety population by treatment group and overall. Assessments will be presented for study eye and non-study eye separately.

1- Best Corrected Visual Acuity (BCVA)

LogMAR Visual Acuity (VA) score for each visit, its CFB, and loss of 3 Lines or more in BCVA LogMAR Score from Baseline at each post-baseline visit will be calculated and summarized using descriptive statistics.

2- Slit-Lamp biomicroscopy

The evaluation of normal, mild, moderate, severe, and very severe for each eye in Eyelid Vascularity (vascular engorgement) and Vascular Engorgement of Eyelid Margin of upper and lower lid, as well as normal, abnormal non-clinically significant, and abnormal clinically significant for each eye in Punctal Appearance, Lid Apposition, Lashes, Conjunctiva, Sclera, Cornea, Anterior Chamber, Iris, Pupil, and Lens will be tabulated for each visit by using the frequency and percentage.

3- Intraocular Pressure (IOP) measurement (mmHg)

Absolute value at baseline and visit 8 (week 16), its CFB, absolute IOP measurement ≥ 30 mmHg at each visit, and CFB in IOP > 5 mmHg as well as >10 mmHg at Visit 8 will be summarized using descriptive statistics.

4- Fundus Examination

The evaluation of normal, abnormal non-clinically significant, and abnormal clinically significant for each eye in vitreous, retina, macula, choroid, and optic nerve exam will be tabulated for visit 1 and visit 8 by using the frequency and percentage. The absolute cup-to-disc ratio at baseline and Visit 8 (Week 16) and its CFB at Visit 8 (Week 16) will be presented using descriptive statistics.

5- Artificial tears use during the study

The use of artificial tears, based on the Daily Subject Diary, since last visit will be tabulated for each post-baseline visit by using frequency and percentage. Number of times AT used since last visit will be reported among all subjects who have any daily subject dairy data since the last visit using descriptive statistics.

4.9.1. Laboratory Data

Safety laboratory tests will not be collected. Urine pregnancy test results will be captured at Visit 1 and Visit 8 (Week 16). Urine pregnancy test results will be provided in data listing.

4.9.2. Vital Signs and Physical Examinations

Vital signs and physical examinations data will not be collected.

4.9.3. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary, WHO DD B3 WHO Drug DDE – Sep 2019. Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term.

Concomitant medications will be defined as those medications that were initiated after study drug administration or those that were ongoing at the time of study drug administration. If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period.

Non-ocular prior and concomitant medications will be summarized by higher ATC level 3 (therapeutic subgroup) and preferred term by treatment group and overall, in the Safety population. ATC Level 3 terms will be sorted alphabetically. Preferred terms will be sorted by descending frequency overall within ATC Level 3 term. Subjects receiving a particular medication or medication of ATC Level 3 will be counted once at the preferred term level and once at ATC Level 3.

Ocular prior and concomitant medications will be summarized at the eye level, separately for study and non-study eyes, and at the subject level (both eyes) by ATC Level 3 and preferred term by treatment group and overall, in the Safety population.

All prior and concomitant medications information will be presented in the data listing.

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5. CHANGES TO PLANNED ANALYSES

The language in the SAP will supersede the language in the protocol should there be a discrepancy.

The primary analysis will be repeated for all visits using observed data (without imputation) for both mITT and PP populations. These results will be provided in sensitivity analyses section.

The difference between two OTX-CSI hydrogel formulations as well as the difference between two HV formulations will not be studied. HV formulations will not be combined.

Wilcoxon rank sum test will be used only to analyze LOCF and observed data.

For Eye Dryness Severity and Eye Dryness Frequency, as well total Corneal Fluorescein Staining (tCFS) and its sub-region the main analysis will be based on MCMC MI and sensitivity analyses will be done using LOCF, observed data, and FCS.

For the first secondary efficacy endpoint analysis, for the main analysis, the two groups of change from baseline in Schirmer test (≥10 mm vs <10 mm) at visit 7 will be compared between treatment groups using the logistic regression and for the sensitivity analyses, the groups will be compared using LOCF and observed data by Fisher's exact test; Clopper-Pearson method will be used to calculate 95% confidence interval of the proportion of subject with change from baseline in Schirmer Test ≥ 10 mm; to calculate 95% confidence interval of the proportion difference, the Chan and Zhang (1999) method will be used.

These analyses will also be performed on all post-baseline visits.

