K-161-2.01US

A Phase 2, Prospective, Double-Masked, Randomized, Multi-Center, Vehicle-Controlled, Parallel-group, 4-week Administration Study Assessing the Safety, Efficacy, and Optimum Dosage of K-161 in non-Japanese and Japanese Adult Subjects with Moderate to Severe Dry Eye Disease Both in Environmental and Controlled Adverse Environmental (CAE®) Settings

NCT #: 04084483

Clinical Trial Protocol

Ver. 1.0

14 September 2018

Clinical Trial Protocol: K-161-2.01US

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Protocol Number:	K-161-2.01US
Study Phase:	2
Investigational Product Name:	K-161
IND/IDE/PMA Number:	N/A
Indication:	Dry eye disease
Investigators:	Multi-Center
Sponsor:	Kowa Research Institute, Inc. (KRI) [redacted]

	Date
Original Protocol:	14 September 2018
Amendment 1:	-

Confidentiality Statement

This protocol contains confidential, proprietary information of [redacted]. and/or Kowa Research Institute, Inc. Further dissemination, distribution or copying of this protocol or its contents is strictly prohibited.

SPONSOR PERSONNEL

[redacted]

[redacted]

[redacted]

MEDICAL MONITOR

[redacted]

SYNOPSIS

Protocol Title:	A Phase 2, Prospective, Double-Masked, Randomized, Multi-Center, Vehicle-Controlled, Parallel-group, 4-week Administration Study Assessing the Safety, Efficacy, and Optimum Dosage of K-161 in non-Japanese and Japanese Adult Subjects with Moderate to Severe Dry Eye Disease Both in Environmental and Controlled Adverse Environmental (CAE) Settings
Protocol Number:	K-161-2.01US
Investigational Product:	1. K-161 Ophthalmic Solution 2. Placebo Ophthalmic Solution (Vehicle)
Study Phase:	2
Objective(s):	The objective of the study is to assess the safety, efficacy, optimum dosage, and dosing regimen of K-161 compared to its vehicle from Day 1 (baseline) to Day 29 in non-Japanese and Japanese adult subjects with moderate to severe dry eye disease both in environmental and CAE settings.
Overall Study Design:	
Structure:	Prospective, double-masked, randomized, multi-center, vehicle-controlled, parallel-group study
Duration:	An individual subject's participation is estimated to be approximately 6 weeks (42 days) with a follow-up phone call.
Controls:	Placebo Ophthalmic Solution (Vehicle)
Dosage/Dose Regimen/ Instillation/Application/Use:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally for 28 days (from Visit 2 to Visit 5). 1) [redacted] K-161 Ophthalmic Solution; [redacted] 2) [redacted] K-161 Ophthalmic Solution; [redacted] 3) [redacted] K-161 Ophthalmic Solution; [redacted] 4) Placebo Ophthalmic Solution (Vehicle); [redacted] During a 14-day study run-in period (for the purpose of subject selection) prior to randomization, all

	subjects will receive Placebo Ophthalmic Solution (Vehicle) [redacted]
Summary of Visit Schedule:	5 visits over the course of approximately 6 weeks with a follow-up phone call. • Visit 1 = Day -14 ± 2, CAE Screening • Visit 2 = Day 1, CAE Confirmation/ Baseline • Visit 3 = Day 8 ± 1 • Visit 4 = Day 15 ± 2 • Visit 5 = Day 29 ± 2
Measures Taken to Reduce Bias:	This is a double-masked, randomized treatment assignment study.
Study Population Characteristics:	
Number of Subjects:	Approximately 600 subjects will be screened to enroll approximately 240 (60 per treatment arm*) subjects [redacted]
Condition/Disease:	Dry Eye Disease (DED)
Inclusion Criteria:	

Subjects who meet all of the following criteria will be eligible to participate in the study.

Subjects must:

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

[redacted]

Exclusion Criteria:

Subjects who meet any of the following criteria will not be eligible to participate in the

study.

