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RESEARCH INSTITUTE, INC.

A Phase 3, Prospective, Double-masked, Randomized, Multi-center, Vehicle-controlled, Parallel-group, 12-week Administration and 40-week Extension Study Confirming the Efficacy and Safety of K-161 Ophthalmic Solution for the Treatment of Moderate to Severe Dry Eye Disease

Clinical Study Protocol

Drug Name:	K-161
Study Number:	K-161-3.01
US IND Number:	138738
Protocol Version Date:	November 22, 2021
NCT #:	NCT05403827
Name of Sponsor:	**Kowa Research Institute, Inc.**
Address:	430 Davis Drive, Suite 200 Morrisville, NC 27560 United States of America

[redacted]

Confidentiality Statement

INVESTIGATOR'S STATEMENT

I, the Investigator, understand that all information concerning the product supplied to me by Kowa Research Institute, Inc. (KRI) in connection with this study and not previously published is confidential information. This information includes the Investigator's Brochure, protocol, case report forms, assay methods, technical methodology, and basic scientific data.

I understand that any changes to the protocol must be approved in writing by KRI or representative and the Institutional Review Board/Independent Ethics Committee/Research Ethics Committee (IRB/IEC/REC) before implementation, except where necessary to eliminate apparent immediate hazards to the patients.

I confirm that I will report all adverse events (AEs) following the regulations indicated in the protocol.

I confirm that I will conduct this study in conformance with the ethical principles that have their origin in the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA), as applicable, and, as applicable, the International Council for Harmonisation (ICH) tripartite guideline E6 (R2): Good Clinical Practice (GCP). I will also conduct this study, as applicable, in compliance with the requirements of the United States (US) Food and Drug Administration (FDA) as outlined in Title 21 of the Code of Federal Regulations (CFR) (Parts 11, 50, 54, 56, and 312) and all other applicable regional or local regulatory requirements.

I confirm that I am informed of the need for record retention and that no data can be destroyed.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this version of the protocol dated November 22, 2021.

Investigator's Signature: _____ Date: _____
mm/dd/yyyy

Investigator's Name: _____

SIGNATURE PAGE

Date _____
mm/dd/yyyy

Kowa Pharma Development Company

Date _____
mm/dd/yyyy

Kowa Pharma Development Company

_____
mm/dd/yyyy

Kowa Pharma Development Company

PROTOCOL SYNOPSIS

Name of Sponsor Company: Kowa Research Institute, Inc.	**Drug Under Study:** K-161	
Title of Protocol: A Phase 3, Prospective, Double-masked, Randomized, Multi-center, Vehicle-controlled, Parallel-group, 12-week Administration and 40-week Extension Study Confirming the Efficacy and Safety of K-161 Ophthalmic Solution for the treatment of Moderate to Severe Dry Eye Disease		
Protocol Number: K-161-3.01	**Phase:** 3	**Indication:** Dry eye disease (DED)
Study Design: Prospective, double-masked, randomized, multi-center, vehicle-controlled, parallel-group study		

Primary Objectives:
The primary objectives of this study are the following:
• Symptom: To demonstrate the efficacy of K-161 [redacted] compared to vehicle from baseline to Day 85 on eye dryness score (EDS) (Visual analog scale [VAS]) in patients with DED
• Sign: To demonstrate the efficacy of K-161 [redacted] compared to vehicle from baseline to Day 85 on conjunctival sum fluorescein staining score in patients with DED as assessed by expanded National Eye Institute (NEI) scale
Secondary Objectives:
The secondary objectives of this study are the following:
• To evaluate the efficacy of K-161 [redacted] in patients with DED in the following order from baseline to Day 85 on:
  • Total eye fluorescein staining score as assessed by expanded NEI scale
  • Corneal sum fluorescein staining score as assessed by expanded NEI scale
  • Ocular Surface Disease Index Score (OSDI©)
  • Schirmer's test (unanesthetized)
  • Tear film break-up time (TFBUT)
• To evaluate the safety and tolerability of K-161 [redacted] at Day 85 in patients with DED		

Extension Objectives: • To confirm the long-term safety and tolerability of K-161 [redacted] compared to vehicle at Day 365 in patients with DED • To evaluate the long-term efficacy of K-161 [redacted] from baseline to Day 365 on all efficacy and exploratory endpoints in patients with DED		
Exploratory Objectives • [redacted]		
Patient Population: Patients with DED		
Number of Patients: Total 620 (310 per arm) 1) 300 (150 per arm) for 52 weeks 2) 320 (160 per arm) for 12 weeks	**Number of Centers:** Approximately 45 sites	
Dose Levels: [redacted] ophthalmic solution [redacted]	**Route of Administration:** Eye drop	
Duration of Treatment: 12 weeks plus 40-week extension (total 52 weeks)		

Criteria for Evaluation:

Primary Efficacy Endpoints:

The primary efficacy endpoint (symptom) is:

- Change in EDS (VAS) from baseline to Day 85

The primary efficacy endpoint (sign) is:

- Change in conjunctival sum fluorescein staining score from baseline to Day 85 as assessed by expanded NEI scale

Key Secondary Efficacy Endpoint:

Change from baseline to Day 85 in:

- Total eye fluorescein staining score as assessed by expanded NEI scale

Secondary Efficacy Endpoints:

Change from baseline to Day 85 in:

- Corneal sum fluorescein staining score as assessed by expanded NEI scale
- OSDI
- Schirmer's test (unanesthetized)
- TFBUT

Safety Endpoints:

Safety assessments from baseline up to Day 85

- Adverse events (AEs)
- [redacted]
- Systemic clinical evaluation (abbreviated physical exams)
- Clinical laboratory measurement
- [redacted]

Extension Endpoints:

- Safety assessments, as described for up to Day 85, from baseline up to Day 365
- Change in all efficacy and exploratory endpoints from baseline to Day 365

Exploratory Endpoints:

- [redacted]

Criteria for Inclusion:

1. Be at least 18 years of age at the time of informed consent visit
2. Have a reported history of DED in both eyes and a history of eye drop use for dry eye symptoms

11. Be willing and able to read, sign, and date the informed consent and Health Insurance Portability and Accountability Act documents after the nature of the study is explained and prior to initiation of Visit 1 procedures or exams
12. Have a negative urine pregnancy test, if the patient is a female of childbearing potential and is not either nursing or planning a pregnancy. Women of childbearing potential who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]), must use adequate birth control throughout the study. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical-spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control
13. Be willing and able to follow instructions and participate in all study assessments and visits

Criteria for Exclusion:

1. Have any clinically significant ocular condition [redacted]
2. Have any clinically significant eye conditions [redacted]
3. Have a history of [redacted] corneal refractive surgery, and/or any other ocular surgical procedure [redacted] within 12 months [redacted]

[redacted]

9. Have any history of immunodeficiency disorder, human immunodeficiency virus (HIV), positive hepatitis B surface antigen (HBsAg), positive hepatitis C virus (HCV) antibody, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin isotype M [HAV IgM]), active coronavirus disease 2019 (COVID-19), or a history of organ or bone marrow transplant. Patients with cured hepatitis C or cured COVID-19 will be allowed
10. Have any significant chronic illness that, in the opinion of the Investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, chronic systemic inflammatory or autoimmune conditions, poorly controlled hypertension, poorly controlled diabetes, autoimmune thyroid diseases, recent history of Bell's Palsy, Parkinson's disease with a significantly decreased blink rate and patients using a Continuous positive airway pressure (CPAP) machine at night, and/or have any abnormal lab values considered clinically significant by the Investigator (retesting is allowed once within the Screening Period)
11. History of cancer within the past 5 years (excluding non-melanoma skin cancer)

[redacted]

13. Have known hypersensitivity to the investigational product or its components

[redacted]

15. Have a known history of alcohol and/or drug abuse within the past 12 months at Visit 1
16. Have any condition or therapy, which, in the opinion of the Investigator, might pose a risk to the patient, make participation in the study not in the best interest of the patient, or limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within a year, and/or history of noncompliance with medication or scheduled appointments
17. Special or vulnerable status (e.g., institutionalized, or person related to or an employee of the sponsor or Investigator)

Permitted Medication and Rescue Therapy:
Any prohibited and restricted medications, devices, and procedures indicated for dry eye disease are permitted as "rescue therapy" after all assessments are completed at Visit 6. All other prohibited medications, other than isotretinoin, systemic [redacted], and restricted medications, devices, and procedures are permitted as "permitted therapy" after all assessments are completed at Visit 6.

Statistical Analysis:
The parameters to be needed for the calculation of sample size were estimated from the previous Phase 2 study (K-161-2.01US). In order to take intercurrent events (ICEs) into account, 4 different patient patterns are considered: (1) patients who were assigned to K-161 [redacted] and had an ICE, (2) patients who were assigned to K-161 [redacted] and did not have an ICE, (3) patients who were assigned to vehicle and had an ICE, and (4) patients who were assigned to vehicle and did not have an ICE.

Regarding EDS (VAS), a population mean in each pattern is assumed as follows:

Assigned Treatment	Intercurrent Event	
	Not Occurred	Occurred
K-161 [redacted]	(1) -10.0	(2) -3.6
Vehicle	(3) -3.6	(4) -3.6

A common variance, 431.2, and a common ICE occurrence rate, 8%, are assumed among the patterns. In order for EDS (VAS) to have at least 90% power when Holm's method is applied, i.e., in order to have 90% probability that EDS (VAS) is statistically significant when an alpha is set to 0.025 (two-sided), 310 patients/arm will be needed.

Targeted Estimand:

The summary of the targeted estimand is as follows:

Treatment Condition

Treatment condition based on the assigned treatment group.

Population

DED patients based on the Inclusion and Exclusion criteria of the study.