6. REFERENCES

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7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be Generated

Table 14.1.1: Overall Disposition and Subject Accountability – All Subjects Screened

Table 14.1.2: Overview of Analysis Sets

Table 14.1.3: Major Protocol Deviations – mITT and Cohort 1

Table 14.1.4: Demographic and Baseline Characteristics – mITT and Cohort 1

Table 14.1.5: Ocular Characteristics at baseline - mITT and Cohort 1

Table 14.1.6.1: Study Eye Ocular Medical History - mITT and Cohort 1

Table 14.1.6.2: Non-Study Eye Ocular Medical History – mITT and Cohort 1

Table 14.1.6.3: Non-ocular Medical History – mITT and Cohort 1

Table 14.1.7.1: Study Eye Ocular Prior Medications – SAFETY

Table 14.1.7.2: Non-Study Eye Ocular Prior Medications – SAFETY

Table 14.1.7.3: Non-ocular Prior Medications – SAFETY

Table 14.1.7.4: Study Eye Ocular Concomitant Medications – SAFETY

Table 14.1.7.5: Non-Study Eye Ocular Concomitant Medications – SAFETY

Table 14.1.7.6: Non-ocular Concomitant Medications – SAFETY

Table 14.1.8: Treatment Exposure – SAFETY

Table 14.2.1.1.1: The Summary and Linear Model with MCMC Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.1.1.2: The Summary and Linear Model with MCMC Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.1.1.3: The Summary and Linear Model with MCMC Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.1.1.4: The Summary and Linear Model with MCMC Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.2.1.1: The Summary and Linear Model with Last Observation Carried Forward (LOCF) of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.2.1.2: The Summary and Linear Model with Last Observation Carried Forward (LOCF) of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.2.1.3: The Summary and Linear Model with Last Observation Carried Forward (LOCF) of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.2.1.4: The Summary and Linear Model with Last Observation Carried Forward (LOCF) of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.2.2.1: The Summary and Linear Model of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT (Observed data)

Table 14.2.2.2.2: The Summary and Linear Model of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP (Observed data)

Table 14.2.2.2.3: The Summary and Linear Model of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT (Observed data)

Table 14.2.2.2.4: The Summary and Linear Model of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP (Observed data)

Table 14.2.2.3.1: The Summary and Linear Model with Fully Conditional Specification (FCS) Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.2.3.2: The Summary and Linear Model withFully Conditional Specification (FCS) Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.2.3.3: The Summary and Linear Model withFully Conditional Specification (FCS) Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.2.3.4: The Summary and Linear Model withFully Conditional Specification (FCS) Multiple Imputation of Change from Baseline in Schirmer Test (mm) on Non-Study Eye at Visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.3.1.1: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Fully Conditional Specification (FCS) Multiple Imputation on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.3.1.2: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Fully Conditional Specification (FCS) Multiple Imputation on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.3.1.3: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Fully Conditional Specification (FCS) Multiple Imputation on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.3.1.4: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Fully Conditional Specification (FCS) Multiple Imputation on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.3.2.1: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Last Observation Carried Forward (LOCF) on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.3.2.2: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Last Observation Carried Forward (LOCF) on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.3.2.3: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Last Observation Carried Forward (LOCF) on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT

Table 14.2.3.2.4: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline Using Last Observation Carried Forward (LOCF) on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP

Table 14.2.3.3.1: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT (Observed data)

Table 14.2.3.3.2: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline on Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP (Observed data)

Table 14.2.3.3.3: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – mITT (Observed data)

Table 14.2.3.3.4: Percent of eyes with ≥10 mm Increase in Schirmer Test from Baseline on Non-Study Eye at visit 7 (Week 12) and other Post-Baseline Visits – PP (Observed data)

Table 14.2.3.4.1: The Summary and Linear Model with MCMC Multiple Imputation of Change from Baseline in Eye Dryness Severity and Frequency Scores (VAS) at each Post-Baseline Visits – mITT

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Table 14.3.10: Summary of Artificial Tear Use from Baseline by Visit – SAFETY

7.2. Data Listings to be Generated

–Listing 16.1.1.1: Subject Disposition – All Subjects Screened

Listing 16.1.1.2: Eligibility – All Subjects

Listing 16.1.1.3: Major Protocol Deviations – All Subjects Randomized

Listing 16.1.1.4: Subjects Excluded from the Efficacy Analysis – All Subject Randomized

Listing 16.1.2: Demographic and Baseline Characteristics - mITT and Cohort 1

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Listing 16.1.4: Treatment Exposure - SAFETY

Listing 16.1.5: Schirmer's Test without Anesthesia Result- mITT and Cohort 1

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Listing 16.1.8: VAS of Eye Dryness Score - mITT and Cohort 1