Subjects must not:

1. Have any ocular condition [redacted]
2. Have a history of [redacted] corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure [redacted] within 12 months [redacted]

[redacted]

Evaluation Criteria:	
Efficacy Measures and Endpoints:	**Primary Efficacy Endpoints:** The primary efficacy endpoint (sign) is: • Change in inferior corneal staining score from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting The primary efficacy endpoint (symptom) is: • Change in Ora Calibra® ODS from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting **Important Secondary Efficacy Endpoints:** The important secondary efficacy endpoints are: • Change in Schirmer's Test value (unanesthetized) from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted]

	[redacted] to its vehicle [redacted] in environmental setting • Change in TFBUT from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting **<u>Secondary Efficacy Endpoints:</u>** The secondary efficacy endpoints are: • Fluorescein staining by region: central, superior, inferior, temporal, nasal and corneal sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale • Lissamine green staining by region: central, superior, inferior, temporal, nasal, and conjunctival sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale • Conjunctival Redness as assessed by the Ora Calibra® Scale • TFBUT • Tear Osmolarity • Schirmer's Test (unanesthetized) • Blink Rate • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire • Visual Analog Scale (VAS) ▪ Burning/ Stinging ▪ Itching ▪ Foreign Body Sensation ▪ Blurred Vision ▪ Eye Dryness ▪ Photophobia ▪ Pain • OSDI© • Daily diary

	[redacted]
Safety Measures:	[redacted] • Adverse event query [redacted] • Maximum dose tolerability by comparing the [redacted] K-161 [redacted] arm to the [redacted] and [redacted] K-161 [redacted] arms
Other:	[redacted]

Analysis Populations

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary analysis will be performed on the ITT population. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock

and unmasking. Subjects in the PP population will be analyzed as treated.

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

Sample Size

This study is expected to enroll 240 subjects in a 1:1:1:1 ratio across four treatment arms, or 60 subjects per treatment arm. In addition, randomization will be stratified such that [redacted] will be randomized in each treatment arm.

The standard deviation for change from baseline in post-CAE inferior corneal fluorescein staining ranges between 0.68 and 0.81 units. Assuming a common standard deviation of 0.77, a sample size of 60 subjects per group will have approximately 90% power to detect a difference of 0.46 units between the active treatment group and the vehicle group using a two-sample t-test at a two-sided significance level of 0.05. Again, it is assumed that adjusting for baseline and site will further reduce variability and provide >90% power.

Likewise, the standard deviation for change from baseline scores in the post-CAE ODS at Day 29 is assumed a common standard deviation of 0.82, a sample size of 60 subjects per group will have approximately 90% power to detect a difference of 0.49 units between the active treatment group and the vehicle group using a two-sample t-test at a two-sided significance level of 0.05. It is assumed that adjusting for baseline and site will further reduce variability and provide >90% power.

Multiplicity Consideration:

Common factors for multiplicity are multiple arms and multiple endpoints.

1) Multiple arms

The primary treatment comparison will be between the [redacted] K-161 [redacted] treatment arm and the vehicle [redacted] treatment arm. Other treatment comparisons will be considered secondary or exploratory.

2) Multiple endpoints

The primary and important secondary endpoints will be tested hierarchically to maintain the study-wise Type I error rate of 0.05. First, change from baseline in inferior corneal fluorescein staining will be tested at an alpha level of 0.05. The test for change from baseline scores in the ODS will be conducted at an alpha level of 0.05 only if the previous test demonstrates significance. The test for change from baseline in Schirmer's test will be conducted at an alpha level of 0.05 only if the previous test demonstrates significance. The test for change from baseline in TFBUT will be conducted at an alpha level of 0.05 only if the previous test demonstrates significance. All other secondary and exploratory endpoints and treatment comparisons will be considered exploratory.

The hierarchical testing order will be as follows:

Primary comparisons:

1. Comparison of the change from baseline in post-CAE inferior corneal staining at Day 29 ([redacted] K-161 [redacted] vs vehicle)
2. Comparison of the change from baseline in post-CAE ocular discomfort at Day 29 ([redacted] K-161 [redacted] vs vehicle)

Important Secondary comparisons:

3. Comparison of the change from baseline in pre-CAE Schirmer's test value at Day 29 ([redacted] K-161 [redacted] vs vehicle)
4. Comparison of the change from baseline in post-CAE TFBUT at Day 29 ([redacted] K-161 [redacted] vs vehicle)

Thus, the study-wise Type I error rate will be maintained at 0.05 by considering only one dose of K-161 as the primary treatment comparison and using a hierarchical testing procedure.