Variable

Change from baseline to Day 85 in total eye stain score and EDS (VAS) including measurements after intercurrent events (i.e., treatment policy strategy). Potential intercurrent events of the study are as follows:

- Discontinuation of the study treatment due to an adverse event
- Discontinuation of the study treatment due to lack of efficacy
- Discontinuation of the study treatment due to uncomfortable feeling of the study drug

Population-level Summary

Difference in means between the two treatment conditions.

Primary Efficacy Analyses:

The primary efficacy endpoints are change from baseline to Day 85 in conjunctival sum fluorescein staining score and EDS (VAS) on study eye, which are used regardless of whether or not the following ICEs occur: discontinuation of the study treatment due to an AE, lack of efficacy, or uncomfortable feeling of the study drug. Patients' measurements will be made even after occurrence of those ICEs. For each of the primary endpoints, the Analysis of Covariance with baseline value, sex and treatment as covariates is used in order to make a comparison between the treatment groups. Least squares means will be calculated for the comparison.

The data set to be used for the primary analyses is the FAS.

Missing values will be imputed using the PMM with MI. Patterns to be used for the PMM are, as feasible, determined in each treatment group by whether or not patients had an ICE, or the type of ICEs if patients had an ICE. For example, if patients who discontinued the study treatment due to an AE had missing values, their missing values will be imputed from the patients who had the same ICE, i.e., discontinuation of the study treatment due to an AE. If enough patients to develop an imputation model in each pattern does not exist, the control-based mean imputation proposed by Mehrotra et al. (2017) will be applied instead of the PMM with MI.

If the MI is applied, multiple parameter estimates will be combined using Rubin's rule (1987).
With regard to multiplicity caused by the 2 primary endpoints, Holm's method (1979) will be utilized. First, an endpoint with a smaller p-value will be tested at alpha=0.025 (two-sided). If the first test is significant, another endpoint will be tested at alpha=0.05 (two-sided). Otherwise, the second test will not be performed.
Planned analyses at Day 85 including the primary analyses will be performed by unmasked team not involved in the conduct of the study once all patient data until Day 85 are obtained in a fashion to protect the masking of all patients who will be followed in extension. Masked team will have access only to a summary of the results comparing the two arms so the same study team can continue to be masked while conducting the remaining part of the trial until the end of the 52-week Overall Period. The investigational sites will not be unmasked and will not have access to the summary of the results comparing the two arms.
As a sensitivity analysis, a tipping point, at which the primary analysis result turns out to be not-significant, is examined in each ICE.

Secondary Efficacy Analyses:

The key secondary efficacy endpoint is change from baseline of total eye fluorescein staining score as assessed by expanded NEI scale for study eye will be analyzed in a similar manner as performed for primary endpoint. All other secondary endpoints will also be analyzed in a similar manner.

The other secondary efficacy endpoints are ordered as follows: corneal sum fluorescein staining score as assessed by expanded NEI scale, OSDI, Schirmer's test (unanesthetized), and TFBUT.

Key secondary efficacy endpoint will be tested at alpha=0.05 (two-sided) if primary endpoints are both significant at alpha=0.05.

The other secondary efficacy endpoints will be tested in order by fixed sequence method if the key secondary endpoint is significant.

Safety:
AEs will be coded using the Medical Dictionary for Regulatory Activities dictionary (the most recent version, ver. 24.1 or later). Frequencies, percentages, severity, and relationship to study drug of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature study withdrawal and study drug discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies of occurrence will be given of patients with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term, and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be additionally performed for ocular and non-ocular AEs.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values, which are identified as being clinically significant, will be flagged.

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	adverse event(s)
BA/BE	bioavailability/bioequivalence
[redacted]	[redacted]
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CPAP	continuous positive airway pressure
CRO	clinical research organization
DED	dry eye disease
eCRF	electronic case report form
EDC	electronic data capture
EDS	eye dryness score
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV IgM	anti-hepatitis A virus immunoglobulin isotype M
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
ICE(s)	intercurrent event(s)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IND	Investigational New Drug
[redacted]	[redacted]
IRB	Institutional Review Board
IWRS	interactive web response system
[redacted]	[redacted]
KRI	Kowa Research Institute, Inc.
LASIK	laser in situ keratomileusis
LFA-1	lymphocyte function-associated antigen-1
[redacted]	[redacted]
MI	multiple imputation
[redacted]	[redacted]
NCS	not clinically significant
NEI	National Eye Institute
NSAIDs	non-steroidal anti-inflammatory drugs

OD	oculus dexter; right eye
OS	oculus sinister; left eye
OSDI	ocular surface disease index
OTC	over-the-counter
PI	principal Investigator
PMM	pattern mixture model
PPS	per protocol set
REC	Research Ethics Committee
SAE	serious adverse event
SUSAR	serious unexpected suspected adverse reaction
TEAE	treatment-emergent adverse event
TFBUT	tear film break-up time
[redacted]	[redacted]
US	United States
[redacted]	[redacted]
VAS	visual analog scale

1.0 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

1.1 Background Information

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Nelson 2017). Patients with DED often experience ocular discomfort, visual disturbance, and other ocular symptoms. While the prevalence of DED is difficult to report due to varying definitions and diagnostic criteria, the global prevalence of DED is estimated to be between 5% and 50%, and increases with age (Bron 2017). In the United States (US), it is estimated that as many as 3.2 million women and 1.7 million men over the age of 50 have DED, with a projected 40% increase in number of patients affected by the year 2030 (Schaumberg 2002, Schaumberg 2003, Schaumberg 2009).

Current treatment and management of DED consists primarily of tear supplementation with lubricants (artificial tears). While artificial tears improve symptoms associated with DED, they have no effect on resolving the underlying conditions that lead to inflammation of the ocular surface. Other approaches to management and therapy addressing specific symptoms, such as inflammation, meibomian gland physiology, tear film lipid quality and quantity, tear production, loss and runoff are utilized (Jones 2017). Four currently available options for treating inflammation at the ocular surface are Restasis® (cyclosporine ophthalmic emulsion), Cequa™ (cyclosporine ophthalmic solution), Xiidra® (lifitegrast ophthalmic solution), and Eysuvis™ (loteprednol etabonate ophthalmic suspension). It has been shown that only 15% of patients respond to Restasis after 6 months of treatment, as measured by Schirmer's test, and many more report ocular side effects such as burning and stinging (Mah 2012). Xiidra has also been shown to be associated with ocular adverse events (AEs); in a clinical study of Xiidra for patients with DED, patients reported increased ocular irritation upon instillation with Xiidra compared to placebo (7.8% in the Xiidra group compared with 1.4% in the placebo group) (Tauber 2015). Similarly, common adverse reactions reported after use of Cequa include instillation site pain and conjunctival hyperemia (Cequa 2018). Eysuvis is a corticosteroid and can be used for only the short-term (up to 2 weeks) (Eysuvis 2020). The most common adverse drug reaction following the use of Eysuvis™ for two weeks was instillation site pain, which was reported in 5% of patients (Eysuvis 2020). Tyrvaya™ (varenicline solution) nasal spray is another Food and Drug Administration (FDA) approved drug for the treatment of the signs and symptoms of dry eye disease and results in increased production of basal tear film. The most common adverse reactions of Tyrvaya™ was sneezing reported in 82% of patients (Tyrvaya 2021). Thus, there remains a medical need for more efficacious treatment options with a more favorable safety and comfort profile for patients with DED.

1.2 Rationale for Study and Dose Selection

[redacted] a tyrosine kinase involved in cytokine signaling and activation of lymphocytes. [redacted] have been shown to

have potent anti-inflammatory activity both in vitro and in vivo [redacted] was shown to suppress ocular surface inflammation and corneal injury in a mouse model of dry eye disease [redacted] Because inflammation is a key component of DED, targeting the inflammatory pathway via [redacted] to reduce cytokine production and/or immune cell infiltration at the ocular surface may reduce the signs and symptoms of DED.

[redacted]

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of this study are the following:

- Symptom: To demonstrate the efficacy of K-161 [redacted] compared to vehicle from baseline to Day 85 on eye dryness score (EDS) (Visual analog scale [VAS]) in patients with DED
- Sign: To demonstrate the efficacy of K-161 [redacted] compared to vehicle from baseline to Day 85 on conjunctival sum fluorescein staining score in patients with DED as assessed by expanded National Eye Institute (NEI) scale

2.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy of K-161 [redacted] in patients with DED in the following order from baseline to Day 85 on:
  - Total eye fluorescein staining score as assessed by expanded NEI scale
  - Corneal sum fluorescein staining score as assessed by expanded NEI scale
  - Ocular Surface Disease Index Score (OSDI©)
  - Schirmer's test (unanesthetized)
  - Tear film break-up time (TFBUT)
- To evaluate the safety and tolerability of K-161 [redacted] at Day 85 in patients with DED

2.1.3 Extension Objectives

- To confirm the long-term safety and tolerability of K-161 [redacted] compared to vehicle at Day 365 in patients with DED
- To evaluate the long-term efficacy of K-161 [redacted] from baseline to Day 365 on all efficacy and exploratory endpoints in patients with DED

2.1.4 Exploratory Objectives

- [redacted]

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint (symptom) is:

- Change in EDS (VAS) from baseline to Day 85

The primary efficacy endpoint (sign) is:

- Change in conjunctival sum fluorescein staining score from baseline to Day 85 as assessed by expanded NEI scale

2.2.2 Key Secondary Efficacy Endpoint

Change from baseline to Day 85 in:

- Total eye sum fluorescein staining score as assessed by expanded NEI scale

2.2.3 Secondary Efficacy Endpoints

Change from baseline to Day 85 in:

- Corneal sum fluorescein staining score as assessed by expanded NEI scale
- OSDI
- Schirmer's test (unanesthetized)
- TFBUT

2.2.4 Safety Endpoints

Safety assessments up to Day 85:

- AEs
- [redacted]
- Systemic clinical evaluation (abbreviated physical exams)
- Clinical laboratory measurement
- [redacted]

2.2.5 Extension Endpoints

- Safety assessments, as described for up to Day 85, from baseline up to Day 365
- Change in all efficacy and exploratory endpoints from baseline to Day 365

2.2.6 Exploratory Endpoints

3.0 STUDY DESCRIPTION

3.1 Study Design

This is a Phase 3, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. Patients will be randomized to one of the following treatment groups at Visit 2:

- [redacted] K-161; [redacted]
- Placebo Ophthalmic Solution (vehicle); [redacted]

Patients who qualify after the initial Screening Visit will enter the Run-in Period, where they will self-administer vehicle [redacted] for approximately 14 days. Those who qualify at Visit 2 (Day 1) will administer either [redacted] K-161 or vehicle [redacted] in a double-masked fashion during the 12-week Primary Period. At Visit 6 (Day 85), patients entering the 40-week Extension Period will be dispensed study drug. The 52-week Overall Period will comprise the 12-week Primary Period and 40-week Extension Period.