Listing 16.1.9: Ocular Surface Disease Index questionnaire (OSDI©) - mITT and Cohort 1

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Listing 16.1.11: Tear Film Break Up Time (TBUT) - mITT and Cohort 1

Listing 16.1.12: Insert Placement at Visit 2 or Visit 2B - mITT and Cohort 1

Listing 16.1.13: Ease of insertion at Visit 2 or Visit 2B as assessed by the Investigator - mITT and Cohort 1

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Listing 16.1.16.1: All Adverse Events - SAFETY

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Listing 16.1.22: Urine Pregnancy Test - SAFETY

Listing 16.1.23: Concomitant Medications - SAFETY

Listing 16.1.24: Prior Medications - SAFETY

7.3. SAS Codes

7.3.1. variables used in SAS codes:

TRPG1N	Treatment groups with 4 groups
TRPG1N_FG1 TRPG1N_FG2 TRPG1N_FG3	Dummy variables based on TRPG1N
AVAL2	Value at visit 2
AVAL4	Value at visit 3
AVAL5	Value at visit 4
AVAL6	Value at visit 5
AVAL7	Value at visit 6
AVAL8	Value at visit 7
CHG	Change from baseline
CRIT4	Categorical Schirmer test (>=10 mm vs <10 mm) at visit 3
CRIT5	Categorical Schirmer test at visit 4
CRIT6	Categorical Schirmer test at visit 5
CRIT7	Categorical Schirmer test at visit 6
CRIT8	Categorical Schirmer test at visit 7
CRIT9	Categorical Schirmer test at visit 8
SEFN	Study eye flag

7.3.2. SAS codes to impute the missing using MCMC MI

```
PROC MI DATA=pr1t SEED=738493 OUT=pr1mcmcmiy MINIMUM=0 MAXIMUM=35 ROUND=0.1
NIMPUTE=25;
/*The imputation will be done in eye level, SEFL is study eye flag*/
          where SEFL="Y";
          MCMC INITIAL=EM;
          VAR TRPG1N_FG1 TRPG1N_FG2 TRPG1N_FG3 AVAL2 AVAL4 AVAL5 AVAL6 AVAL7 AVAL8
         AVAL9;
RUN;
```

7.3.3. SAS codes to impute the missing using FCS MI

```
PROC MI DATA=pr1t SEED=918411 OUT=pr1fcsy MINIMUM=0 MAXIMUM=35 ROUND=0.1
NIMPUTE=25;
 where SEFL="Y";
 class TRPG1N CRIT4 CRIT5 CRIT6 CRIT7 CRIT8 CRIT9;
 VAR TRPG1N AVAL2 AVAL4 AVAL5 AVAL6 AVAL7 AVAL8 AVAL9;
/*This part imputes the continues Schirmer test */
 fcs nbiter=200 reg (AVAL2=TRPG1N );
 fcs nbiter=200 reg (AVAL4=TRPG1N AVAL2);
 fcs nbiter=200 reg (AVAL5=TRPG1N AVAL2 AVAL4);
 fcs nbiter=200 reg (AVAL6=TRPG1N AVAL2 AVAL4 AVAL5);
 fcs nbiter=200 reg (AVAL7=TRPG1N AVAL2 AVAL4 AVAL5 AVAL6);
 fcs nbiter=200 reg (AVAL8=TRPG1N AVAL2 AVAL4 AVAL5 AVAL6 AVAL7);
 fcs nbiter=200 reg (AVAL9=TRPG1N AVAL2 AVAL4 AVAL5 AVAL6 AVAL7 AVAL8);
RUN;
```

7.3.4. SAS codes to run t-test on MI data

```
ods output statistics=ttest1;
proc ttest data=pr2;
         by AVISITN IMPUT;
          where TRPG1N in (1 3);
          class TRPG1N ;
          var CHG;
run;
```

```
data ttest2;
        set ttest1;
        if class="Diff (1-2)" and method ne "Pooled" then delete;
run;

ods output parameterestimates=pdiff_ttest;
proc mianalyze data=ttest2;
        modeleffects mean;
        stderr stderr;
        by AVISITN CLASS;
run;
```