Primary Efficacy Analyses:

The primary comparisons of change from baseline in post-CAE inferior corneal staining and ocular discomfort between the [redacted] K-161 [redacted] group and the vehicle group at Day 29, will be performed using analysis of covariance (ANCOVA) models. The respective baseline post-CAE score will be included as a covariate in each model and site will be included as a fixed effect. Treatment by baseline and treatment by site interactions will be explored in separate models and, if significant, analyses will be performed by baseline stratification and/or site, respectively, to further examine significant interactions. In addition, unadjusted two-sample t-tests and Wilcoxon rank-sum tests will be performed for each comparison as sensitivity analyses. The primary analyses will use the ITT population.

For the primary endpoints multiple imputation with a control-based pattern mixture model will be used.

Secondary Efficacy Analyses

Secondary and exploratory endpoints will be analyzed similarly to the primary analyses on the ITT population. Continuous and ordinal variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, minimum and maximum), and analyzed with ANCOVA models and two-sample, two-sided t-tests comparing each K-161 [redacted] group to the vehicle group. All visit-based data will be analyzed by visit and for each timepoint, if applicable, as well as the change from baseline.

Data collected pre- and post-CAE will also be analyzed for the change from pre- to post-CAE within each visit. Data collected during the CAE will also be analyzed using repeated measures models including all of the time points from a CAE exposure. Daily subject diary symptom data will be analyzed using each weekly average score from the diaries, as well as using repeated measures models across the diary collection period.

For the two important secondary endpoints, other secondary, and exploratory endpoints, multiple imputation with a control-based pattern mixture model will be used.

[redacted]

Safety Variables

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature 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 will be given of subjects 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 performed for ocular and non-ocular AEs.

[redacted]

Other analyses may be conducted and the details will be included in a separate statistical analysis plan.

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
[redacted]	[redacted]
[redacted]	[redacted]
CAE	controlled adverse environment
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
CRF	case report form
CRO	contract research organization
[redacted]	[redacted]
DED	dry eye disease
eCRF	electronic case report form
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
IND	investigational new drug application
[redacted]	[redacted]
IP	investigational product
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
[redacted]	[redacted]
LASIK	laser in situ keratomileusis
LOCF	last observation carried forward
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities

[redacted]	[redacted]
NCS	not clinically significant
ODS	Ocular Discomfort Score
OSDI	Ocular Surface Disease Index
[redacted]	[redacted]
PP	per protocol
[redacted]	[redacted]
SAE	serious adverse event
[redacted]	[redacted]
SOP	standard operating procedure
[redacted]	[redacted]
TFBUT	tear film break-up time
[redacted]	[redacted]

1 INTRODUCTION

Dry eye disease is a multifactorial, progressive disorder of the ocular surface resulting from insufficient tear coverage of the surface of the eye in combination with ocular surface inflammation. Patients with DED often experience severe pain, visual impairment, tear film hyperosmolarity and instability, inflammation, and corneal wounding. 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 et al. 2017). In the United States, 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 2030 (Schaumberg et al. 2002, Schaumberg et al. 2003, Schaumberg et al. 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. Three currently available options for treating inflammation at the ocular surface are Restasis® (cyclosporine ophthalmic emulsion) CEQUA™ (cyclosporine ophthalmic solution), and Xiidra® (lifitegrast ophthalmic solution). 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 et al. 2012). Xiidra® has also been shown to be associated with ocular adverse events; in a clinical study of Xiidra® for subjects with DED, subjects reported increased ocular irritation upon instillation with Xiidra® compared to placebo (7.8% compared to 1.4% in the placebo group) (Tauber et al. 2015). Similarly, common adverse reactions reported after use of CEQUA include instillation site pain and conjunctival hyperemia (CEQUA 2018). Thus, there remains a medical need for more efficacious treatment options with a more favorable safety and comfort profile for patients with DED.

1.1 Drug Profile from Non-clinical Studies

[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]. [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]

[redacted]

This will be the first clinical study of K-161 Ophthalmic Solution.

2 STUDY OBJECTIVES

Prior to any changes in a subject's medical treatment and/or study visit procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent (and/or assent) and sign a HIPAA form.

The objectives of the study are to assess the safety, efficacy, optimum dosage, and dosing regimen of K-161 compared to its vehicle from Day 1 (baseline) to Day 29 in non-Japanese and Japanese adult subjects with moderate to severe dry eye disease both in environmental and Controlled Adverse Environment (CAE) settings.