A total of 620 patients (310 per arm) will be randomized for the study. [redacted] The first 300 randomized patients (150/arm) will be assigned into the 52-week Overall Period and the rest of study population (approximately 320 [160/arm] patients) will be assigned into 12-week Primary Period. The patients who are assigned into the 12-week Primary Period will proceed to Visit 6.5 (Day 99) for post-dose assessments and complete the study. Patients, sponsor, clinical research organization (CRO), and site personnel will be masked to treatment assignment. Patients will be instructed not to discuss their assigned dosing regimen or perceived treatment effects with other study participants.

The schedule of required assessments is provided in Table 1. The timing of patient visits and examinations will be consistent throughout the study. For the order of assessments refer to Section 5.1.

Table 1 Clinical Evaluation Schedule

	STUDY PERIOD									
	Screening /Run-in Period	Days of Dosing and Assessments								Post-dose Assessments
		52-week Overall Period								
		12-week Primary Period					40-week Extension Period			
ASSESSMENTS PERFORMED	**Visit 1 Day -14 (Day -21 to -12)**	**Visit 2 Day 1 (Baseline)**	**Visit 3 Day 15 ± 2 (Remote)[a]**	**Visit 4 Day 29 ± 2**	**Visit 5 Day 57 ± 7**	**Visit 6 Day 85 ± 7**	**Visit 7[b] Day 169 ± 7**	**Visit 8[b] Day 253 ± 7**	**Visit 9[b] Day 365 ± 7**	**Visit 6.5[b] Day 99 ± 7[c] or Visit 10[b] Day 379 ± 7[c]**
Informed Consent/HIPAA	X									
Medical/Medication/Ocular History and Demographics	X									
[redacted]										
Medical/Medication Update		X	X	X	X	X	X	X	X	X
Vehicle Run-In Dispensation	X									
Vehicle Run-In Instillation	X									
Vehicle Run-in Collection and Accountability		X								
Determination/assignment of the study eye		X								
Randomization		X								
Study Drug Dispensation		X				X[d]	X[d]	X[d]		
Study Drug Instillation		X		X	X	X[d]	X[d]	X[d]		
Study Drug Collection and Accountability				X[e]	X[e]	X	X[d]	X[d]	X[d]	
Fluorescein Staining Scoring	X	X		X	X	X	X	X	X	
VAS	X	X		X	X	X	X	X	X	
[redacted]										

	STUDY PERIOD									
	Screening /Run-in Period	Days of Dosing and Assessments								Post-dose Assessments
		52-week Overall Period								
		12-week Primary Period					40-week Extension Period			
ASSESSMENTS PERFORMED	**Visit 1 Day -14 (Day -21 to -12)**	**Visit 2 Day 1 (Baseline)**	**Visit 3 Day 15 ± 2 (Remote)[a]**	**Visit 4 Day 29 ± 2**	**Visit 5 Day 57 ± 7**	**Visit 6 Day 85 ± 7**	**Visit 7[b] Day 169 ± 7**	**Visit 8[b] Day 253 ± 7**	**Visit 9[b] Day 365 ± 7**	**Visit 6.5[b] Day 99 ± 7[c] or Visit 10[b] Day 379 ± 7[c]**
TFBUT	X	X		X	X	X	X	X	X	
Schirmer's Test	X	X		X	X	X	X	X	X	
[redacted]										
Adverse Event Collection	X	X	X	X	X	X	X	X	X	X
[redacted]										
Systemic Clinical Evaluation (abbreviated physical exams)		X				X			X	
Clinical Laboratory Measurement	X					X			X	
[redacted]										
Exit Patient from Study										X

[redacted] HIPAA=Health Insurance Portability and Accountability Act; OSDI=Ocular Surface Disease Index; TFBUT=tear film break-up time; VAS=Visual analog scale.

Note: The visit schedule will always be calculated from randomization visit date (Visit 2).

a. Visit 3 will be a remote visit.

b. Only first 150 patients of each arm, total 300 patients will proceed to Visit 7 (Day 169) and following visits. Other patients will proceed to Visit 6.5 (Day 99) for post-dose assessments.
c. Post-dose assessments will be performed at least 14 days after the last dose of study medication.
d. Only patients in the Extension Period will be dispensed and instilled with the study drugs and will be examined for [redacted]
e. Patients will be instructed to bring all [redacted] to assess dosing compliance, however, only the used empty [redacted] will be collected and the [redacted] will be returned to patients at Visit 4 and Visit 5.

[redacted]

4.0 PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Inclusion Criteria

Patients are eligible for the study if all of the following criteria are met:

1. Be at least 18 years of age at the time of Informed Consent Visit
2. Have a reported history of DED in both eyes [redacted] and a history of eye drop use for dry eye symptoms [redacted]

11. Be willing and able to read, sign, and date the informed consent and Health Insurance Portability and Accountability Act (HIPAA) documents after the nature of the study is explained and prior to initiation of Visit 1 procedures or exams
12. Have a negative urine pregnancy test, if the patient is a female of childbearing potential and is not either nursing or planning a pregnancy. Women of childbearing potential who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]), must use adequate birth control throughout the study. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical-spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control
13. Be willing and able to follow instructions and participate in all study assessments and visits

4.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met in either eye:

1. Have any clinically significant ocular condition [redacted]
2. Have any clinically significant eye conditions [redacted]
3. Have a history of [redacted] corneal refractive surgery, and/or any other ocular surgical procedure [redacted] within 12 months [redacted]

9. Have any history of immunodeficiency disorder, human immunodeficiency virus (HIV), positive hepatitis B surface antigen (HBsAg), positive hepatitis C virus (HCV) antibody, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin isotype M [HAV IgM]), active coronavirus disease 2019 (COVID-19), or a history of organ or bone marrow transplant. Patients with cured hepatitis C or cured COVID-19 will be allowed
10. Have any significant chronic illness that, in the opinion of the Investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, chronic systemic inflammatory or autoimmune

conditions, poorly controlled hypertension, poorly controlled diabetes, autoimmune thyroid diseases, recent history of Bell's Palsy, Parkinson's disease with a significantly decreased blink rate and patients using a continuous positive airway pressure (CPAP) machine at night, and/or have any abnormal lab values considered clinically significant by the Investigator (retesting is allowed once within the Screening Period)

11. History of cancer within the past 5 years (excluding non-melanoma skin cancer)

[redacted]

13. Have known hypersensitivity to the investigational product or its components

[redacted]

15. Have a known history of alcohol and/or drug abuse within the past 12 months at Visit 1
16. Have any condition or therapy, which, in the opinion of the Investigator, might pose a risk to the patient, make participation in the study not in the best interest of the patient, or limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within a year, and/or history of noncompliance with medication or scheduled appointments
17. Special or vulnerable status (e.g., institutionalized, or person related to or an employee of the sponsor or Investigator)

4.3 Study Drug Discontinuation Criteria

It will be necessary to make a distinction between patients who prematurely discontinue study drug treatment and those who withdraw from the study for any reason. Patients who discontinue study drug are not required to withdraw from the study and will be encouraged to remain in the study and asked to attend all of the remaining study visits through Visit 6 (for the patients who are assigned into the 12-week Primary Period) or Visit 9 (for the patients who are assigned into the 52-week Overall Period), regardless of whether patients are on the study treatment or not.

All study drug discontinuations should be considered temporary interruptions because patients are allowed to restart medication at any time if the condition leading to study drug interruption has resolved and, in the opinion of the Investigator, the patient is not put at undue risk by restarting the study drug.

If the patient discontinues study drug, the reason should be captured and could include the following:

1. The patient requests discontinuation of the study drug
2. The patient develops an AE that, in the opinion of the Investigator, would compromise the patient's safety to continue the study drug
    a. Study medication should be stopped if a subject develops severe ocular/periocular infection disease. In case of a mild or moderate

infectious event, the study medication can be continued at the Investigator's discretion.

3. Violation of the protocol inclusion or exclusion criteria is discovered, and if, in the opinion of the Investigator or the sponsor, the violation will significantly compromise data interpretation or safety
4. The patient undergoes rescue ophthalmic surgery (Section 8.3)
5. The female patient becomes pregnant during the study (Section 9.3)
6. In the Investigator's judgment, it is in the patient's best interest
7. Lost to follow-up
8. Sponsor termination of study
9. Other

Although a patient is not obligated to give his/her reason for discontinuing study drug, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. The reason for discontinuation of study drug must be documented in the electronic case report form (eCRF). The clinical study report will include the reason(s) for discontinuation of study drug.

4.4 Withdrawal Criteria

The patient has the right to withdraw from the study at any time and for any reason without prejudice to the patient's future medical care. Nevertheless, every attempt will be made to prevent missing data and to obtain complete follow-up of all patients.