7.3.5. SAS codes to run ANCOVA (using PROC MIXED) on MI data

```
ods output LSMESTIMATEs=LSMESTIMATEs;
proc mixed data= pr2;
 by AVISITN IMPUT;
 CLASS TRPG1N (ref=last);
 MODEL CHG=TRPG1N base;
 lsmeans TRPG1N/ cl  pdiff;
 LSMESTIMATE TRPG1N                  "1G1" 1 0 0 0,
                                     "2G2" 0 1 0 0,
/* WF1 and WF2 are the sample size weighted coefficient for group 1 and 2 respectively*/
                                     "3G(1/2)" &WF1. &WF2A. 0 0,
                                     "4G3" 0 0 1 0,
                                     "5G4" 0 0 0 1,
                                     "6G1 vs G3" 1 0 -1 0 ,
                                     "7G2 vs G3" 0 1 -1 0 ,
                                     "8G1 vs G4" 1 0 0 -1,
                                     "91G2 vs G4" 0 1 0 -1,
                                     "92G(1/2) vs G3" &WF1. &WF2A.  -1 0 ,
                                     "93G(1/2) vs G4" &WF1. &WF2A.  0 -1  / cl;
run;

proc sort data=LSMESTIMATEs;
  by  AVISITN LABEL;
run;
```

```
ods output ParameterEstimates=outlsmean;
PROC MIANALYZE DATA=LSMESTIMATEs;
 modeleffects estimate;
 stderr stderr;
 by  AVISITN LABEL;
RUN;
```

7.3.6. SAS codes to generate and pool proportions using MI data

```
proc surveyfreq data= pr1fcsy;
        by avisitn imput;
        tables TRPG1*CRIT8 / row ;
        ods output CrossTabs=mi_perc_out;
run;

proc mianalyze data=mi_perc_out;
        by  TRPG1 CRIT8;
        modeleffects RowPercent;
        stderr  RowStdErr;
        ods output ParameterEstimates=pooled_percent;
run; quit;
```

7.3.7. SAS codes to generate and pool the Odds Ratio (OR) using MI data

```
ods output ParameterEstimates =OR_out;
proc surveylogistic data= pr1fcsy;
        by avisitn imput;
        class TRPG1 / param = ref;
        model CRIT8 (desc) =TRPG1;
        where TRPG1N in (1 3);
run;

proc mianalyze data=OR_out;
        modeleffects Estimate  ;
        stderr  StdErr;
        ods output ParameterEstimates=pooled_OR;
run; quit;
```

7.3.8. SAS codes to output 95% CI for proportions using Clopper-Pearson method and 95% CI for the proportion difference using Chan and Zhang (1999) method using observed and LOCF data

```
ods output RiskDiffCol1=RiskDiffCol1 FishersExact=FishersExact;
proc freq data=adoe;
        table   TRPG1N* CRIT8 / fisher;
        exact riskdiff(method=score);
run;
```

7.3.9. SAS codes to designate study eye randomly in a case both eyes have the same total corneal fluorescein staining score

```
*****
1-   Create a SAS dataset RND1 with 1000 observations,
2-   Create a variable named FOCID. The first 500 observation with value of "OD" (Right Eye) the last
500 observation with value of "OS" (Left Eye)
3-   Generate a random number using RANUNI (Uniform distribution)
4-   Sort this dataset by random variable ****;
data rnd1;
do i=1 to 500;
 FOCID="OD";
 rand=ranuni(54603);
 output;
end;
do i=501 to 1000;
 FOCID="OS";
 rand=ranuni(54603);
 output;
end;
run;
proc sort data=rnd1(drop=i); by rand; run;
data rnd1; set rnd1; VSORT=_n_; run;
proc sort data=rnd1; by VSORT; run;
*****
5-   Sort the subject by using 2 variables
   a- date of randomization for randomized subjects / date of informed consent for open label subjects
   b- random number
   c- subject number
```

```
6-    Then merge this dataset with RND1 and then selected FOCID will be their study eye.*****;
proc sort data=idsd.suppdm out=dm1(keep=USUBJID QVAL);
where QNAM="RANDNUMB";
by USUBJID;
run;
proc sort data=idsd.ds out=dm2(keep=USUBJID DSSTDTC);
where DSDECOD="RANDOMIZED" or (DSDECOD="INFORMED CONSENT OBTAINED" and USUBJID in
("CLN-0054-02-02001" "CLN-0054-02-02002" "CLN-0054-02-02003" "CLN-0054-02-02004" "CLN-0054-
02-02005"));
by USUBJID;
run;
data dm3;
merge dm1 dm2;
by USUBJID;
run;
proc sort data=dm3;
by DSSTDTC QVAL USUBJID;
run;
data dm3; set dm3; VSORT=_n_; run;
proc sort data=dm3; by VSORT; run;
data rnd2;
merge dm3(in=dm) rnd1;
 by VSORT;
 if dm then output;
run;
proc sort data=rnd2; by USUBJID FOCID; run;
```