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study is that [redacted] K-161 Ophthalmic Solution [redacted] is superior to its vehicle [redacted] for the primary endpoints of signs and symptoms of dry eye, as follows:

- Sign: Post-CAE inferior corneal fluorescein staining score on the Ora Calibra® scale, measured by mean change from baseline (Visit 2) to Visit 5
- Symptom: Post-CAE ocular discomfort scale on the Ora Calibra® scale, measured by mean change from baseline (Visit 2) to Visit 5

4 OVERALL STUDY DESIGN

This is a Phase 2, multicenter, randomized, double-masked, vehicle-controlled, parallel-group design with block enrollment. Subjects will be randomized to one of the following treatment groups at Visit 2:

- [redacted] K-161; [redacted] (N=~60)
- [redacted] K-161; [redacted] (N=~60)
- [redacted] K-161; [redacted] (N=~60)
- Placebo Ophthalmic Solution (Vehicle); [redacted] (N=~60)

Approximately 240 subjects will be randomly assigned to one of the four treatment groups (1:1:1:1). [redacted] Subjects, Sponsor, Contract research organization (CRO), and site personnel will be masked to treatment assignment. To ensure masking, a dedicated unmasked staff member/technician will be delegated to dispense and observe instillation of randomized study drug and collect randomized study drug from a subject for drug accountability. This person cannot perform any other study-related procedures. Additionally, the informed consent form (ICF) will not indicate any relationship between dosing regimen and treatment. Subjects will be instructed not to discuss their assigned dosing regimen or perceived treatment effects with other study participants.

During the screening period, two 90-minute exposures to the CAE will be conducted to ascertain eligibility to enter the study. Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle [redacted] for approximately 14 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double-masked fashion for 28 days. Randomization will be stratified on Visit 2 Post-CAE inferior fluorescein staining and Post-CAE ocular discomfort on the Ora Calibra® scale. Subjects will self-administer drops either [redacted] or [redacted] and will complete daily diary assessments as instructed.

At Visit 4 (Day 15) and Visit 5 (Day 29), CAE exposure will occur, with pre-CAE, during CAE (symptoms only) and post-CAE assessments of ocular signs and symptoms. At Visit 3, no CAE exposure will occur but signs and symptoms will be assessed. Study drug will be discontinued at Visit 5. Subjects will exit from the study at this visit. The follow-up phone call will occur about 7 days after the final day of randomized study drug treatment.

The timing of visit including each examinations should be consistent in each subject through the study phase.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

It is estimated that approximately 600 subjects will be screened to enroll approximately 240 randomized subjects (60 in each group). [redacted] Subjects will be randomized in a 1:1:1:1 ratio of

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

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Each subject <u>must</u>:

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

[redacted]

[redacted]

5.4 Exclusion Criteria

Each subject may <u>not</u>:

1. Have any ocular condition [redacted]
2. Have a history of [redacted] corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure [redacted] within 12 months [redacted]

[redacted]

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Sponsor and/or investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6.2).

The subject has the right to withdraw from the study at any time. Nevertheless, in this study, every attempt will be made to prevent missing data and to obtain complete follow up of all subjects during the study period. Investigators will be trained to minimize full withdrawals from the study period wherever possible. Subjects who discontinue study drug during the study period are not required to withdraw from the study. These subjects

will be encouraged to remain in the study and asked to conduct the remaining study visits as outlined in the protocol through Visit 5. If a subject fails to actively maintain contact with the Investigator, reasonable efforts (telephone calls to family members or friends, e-mail contacts, etc.) will be made in order to encourage the subject to complete the study visits.