Patients who meet study drug discontinuation criteria described in Section 4.3 will be discontinued from study drug; however, are not required to withdraw from the study unless the patient withdraws consent completely. As such, these patients will be encouraged to remain in the study and asked to attend all of the remaining study visits through Visit 6 (for the patients who are assigned into the 12-week Primary Period) or Visit 9 (for the patients who are assigned into the 52-week Overall Period) (Table 1). Patients who choose to withdraw from the study will be asked if they are prepared to complete a last visit. In this case, the same evaluations as the End of Treatment Period (Visit 6 or 9), or at least, the same evaluations as the Post-dose Assessment Visit (Visit 6.5 or 10) should be performed. If a patient fails to actively maintain contact with the Investigator, reasonable efforts (telephone calls to family members or friends, email contacts, etc.) will be made in order to encourage the patient to complete the study visits.

If the patient withdraws from the study, the reason should be captured.

The patient will be withdrawn from the study if:

1. The patient withdraws consent to attend the remaining study visits
2. Lost to follow-up
3. Sponsor termination of study
4. Other

Although a patient is not obligated to give his/her reason for withdrawing from the study, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. Unless revoked, further contact in the case of withdrawal from the study will occur consistent with methods listed in the informed consent form (ICF). The reason for withdrawal from the study must be documented in the eCRF. The clinical study report will include the reason(s) for withdrawal from the study.

If a patient withdraws from the study due to an AE, the patient will be asked to return to the clinic for, at a minimum, the evaluations scheduled for post-dose assessments. If the AE has still not resolved, additional follow-up will be performed, as appropriate. Every effort will be made by the Investigator or delegate to contact the patient until the AE is resolved or stabilized, or the medical monitor and Investigator agree that further follow-up is not necessary. If patients are lost to follow-up, the Investigator will make 3 reasonable attempts to contact the patient via telephone, US postal service, or certified mail. All attempts to contact them must be made and documented in the study records.

4.5 Replacement, Rescreening, and Retesting

4.5.1 Replacement

Patients who are screened for the study may be replaced if they never are randomly assigned study drug or are withdrawn from the study before they administer any study drug after randomization. The replacement patients will receive a new randomly assigned treatment and not the treatment assignment of the replaced patient. Patients who self-administer any study drug after randomization and subsequently are withdrawn early from the study will not be replaced.

4.5.2 Rescreening

Patients who fail to satisfy inclusion and exclusion criteria at screening may be rescreened 1 additional time at the discretion of the sponsor. Screen failures due to inclusion and/or exclusion criteria that could transiently change and do not compromise the patient's safety as judged by the Investigator can be rescreened once. All eligibility assessments will be repeated regardless of the reason for the initial screen failure and new subject number will be assigned. Rescreening decision must be confirmed by the sponsor's medical monitor.

4.5.3 Retesting

Clinical labs with clinically significant abnormalities (per the principal Investigator's [PI] assessment) can be retested 1 time if there is a reasonable expectation that abnormality will resolve within the Screening Period (21 days at maximum). Unscheduled visits should be allowed within Screening Period.

5.0 PROCEDURES FOR SAFETY AND EFFICACY EVALUATIONS

5.1 Examination Procedures

The timing of patient visits and examinations should be consistent throughout the study (e.g., morning, afternoon, etc.). The schedule of required assessments is provided in Table 1.

Procedures listed below should be performed in the given order.

5.1.1 Scheduled Visits

5.1.1.1 Visit 1 at Day –14 (Day -21 to -12): Screening

All patients will undergo the following screening assessments in the order below:

1. Informed consent/HIPAA
2. Demographic data and medical/medication/ocular history
[redacted]
5. VAS [redacted]
9. TFBUT
10. Corneal and conjunctival fluorescein staining scoring
[redacted]
12. Schirmer's test (without anesthesia)
[redacted]
16. Clinical laboratory sample collection
17. Dispensation of run-in drops (vehicle) for [redacted] dosing until the day before Visit 2

[redacted]

19. Patient instructions dispensation

[redacted]

20. AE collection
21. Patients will be scheduled for Visit 2.

5.1.1.2 Visit 2: Day 1 – Baseline

1. Vehicle run-in drops collection
2. Medical/medication history update
3. AE collection
4. VAS [redacted]

8. Systemic clinical evaluation (abbreviated physical exams)

[redacted]

12. TFBUT
13. Corneal and conjunctival fluorescein staining scoring

[redacted]

[redacted]

18. Schirmer's test

[redacted] after completing the above steps: The following procedures will be conducted for eligible patients only.

[redacted]

21. Determination/assignment of the study eye
22. Randomization
23. Study drug kit dispensation: All patients meeting all other screening eligibility criteria at the end of Visit 2 will be randomized to 1 of 2 treatment groups utilizing the Interactive Web Response System (IWRS) system. Patients will receive their assigned study drug kit with sufficient supply to last until the day before Visit 6.

[redacted]

28. Patient instructions dispensation

[redacted]

29. AE collection
30. Patients will be scheduled for Visit 3 (remote visit).

5.1.1.3 Visit 3: Day 15 (± 2) – Remote Visit

1. Medical/medication history update
2. AE collection
3. Patient instructions dispensation

[redacted]

[redacted]

4. Patients will be scheduled for Visit 4.

5.1.1.4 Visit 4: Day 29 (± 2)

1. Study drug accountability
2. Medical/medication history update
3. AE collection
4. VAS [redacted]

11. TFBUT
12. Corneal and conjunctival fluorescein staining scoring [redacted]

16. Schirmer's test [redacted]

20. AE collection
21. Patient instructions dispensation [redacted]

[redacted]

22. Patients will be scheduled for Visit 5.

5.1.1.5 Visit 5: Day 57 (± 7)

1. Study drug accountability
2. Medical/medication history update
3. AE collection
4. VAS [redacted]

11. TFBUT
12. Corneal and conjunctival fluorescein staining scoring [redacted]

16. Schirmer's test [redacted]

20. AE collection
21. Patient instructions dispensation

[redacted]

22. Patients will be scheduled for Visit 6.

5.1.1.6 Visit 6: Day 85 (± 7)

1. Study drug collection/accountability
2. Medical/medication history update

[redacted]

4. AE collection
5. VAS [redacted]

9. Systemic clinical evaluation (abbreviated physical exams)

[redacted]

13. TFBUT
14. Corneal and conjunctival fluorescein staining scoring

[redacted]

19. Schirmer's test

[redacted]

[redacted]

27. Clinical laboratory sample collection
28. AE collection
29. Patient instructions dispensation (only patients in the Extension Period will be dispensed and instilled)

[redacted]

5.1.1.7 Visit 6.5: Day 99 (± 7; at least 14 days after the last dose of study medication) (Only Patients Who Are Assigned Into the 12-week Primary Period)

1. Medical/medication history update
2. AE collection

[redacted]

5. Exit patient from study

5.1.1.8 Visit 7: Day 169 (± 7) (Only Patients Who Are Assigned into the 52-week Overall Period)

1. Study drug collection/accountability
2. Medical/medication history update
3. AE collection
4. VAS [redacted]

11. TFBUT
12. Corneal and conjunctival fluorescein staining scoring [redacted]

17. Schirmer's test [redacted]

22. AE collection
23. Patient instructions dispensation [redacted]

[redacted]

24. Patients will be scheduled for Visit 8.

5.1.1.9 Visit 8: Day 253 (± 7) (Only Patients Who Are Assigned into the 52-week Overall Period)

1. Study drug collection/accountability
2. Medical/medication history update
3. AE collection
4. VAS [redacted]

11. TFBUT
12. Corneal and conjunctival fluorescein staining scoring [redacted]

16. Schirmer's test [redacted]

21. AE collection
22. Patient instructions dispensation (only patients in the Extension Period will be dispensed and instilled)

[redacted]

23. Patients will be scheduled for Visit 9.

5.1.1.10 Visit 9: Day 365 (± 7) (Only Patients Who Are Assigned into the 52-week Overall Period)

1. Study drug collection/accountability
2. Medical/medication history update
3. AE collection

[redacted]

5. VAS [redacted]

8. Systemic clinical evaluation (abbreviated physical exams)

[redacted]

12. TFBUT
13. Corneal and conjunctival fluorescein staining scoring

[redacted]

18. Schirmer's test

[redacted]

[redacted]

22. Clinical laboratory sample collection
23. AE collection
24. Patients will be scheduled for Visit 10.

5.1.1.11 Visit 10: Day 379 (± 7; at least 14 days after the last dose of study medication) (Only Patients Who Are Assigned into the 52-week Overall Period)

1. Medical/medication history update
2. AE collection

[redacted]

5. Exit patient from study

5.1.2 Unscheduled Visits

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

5.2 Efficacy Evaluations

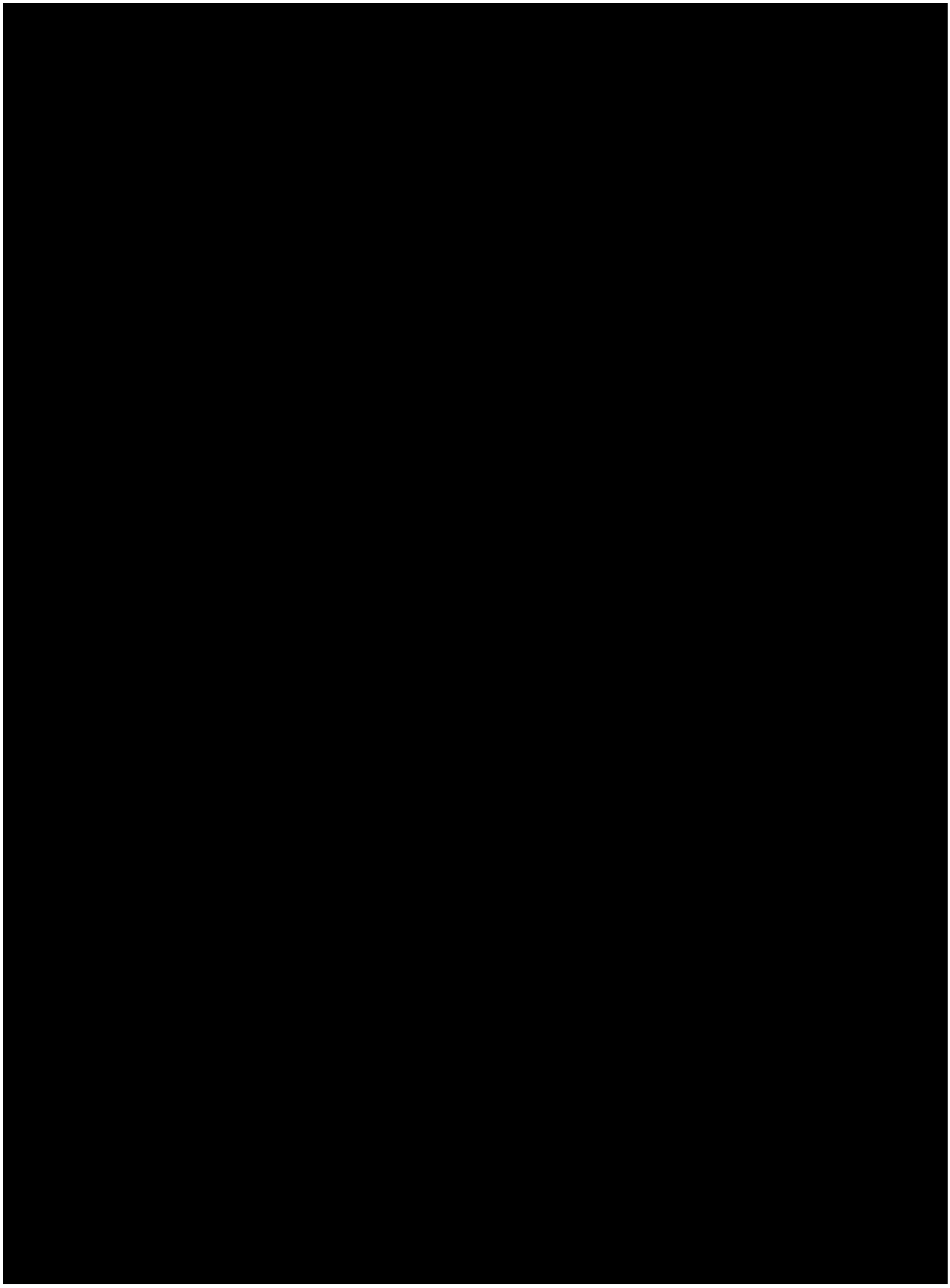
Primary and secondary efficacy endpoints are specified in the Sections 2.2.1, 2.2.2, and 2.2.3.

Worst Eye (**study eye**): Eyes are eligible for analysis if they meet all of the inclusion criteria and do not meet any of the exclusion criteria. At least one eye (the right eye or the left eye) must meet all of the inclusion criteria and neither eye must meet any of the exclusion criteria. In the case that both eyes are eligible for analysis, the worst eye will be selected. The worst eye will be defined as the eye with the worst conjunctival sum staining score at Visit 2. If the staining score is the same in both eyes, then the right eye will be selected as the study eye. The contralateral eye will be defined as fellow eye.

5.2.1 [redacted]

[redacted]

[redacted]



5.2.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2.3 [redacted]

[redacted]

[redacted]

[redacted]

5.2.4 [redacted]

5.2.5 [redacted]

[redacted]

5.2.6 [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

5.2.7 [redacted]

[redacted]

[redacted]

5.2.8 [redacted]

5.2.9 [redacted]

[redacted]

5.2.10 [redacted]

5.2.11 [redacted]

5.3 Safety Evaluations

The following assessments will be performed to assess safety in this study:

- AEs
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- Clinical evaluation (abbreviated physical exams)
- Clinical laboratory measurement
- [redacted]
- [redacted]

5.3.1 AEs

Refer to Section 9.1 for further information regarding AEs.

5.3.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

5.3.3 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

5.3.4 [redacted]

[redacted]

5.3.5 [redacted]

5.3.6 Clinical Laboratory

The following clinical laboratory assessments will be conducted:

Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, platelets, red blood cell, white blood cell, red blood cell morphology, and differentials (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)

Clinical chemistry: alanine aminotransferase, aspartate aminotransferase, albumin, calcium, chloride, alkaline phosphatase, bicarbonate, cholesterol, creatine kinase, creatinine, direct bilirubin, lactate dehydrogenase, magnesium, globulin, glucose, γ-glutamyltransferase, indirect bilirubin, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, urea nitrogen, and uric acid

Urinalysis: bilirubin, blood, clarity, color, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity, urobilinogen, and microscopic examination (if needed)

5.3.7 [redacted]

[redacted]

[redacted]

5.3.8 Abbreviated Physical Exams

Abbreviated physical examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner (as acceptable according to local regulations) at visits specified in the Clinical Evaluation Schedule in Table 1. The person conducting the physical examinations will document this in the patient's medical records and eCRF. Clinically significant abnormal findings should be recorded as AEs.

5.3.9 [redacted]

[redacted]

5.4 Data Monitoring Committee

No data monitoring committee is planned for this study.

6.0 CONDUCT OF STUDY

6.1 Study Masking and Randomization

All arms will be double-masked.

Before the initiation of study run-in at Visit 1, each patient who provides written informed consent will be assigned a subject code. All subject codes will be assigned in strict numerical sequence at a site and no numbers will skipped or omitted. If a patient is retested on clinical labs, the same subject code will be used (Section 4.5.3). If a patient is rescreened, the patient will be assigned with a new subject code (Section 4.5.2).

Patients who have signed informed consent and subsequently fail to satisfy inclusion and exclusion criteria are defined as screen failures. For all screen failures, the reason(s) for screen failure will be recorded on the patient's source document and eCRF.

Each patient who meets all the inclusion and none of the exclusion criteria at Visit 1 and Visit 2 will be randomized at the end of Visit 2 by using the IWRS.

Subject codes and kit numbers will be assigned automatically to each patient as they are entered into the IWRS. All patients will be randomized into either vehicle or active treatment group at Visit 2 (Day 1) in a 1:1 ratio. [redacted] The first 300 (150/arm) randomized patients will be assigned into the 52-week Overall Period and the rest of study population (approximately 320 [160/arm] patients) will be assigned into the 12-week Primary Period.

The site staff will dispense the required kit(s). Both the subject codes and the dispensed study drug kit number(s) will be recorded on the patient's source document and eCRF. Patients, sponsor, CRO, and site personnel will be masked to treatment assignment.

After Visit 6 (Day 85), patients who are randomized to enter the 40-week Extension Period will proceed to Visit 7 (Day 169) until Visit 10 (Day 379). Other patients, who are randomized to enter the 12-week Primary Period only, will proceed to Visit 6.5 (Day 99) for post-dose assessments and will complete the study.

Planned analyses at Day 85 including the primary analyses will be performed by an unmasked team not involved in the conduct of the study once all patient data until Day 85 are obtained in a fashion to protect the masking of all patients who will be followed in the 40-week Extension Period. The masked team will have access only to a summary of the results comparing the two arms so the same study team can continue to be masked while conducting the remaining part of the trial until the end of the 52-week Overall Period. The investigational sites will not be unmasked and will not have access to the summary of the results comparing the two arms.

6.2 Study Visits

For each patient, a maximum of 10 scheduled visits will be performed:

- Visit 1 at Day -14 (Day -21 to -12): Screening: The screening examination to determine patient eligibility can take place anytime within this time period.

- Visit 2 at Day 1: Baseline (12-21 days after Visit 1)
- Visit 3 at Day 15 ± 2 days
- Visit 4 at Day 29 ± 2 days
- Visit 5 at Day 57 ± 7 days
- Visit 6 at Day 85 ± 7 days

For the patients who are assigned into the 12-week Primary Period

- Visit 6.5 (post-dose) at Day 99 ± 7 days (at least 14 days after the last dose of study medication)

For the patients who are assigned into the 52-week Overall Period (with the 40-week Extension Period):

- Visit 7 at Day 169 ± 7 days
- Visit 8 at Day 253 ± 7 days
- Visit 9 at Day 365 ± 7 days
- Visit 10 (post-dose) at Day 379 ± 7 days (at least 14 days after the last dose of study medication)

The procedures and assessments to be performed at each visit are indicated in Table 1.

6.3 Compliance with The Protocol

The Investigator must agree to implement the study protocol as written and adhere to the guidelines given in the Investigator's Statement, which will be signed prior to the start of the study. The study will be performed in accordance with HIPAA, Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local laws, FDA GCP regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312), and other applicable guidance documents.

If the Investigator considers enrolling a patient that does not meet all inclusion or exclusion criteria, an exemption must be requested from the sponsor's medical monitor prior to patient enrollment. The justification for the exemption must be document by the Investigator. The approval or rejection of the exemption must be documented by the sponsor's medical monitor prior to the patient's enrollment or screen failure.

Protocol non-compliance must be reported to the sponsor or its representatives. Each deviation and the reason for its occurrence must be documented. The sponsor retains the right to require the withdrawal of any patient who violates the protocol.

6.4 Termination of the Study

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the study may be terminated after consultation with the sponsor. A written statement fully documenting the reason(s) for the termination will be provided to the sponsor. In addition, the sponsor may terminate the study at any time.

If it becomes apparent that patient enrollment is unsatisfactory with respect to quality or quantity, or data recording is inaccurate or incomplete on a chronic basis, the sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the Institutional Review Board/Independent Ethics Committee/Research Ethics Committee (IRB/IEC/REC), and regulatory authorities, if required. In the event of any serious or non-serious AEs having occurred at a site, all documentation relating to the event(s) must be obtained.

7.0 STUDY MEDICATION

7.1 Description of Study Medication

K-161 ophthalmic solution is formulated as a [redacted] for topical ophthalmic administration. The drug product is supplied in [redacted] suitable for administration directly onto the eye. A placebo to match sterile product (vehicle) is provided using the same excipient formulation as the active K-161 product.

Each drug product contains the following excipients: [redacted]

7.2 Drug Packaging

The drug product is packaged into [redacted] that are sealed within [redacted] and ultimately contained in carton kits [redacted] Each patient will receive 1 kit at Visit 1; 4 kits at Visit 2, 6, and 7; and 6 kits at Visit 8, as applicable, to provide a sufficient supply of run-in and randomized study drug.

7.3 Drug Labeling

Study drug will be labeled according to country/state/province specific requirements, with the following information:

1. Name and address of sponsor (e.g., KRI)
2. Drug name, dosage form, and quantity of dosage units
3. Lot number (as required)
4. "Caution - New Drug - Limited by Federal (US) Law to Investigational Use"
5. The storage conditions
6. "Keep out of reach of children"
7. Expiration date (as required)

7.4 Drug Storage

The study drug must be stored in a secure area accessible only to the Investigator and his/her designees. K-161 must be stored [redacted] as indicated on the product label.

7.5 Dispensing and Administration of Treatment

All arms will be double-masked. The treatments administered will be:

- [redacted] K-161; [redacted]
- Placebo ophthalmic solution (vehicle); [redacted]

7.5.1 Drug Administration

Patients will be instructed to administer study drug [redacted]. If missed, the patient must not administer the eye drop if the next dosing is in less than 2 hours. At every study visit (except remote), all patients must visit their study sites without administering any topical ophthalmic preparations, including study drug, and must not administer topical ophthalmic preparations until all required examinations are finished.

Patients, sponsor, CRO, and site personnel will be masked to treatment assignment. Patients will be instructed not to discuss their assigned dosing regimen or any perceived treatment effects with other study participants.

7.5.2 Diet or Physical Exercise

No special diets or activity restrictions are required for this study. Patients are asked not to change their personal routines (e.g., the use of eyelid scrubs and warm compresses) throughout the study.

7.6 Compliance with Dispensed Study Drug Dosing Regimen

Patients will be given written instructions, instructed on proper instillation, and instructed on proper storage of the study drug at the end of every study visit except for the end of treatment period and post-dose assessments (Visit 6.5 and 10). To assess dosing compliance, patients will be instructed to bring all [redacted] at their next visit throughout the study duration. The patient [redacted] will be collected at Visit 2 and Visit 6 for all patients and from Visit 7 to Visit 9 for patients entering the 40-week Extension Period. At Visit 4 and Visit 5, only the [redacted] will be collected and the [redacted] will be returned to patients. Dosing compliance will be based on the [redacted]. If the patient is less than 80% or more than 125% compliant during each visit interval, 12-week Primary Period, 40-week Extension Period, and 52-week Overall Period, with dosing based on the expected number of [redacted], then the patient will be deemed non-compliant and a dosing deviation should be recorded in the source document. The Investigator will use these guidelines to determine patient study compliance and deviation.

7.7 Drug Accountability

The study drug is to only be dispensed by the PI or his/her named sub-Investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to patients properly qualified as described in this protocol to receive study drug.

The Investigator must keep an accurate account of the study drug received from the supplier. This includes the amount of study drug dispensed to patients, amount of study drug returned to the Investigator by the patients, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

7.8 Procedure for Unmasking

As needed, the randomization code may be broken by the Investigator to manage an urgent medical safety event. If possible, the medical monitor should be contacted to discuss the case before the code is broken.

If it becomes necessary to unmask treatment information during the study, the reason for unmasking must be documented in the eCRF. If the medical monitor cannot be notified prior to unmasking, the Investigator must contact the medical monitor promptly and explain the reason for the premature unmasking (e.g., unmasking due to an SAE).

Planned analyses at Day 85 including the primary analyses will be performed by unmasked team not involved in the conduct of the study once all patient data until Day 85 are obtained in a fashion to protect the masking of the patients who will be followed in the 40-week Extension Period.

8.0 CONCOMITANT MEDICATION

The Investigator must record the use of all concomitant medications and any historical use of [redacted] before Visit 1, both dispensed and OTC, in the eCRF along with the reason the medication was taken. This includes drugs used on a chronic and as-needed basis. Patients must be discouraged from starting any new medication, both dispensed and OTC, without consulting the Investigator, unless the new medication is required for emergency use.

8.1 General Considerations

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

8.2 Prohibited Medication

Disallowed medications/treatments during the study are outlined in the exclusion criteria (Section 4.2).

8.3 Permitted Medication and Rescue Therapy

Contact lenses are allowed only during the 40-week Extension Period. Contact lenses should be removed prior to the administration of study drug and may be reinserted at least 15 minutes following administration. If a subject is using another prescription eye drop in combination with the study medication, the concomitant use of contact lenses is not recommended for the duration of such combination therapy.

The following medications are permitted as long as the dosage is stable:

- Systemic tetracycline compounds (e.g., tetracycline, doxycycline, or minocycline), macrolides (e.g., azithromycin): for at least 30 days prior to Visit 1 and dose will remain stable until the end of the 12-week Primary Period
- Any medication (topical and systemic) known to cause ocular drying, such as systemic anticholinergic medications (e.g., atropine, homatropine), antidepressants and antipsychotic agents, statins, diuretics, beta-blockers, NSAIDs: for at least 30 days prior to Visit 1 and dose will remain stable until the end of the 12-week Primary Period
    - Episodic use of anticholinergic drops for eye examination and episodic use of systemic NSAIDs are allowed during the study except for within 2 days prior to any study visit.
- Omega-3 fatty acid supplements in doses above 3000 mg/day, oral hormonal contraceptives, hormone replacement therapy for menopause: for 12 weeks prior to Visit 1 and dose will remain stable until the end of the 12-week Primary Period. Omega-3 fatty acid supplements in doses equal to or below 3000 mg/day are permitted.

Any prohibited and restricted medications, devices, and procedures indicated for dry eye disease are permitted as “rescue therapy” after all assessments are completed at Visit 6

(Table 1). Especially, [redacted] will be summarized as described in Section 5.2.10. All other prohibited medications, other than isotretinoin, systemic [redacted], and restricted medications, devices, and procedures are permitted as "permitted therapy" after all assessments are completed at Visit 6. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 15 minutes apart.

Any non-emergent ocular surgical procedure is prohibited until the end of the 12-week Primary Period. However, if the patient's condition necessitates a surgical ocular procedure during the study, the patient may undergo rescue ophthalmic surgery. In this case, the use of study medication should be interrupted in the eye undergoing the procedure until resolution or stabilization of this condition and full recovery after surgery as determined by the Investigator. The decision to interrupt or restart the study medication for a specific ocular procedure/condition should be based on the best clinical judgment of the Investigator and preferably after consultation with the medical monitor.

9.0 AEs AND SAEs

9.1 AEs

9.1.1 AE Definition

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the patient's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that patient.

Clinically meaningful (for a given patient) changes in physical examination findings and abnormal objective test findings (e.g., clinical laboratory tests) are also recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms, and/or;
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
3. Test result leads to a change in study dosing or withdrawal from the study, significant additional concomitant drug treatment or other therapy, and/or;
4. Test result leads to any of the outcomes included in the definition of an SAE (Section 9.2).

Merely repeating a test, in the absence of any of the above conditions, does not meet condition number 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

A treatment-emergent AE (TEAE) is defined as an AE that begins after the start of study drug or an event that begins before the start of the study drug and worsens in intensity after starting treatment.

9.1.2 Reporting of AEs

At each evaluation, the Investigator will determine whether any AEs have occurred. The patient will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the eCRF and in the patient's medical record. If known, the diagnosis will be recorded, in preference to the listing of individual signs and symptoms.

AE reporting begins when informed consent is obtained and ends at the conclusion of the study, unless an unresolved AE is still being followed.

The severity of the AE will be graded as follows:

Mild	The AE is easily tolerated and does not interfere with normal daily activities.
Moderate	The AE causes some interference with daily activities.
Severe	The AE causes all normal daily activities to be completely halted.

The relationship of each AE to the study drug will be determined by the Investigator using these explanations:

- ***Related*:** A reasonable possibility exists that the study drug caused the AE. A related AE can be further defined as follows:
    - Occurs within a reasonable temporal sequence to administration of study drug
    - Cannot be explained by concurrent disease or other drugs or chemicals
    - Improves or disappears on stopping or reducing study drug (de-challenge)
    - Reappears on repeated exposure to study drug (re-challenge)
    - Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the participant's physical condition
    - Unlikely to be attributed to concurrent disease or other drugs or a clinically reasonable response on withdrawal (de-challenge)
- ***Not Related:*** A reasonable possibility does not exist that the study drug caused the AE. A not related AE can be further defined as follows:
    - Occurs with a temporal relationship to administration of study drug which makes a causal relationship improbable
    - Other drugs, chemicals or underlying disease provide plausible explanations of causality
    - Is known to be associated with the participant's clinical condition, or with other medication taken by the participant

The Investigator will record each action taken and outcome for each AE according to the following:

Action taken

- None
- Treatment required
- Hospitalization
- Study drug interrupted
- Study drug discontinued

- Patient withdrawn
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Recovering
- Ongoing
- Death
- Lost to follow-up

Whether each AE is ocular or non-ocular will be determined by the Investigator for each AE and it will be recorded on the AE pages of the eCRF.

9.1.3 Follow-up of AEs

If any AEs are present when a patient completes the study, or if a patient is withdrawn from the study, the patient will be re-evaluated. At the Investigator's discretion, minor AEs can be re-evaluated via telephone and documented. If the AE is still not resolved, additional follow-up will be performed as appropriate. Every effort will be made by the Investigator or delegate to contact the patient until the AE is resolved or stabilized, or the medical monitor and Investigator agree that further follow-up is not necessary. The follow-up of AEs after post-dose assessments at Visits 6.5 or 10 will be documented in the patient's medical records.

9.2 SAEs

9.2.1 SAE Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

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

9.2.1.1 Life-Threatening AEs

The term *life-threatening* in the definition of *serious* refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

9.2.1.2 Hospitalization

Hospitalization is defined as the patient being hospitalized overnight, or the patient's hospital stay being prolonged for at least an additional overnight stay. Pre-planned hospital stays or hospital stays for non-medical social reasons are not applicable. Twenty-three-hour hospitalizations for observation will be discussed with the medical monitor to determine whether they are appropriate for SAE reporting.

9.2.2 Reporting of SAEs

All SAEs occurring from the time of informed consent until Visit 6.5 (patients enrolled in the Primary Period only) or Visit 10 (all other patients) must be reported to the CRO safety personnel within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after post-dose assessments at Visits 6.5 or 10 must be reported to the CRO or the sponsor/designee.

To report the SAE, the site staff will complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, the CRO safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, site staff will send a completed paper SAE form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours.

[redacted]

The Investigator must continue to follow-up with the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs. Written confirmation that any serious, unexpected, and related AEs have been submitted to the IRB/IEC/REC must be forwarded to the sponsor and kept in the Investigator files.

9.2.3 Serious Unexpected Suspected Adverse Reactions

According to FDA CFR 312.32(a) and FDA Guidance "Safety Reporting Requirements for Investigational New Drugs (INDs) and BA/BE (Bioavailability/Bioequivalence) Studies" finalized December 2012, *suspected adverse reaction* means any AE for which there is a reasonable possibility that the medicinal product caused the AE. The phrase reasonable possibility means there is evidence to suggest a causal relationship between the AE and the medicinal product.

The following are examples of types of evidence that would suggest a causal relationship between the drug and the AE (i.e., *reasonable possibility*):

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event. The Investigator will initially classify the relatedness of an AE, but the final classification is subject to the medical monitor's determination unless revised by the sponsor, which has the ultimate responsibility for judging relatedness.

A suspected adverse reaction is considered *unexpected* if it is not listed in the Reference Safety Information in Section 6 of the K-161 Investigator's Brochure or is not listed at the specificity or severity that has been described in the K-161 Investigator's Brochure.

An AE or suspected adverse reaction is considered *serious* if, in the view of either the Investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (Section 9.2.1). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any AE meeting the definitions of suspected adverse reaction, unexpected, and serious is considered a serious unexpected suspected adverse reaction (SUSAR). In accordance with the FDA Guidance "Safety Reporting Requirements for INDs and BA/BE Studies" finalized December 2012, the sponsor will unmask the study data for patients experiencing SUSARs and only report those for patients who are on the active K-161 product. All such reports will be submitted to the Investigator(s), FDA, and IRB/IEC/REC in an expedited manner.

9.3 [redacted]

[redacted]

9.4 Patient Withdrawal and Drug Discontinuation

If a patient experiences an AE that leads to discontinuation of study drug treatment, the eCRF will identify the AE as the reason for drug discontinuation.

If a patient experiences an AE and withdraws informed consent and rejects the remaining scheduled visits, it is considered a patient withdrawal and the eCRF will identify the AE as the reason for withdrawal.

10.0 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Sample Size Justification

The parameters to be needed for the calculation of sample size were estimated from the previous Phase 2 study (K-161-2.01US). In order to take intercurrent events (ICEs) into account, 4 different patient patterns are considered: (1) patients who were assigned to K-161 [redacted] and had an ICE, (2) patients who were assigned to K-161 [redacted] and did not have an ICE, (3) patients who were assigned to vehicle and had an ICE, and (4) patients who were assigned to vehicle and did not have an ICE.

Regarding EDS (VAS), a population mean in each pattern is assumed as follows:

Assigned Treatment	**Intercurrent Event**	
	Not Occurred	**Occurred**
K-161 [redacted]	(1) -10.0	(2) -3.6
Vehicle	(3) -3.6	(4) -3.6

A common variance, 431.2, and a common ICE occurrence rate, 8%, are assumed among the patterns. In order for EDS (VAS) to have at least 90% power when Holm's method is applied, i.e., in order to have 90% probability that EDS (VAS) is statistically significant when an alpha is set to 0.025 (two-sided), 310 patients/arm will be needed.

10.2 Targeted Estimand

The summary of the targeted estimand is as follows:

Treatment Condition

Treatment condition based on the assigned treatment group.

Population

DED patients based on the Inclusion and Exclusion criteria of the study.

Variable

Change from baseline to Day 85 in total eye stain score and EDS (VAS) including measurements after intercurrent events (i.e., treatment policy strategy). Potential intercurrent events of the study are as follows:

- Discontinuation of the study treatment due to an adverse event
- Discontinuation of the study treatment due to lack of efficacy
- Discontinuation of the study treatment due to uncomfortable feeling of the study drug

Population-level Summary

Difference in means between the two treatment conditions.

10.3 Study Populations

The following analysis populations will be considered:

Full Analysis Set (FAS) in the 12-week Primary Period: will include all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment. The FAS will be used as the primary efficacy analyses.

Per Protocol Set (PPS) in the 12-week Primary Period: will include all randomized patients without any major protocol deviations and have valid baseline and Day 85 primary endpoint values. Major protocol deviations will be pre-specified prior to unmasking the study. PPS will be used to assess robustness of the primary analysis results.

Safety Population in the 12-week Primary Period: will include all randomized patients who have received at least 1 dose of study treatment.

FAS in the 52-week Overall Period: will include the randomized patients who are assigned into the 52-week Overall Period and received at least 1 dose of study treatment. Patients will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment.

Safety Population in the 52-week Overall Period: will include randomized patients for the 52-week Overall Period and who had at least 1 dose of study treatment.

10.4 Analysis of Efficacy Parameters

The primary efficacy endpoints are change from baseline to Day 85 in conjunctival sum fluorescein staining score on study eye and EDS (VAS), which are used regardless of whether or not the following ICEs occur: discontinuation of the study treatment due to an AE, lack of efficacy or uncomfortable feeling of the study drug. Patients' measurements will be made even after occurrence of those ICEs. For each of the primary endpoints, the analysis of covariance with baseline value, sex and treatment as covariates is used in order to make a comparison between the treatment groups. Least squares means will be calculated for the comparison.

The data set to be used for the primary analyses is the FAS.

Missing values will be imputed using the pattern mixture model (PMM) with multiple imputation (MI). Patterns to be used for the PMM are, as feasible, determined in each treatment group by whether or not patients had an ICE, or the type of ICEs if patients had an ICE. For example, if patients who discontinued the study treatment due to an AE had missing values, their missing values will be imputed from the patients who had the same ICE, i.e., discontinuation of the study treatment due to an AE. If enough patients to develop an imputation model in each pattern do not exist, the control-based mean

imputation proposed by Mehrotra (Mehrotra 2017) will be applied instead of the PMM with MI.

If the MI is applied, multiple parameter estimates will be combined using Rubin's rule (Rubin 1987).

With regard to multiplicity caused by the 2 primary endpoints, Holm's method (Holm 1979) will be utilized. First, an endpoint with a smaller p-value will be tested at alpha=0.025 (two-sided). If the first test is significant, another endpoint will be tested at alpha=0.05 (two-sided). Otherwise, the second test will not be performed.

Planned analyses at Day 85 including the primary analyses will be performed by unmasked team not involved in the conduct of the study once all patient data until Day 85 are obtained in a fashion to protect the masking of the patients who will be followed in extension. Masked team will have access only to a summary of the results comparing the two arms so the same study team can continue to be masked while conducting the remaining part of the trial until the end of the 52-week Overall Period. The investigational sites will not be unmasked and will not have access to the summary of the results comparing the two arms.

As a sensitivity analysis, a tipping point, at which the primary analysis result turns out to be not-significant, is examined in each ICE.

Further details will be included in a separated statistical analysis plan.

10.4.1 Analysis of Secondary Efficacy Parameters

The key secondary efficacy endpoint is change from baseline of total eye fluorescein staining score as assessed by expanded NEI scale for study eye will be analyzed in a similar manner as performed for primary endpoint. All other secondary endpoints will also be analyzed in a similar manner.

The other secondary efficacy endpoints are ordered as follows: corneal sum fluorescein staining score as assessed by expanded NEI scale, OSDI, Schirmer's test (unanesthetized), and TFBUT.

Key secondary efficacy endpoint will be tested at alpha=0.05 (two-sided) if primary endpoints are both significant at alpha=0.05.

The other secondary efficacy endpoints will be tested in order by fixed sequence method if the key secondary endpoint is significant.

10.5 Analysis of Safety Data

AEs will be coded using the Medical Dictionary for Regulatory Activities dictionary (the most recent version, ver. 24.1 or later). Frequencies, percentages, severity, and relationship to study drug of patients with TEAEs, serious TEAEs, and TEAEs causing premature study withdrawal and study drug discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies of occurrence will be given of patients with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term, and maximal severity; by system organ class and preferred term for

treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be additionally performed for ocular and non-ocular AEs.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values, which are identified as being clinically significant, will be flagged.

[redacted] systemic clinical evaluation (abbreviated physical exams), [redacted]

Further details will be included in a separated statistical analysis plan.

10.6 Analysis of Exploratory Endpoints

Details will be included in a separated statistical analysis plan.

10.7 Demographic/Baseline Information

Summary statistics will be provided by treatment group for demographics (e.g., age, sex, race, ethnicity, eye color groups, and the prior use of [redacted]).

The baseline for all efficacy and safety variables will be Visit 2 (Day 1), while the baseline for clinical laboratory measurements and [redacted] will be Visit 1 (Screening Visit).

Further details will be included in a separated statistical analysis plan.

10.8 Interim Analysis

No interim analysis is planned for this study. Planned analyses at Day 85 including the primary analyses will be performed by unmasked team not involved in the conduct of the study once all patient data until Day 85 are obtained in a fashion to protect the masking of the patients who will be followed in extension. Masked team will have access only to a summary of the results comparing the two arms so the same study team can continue to be masked while conducting the remaining part of the trial until the end of the 52-week Overall Period. The investigational sites will not be unmasked and will not have access to the summary of the results comparing the two arms.

10.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

11.0 STUDY MANAGEMENT AND DATA COLLECTION

11.1 Ethical Conduct of the Trial

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the HIPAA, and the ICH harmonised tripartite guideline E6(R2): GCP. The study will also be performed in compliance with the requirements of the US FDA as outlined in Title 21 of the CFR (Parts 11, 50, 54, 56, and 312) and all other applicable regional or local regulatory requirements.

11.2 IRB/IEC/REC

The IRB/IEC/REC must be assembled according to the applicable state and federal requirements of each participating location, including ICH E6(R2) guidelines, and US FDA 21 CFR Part 56.

It is the responsibility of the clinical site to submit the Protocol, Investigator's Brochure, patient ICF, patient recruitment materials (if applicable), and other documentation as required by the IRB/IEC/REC for review and approval. A copy of the written approval must be provided to KRI. The documentation must clearly mention the approval/favorable opinion of the Protocol, the patient ICF, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRB/IEC/REC and provided to KRI before the release of clinical study supplies to the clinical site and commencement of the study. If any member of the IRB/IEC/REC has direct participation in the study, written notification regarding his or her abstinence from voting must also be obtained.

The clinical site must adhere to all requirements stipulated by the IRB/IEC/REC. This includes notification to the IRB/IEC/REC regarding the following: protocol amendments, updates to the patient ICF, recruitment materials intended for viewing by patients, IND safety reports, serious and unexpected AEs, reports and updates regarding the ongoing review of the study at intervals specified by the IRB/IEC/REC, and submission of final study reports and summaries to the IRB/IEC/REC.

It is the responsibility of each investigational site to submit information to the appropriate IRB/IEC/REC for annual review and annual re-approval.

11.3 Patient Informed Consent

Written consent must be obtained from the patient prior to any study-specific procedure or investigation.

Prior to the implementation of study procedures, patients and persons conducting the consent discussion will be required to sign and date the IRB/IEC-approved ICF, and each patient will be given a copy. In addition, this information will be recorded in the patient's medical record (i.e., source document).

The written consent document will embody the elements of informed consent as described in the HIPAA, World Medical Association Declaration of Helsinki, FDA 21 CFR Part 50.25, ICH GCP, and in accordance with any local regulations. The Investigator is responsible for the preparation, content, and IRB/IEC/REC approval of the ICF. The ICF must be approved by the clinical site-designated IRB/IEC/REC and be acceptable to KRI or its designee prior to their use.

The ICF must be written in a language fully comprehensible to the prospective patient. The written patient ICF will explain the objectives of the study and its potential risks and benefits. The information included on the ICF must be provided to the patient both verbally and in writing whenever possible and in a manner deemed appropriate by the IRB/IEC/REC. Patients must be given ample opportunity to read the information and inquire about details of the study. The Investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient must not be allowed to enter the study.

If a patient agrees to participate, he or she will be asked to sign and date an ICF, the original copy of which will be kept by the Investigator. A copy of the signed ICF will be given to the patient. Information documenting the informed consent procedure will be recorded in the patient's medical records (i.e., source document), and the original signed ICF must be made available to the study monitor for inspection.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by CRO and/or the sponsor and provided in writing by CRO and/or the sponsor prior to the consent process.

All ICFs must be approved for use by the sponsor or designee and receive approval/favorable opinion from an IRB/IEC/REC prior to their use. If the ICF requires revision (e.g., due to a protocol amendment or significant new safety information), it is the PI's responsibility to ensure that the amended form is reviewed and approved by the sponsor prior to submission to the governing IRB/IEC/REC and that it is read, signed, and dated by all patients or their designees currently and subsequently enrolled in the study.

11.4 Amendments to the Protocol

An amendment must be agreed to in writing by the sponsor, submitted to FDA as an IND application amendment, and submitted to and approved by the respective IRB/IEC/REC for each investigational site before it is implemented. Written approval of a protocol amendment is not required prior to implementation for changes to the protocol, which eliminate immediate hazard to the patient; however, approval must be obtained as soon as possible thereafter. Approved amendments must also be signed by the Investigator.

11.5 Study Initiation

The Investigator must not enroll any patients prior to the completion of a formal meeting conducted by a representative of the sponsor. This meeting will include a detailed review of the study protocol and eCRFs. Study drug will not be supplied to an Investigator until

all the necessary pre-study requirements have been completed and essential signed documents are received by the sponsor or its representative.

11.6 Study Monitoring

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH/FDA GCPs, applicable regulatory requirements, HIPAA, and the current Declaration of Helsinki. Valid data are to be entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the sponsor in the maintenance of accurate, complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol with the Investigator. In addition, the monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of the sponsor to monitor the study as frequently as the sponsor deems is necessary to determine that data recording and protocol adherence are acceptable. The eCRFs and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant standard operating procedures, ICH GCP guidance, and FDA GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses. The Investigator and staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.7 Case Report Form

All patient data generated during the study will be recorded on the eCRF.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs, designed specifically for this study and supplied by the representatives of the sponsor for each patient.

The representatives of the sponsor will only consider the eCRFs to be complete after they are reviewed and signed by the Investigator, indicating his/her assurance of the accuracy of all recorded data. It is expected that the Investigator and staff will cooperate with the monitoring team and provide missing data in a timely manner.

11.8 Verification Procedures

In fulfillment of their obligations to the sponsor and to verify compliance with this protocol, ICH GCP guidance, and FDA GCP regulations, the Investigator will permit the representatives of the sponsor, the IRBs/IECs/RECs, the monitor, and regulatory authorities to have direct access to the patient's medical records.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical record, eCRFs, and on study forms, when applicable, according to procedures provided in the protocol and/or supplemental instructions.

The Investigator will maintain a Patient Identification Code List to enable unambiguous identification of the patients (patient names and corresponding subject codes). The Patient Identification Code List is an essential document and as such must be maintained according to the ICH GCP guidelines.

11.9 Retention of Records

All documentation pertaining to the study will be retained by the sponsor in accordance with US FDA regulations and the ICH GCP guidance document.

The representatives of the sponsor will provide each Investigator with a study file, which will be used to file the Investigator's Brochure, protocol, drug accountability records, correspondence with the IRB/IEC and the sponsor, and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and the sponsor or its designees.

The Investigator will retain records required to be maintained under federal regulations for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, these documents will be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the Investigator must make provision for the patient's medical records to be kept for the same period of time.

Patients' medical records and other original data will be archived in accordance with applicable regulations and requirements established by the investigational sites.

11.10 Insurance and Indemnity

The sponsor's obligations regarding insurance and indemnification are described in other documents or agreements.

11.11 Audit and Inspection

The Investigator must permit study-related quality oversight monitoring, quality assurance audits, IRB/IEC/REC review, and regulatory agency inspections and provide direct access to source data documents. It is important that the Investigator(s) and their relevant personnel are available during the monitoring, audit, or inspection visits and that sufficient time is devoted to the process.

It is the responsibility of KRI to perform sponsor quality oversight, as part of the quality assurance and quality control programs. The purpose of a quality assurance audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, the principles of ICH GCP, and other applicable regulatory requirements.

12.0 USE OF INFORMATION

12.1 General Aspects

All information concerning KRI, such as patent applications, formula, manufacturing processes, basic scientific data or formulation information supplied by KRI and not previously published, are considered confidential and will remain the sole property of KRI. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of KRI, except for official representatives, such as regulatory authorities.

It is understood by the Investigator that the information developed in this clinical study, in connection with the development of K-161 will be used by KRI and, therefore, may be disclosed by KRI as required to other clinical Investigators, other pharmaceutical companies and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to KRI complete test results and all data compiled in this study.

12.2 Patient Confidentiality and Data Protection

KRI and its designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, all data will be linked to the eCRF via a unique identification number and the patient's initials. The data will be masked correspondingly in all data analyses.

However, in compliance with the guidelines and regulations of the US FDA concerning the acceptance of clinical studies in support of IND applications and the ICH GCP (whether performed in the US or elsewhere), and in fulfillment of its obligations to KRI to verify compliance with this protocol, KRI's designee requires that the Investigator to permit its monitor, representatives from the FDA, KRI's designated auditors, IRBs/IECs, and other governmental regulatory authorities to review the patient's primary medical records (source data or documents) including, but not limited to laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports related to deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the patient before the patient is entered into the study.

12.3 Final Report and Publication Policy

All information regarding this study will be kept strictly confidential. All data derived from the study will be the property of KRI. The Investigator must undertake not to submit any part of the data from this study for publication without prior consent of KRI. KRI may disclose data derived from the study to other Investigators and drug regulatory authorities.

After completion of the study, and as agreed by the Investigator and KRI, the Investigator may send a draft manuscript to KRI to be reviewed in order to reach an agreement regarding publication. The Investigator must receive written approval from KRI before the final version of the manuscript is submitted for publication.

At the conclusion of the study, after the data are analyzed, KRI or its designee will prepare a final clinical report.

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