6 STUDY PARAMETERS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint (sign) is:

- Change in inferior corneal staining score from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting

The primary efficacy endpoint (symptom) is:

- Change in Ora Calibra® ODS from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting

6.1.2 Important Secondary Efficacy Endpoints

The important secondary endpoints are:

- Change in Schirmer's Test value (unanesthetized) from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in environmental setting
- Change in TFBUT from Day 1 (baseline) to Day 29 by comparing [redacted] K-161 [redacted] to its vehicle [redacted] in CAE setting

6.1.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are compared between vehicle [redacted] and K-161 [redacted] (i.e., [redacted] K-161 [redacted] and [redacted] K-161 [redacted]) for:

- Fluorescein staining by region: central, superior, inferior, temporal, nasal and corneal sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale
- Lissamine green staining by region: central, superior, inferior, temporal, nasal, and conjunctival sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale
- Conjunctival Redness as assessed by the Ora Calibra® Scale
- TFBUT
- Tear Osmolarity
- Schirmer's Test (unanesthetized)
- Blink Rate

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
  - Burning/ Stinging
  - Itching
  - Foreign Body Sensation
  - Blurred Vision
  - Eye Dryness
  - Photophobia
  - Pain
- OSDI©
- Daily diary

6.1.4 [redacted]

[redacted]

6.2 Safety Measures

The safety measures being evaluated are:

- [redacted]
- AE query
- [redacted]
- Maximum dose tolerability by comparing the [redacted] K-161 [redacted] arm to the [redacted] and [redacted] K-161 [redacted] arms

6.3 Other Measures

The other measures being evaluated are:

[redacted]

6.4 [redacted]

[redacted]

6.5 [redacted]

[redacted]

6.6 [redacted]

[redacted]

6.7 Clinical Laboratory Measurements

The following assessments are being conducted:

Hematology: [redacted]

Clinical chemistry: [redacted]

[redacted]

Urinalysis: [redacted]

7 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Masking

All arms will be double-masked. To ensure masking, an unmasked technician delegated by the Investigator will perform all study drug instruction, dispensation, collection and accountability. This technician cannot perform any other study visit procedures. Study Treatments/Formulations

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

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

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen were selected based on non-clinical studies. The proposed treatment period of 4 weeks is based on results from pre-clinical studies and on the anti-inflammatory mechanism of action of the drug.

7.1.3 Instructions for Use and Administration

Subjects who were randomized to [redacted] arm must administer study drug at [redacted]. Subjects who were randomized to [redacted] arm must at [redacted] If missed, the subject must not administer the eye drop if the next dosing is in less than 2 hours. At Visits 2, 3, 4, and 5, all subjects must visit their study sites without administering any topical ophthalmic preparations, including study drug, and must not administer topical ophthalmic preparations until all examinations are finished. Subjects, Sponsor, CRO, and site personnel (with the exception of the following person) will be masked to treatment assignment. To ensure masking, a dedicated unmasked staff member/technician will be delegated to dispense and observe instillation of randomized study drug and collect randomized study drug from a subject for drug accountability. This person cannot perform any other study-related procedures. Additionally, the informed consent form (ICF) will not indicate any relationship between dosing regimen and treatment. Subjects will be instructed not to discuss their assigned dosing regimen or any perceived treatment effects with other study participants.

7.2 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

7.2.1 Labeling/Packaging

Investigational product (IP) will be packaged and labeled into clinical kits.

Run-in Period

For the run-in period, [redacted] to provide a sufficient medication supply.

Treatment Period

[redacted] For the treatment period, [redacted] to provide a sufficient supply of randomized study drug.

[redacted] For the treatment period, [redacted] to provide a sufficient supply of randomized study drug.

7.2.2 Storage of Investigational Product

The study drugs must be stored in a secure area accessible only to the investigator and his/her designees.K-161 drug product must be stored at controlled room temperature of 20-25°C (68-77°F) with excursions permitted between 15°C and 30°C (59-86°F) as indicated on the drug label.

7.2.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s), and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP dispensed to subjects, amount of IP returned to the investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP. Study drug accountability will be performed by an Unmasked Technician as delegated by the Investigator. To ensure masking, a dedicated unmasked staff member/technician will be delegated to dispense and collect randomized study drug from a subject for drug accountability. This person cannot perform any other study-related procedures.

7.2.4 Return or Disposal of Investigational Product

All IP (used or unused) will be returned to the sponsor or their designee. The return of IP will be specified in writing.

7.3 Other Study Supplies

Other study supplies include [redacted] Schirmer's test strips, Tear meniscometry strips, sodium fluorescein, lissamine green, [redacted] Tear

Osmolarity cards and [redacted]

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in sections 5.2 and 5.3 will be considered for entry into this study.

8.1.2 Informed Consent

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

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria (Section 5.4).

8.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion and none of the exclusion criteria (Section 5.3 and 5.4).

8.1.5 Methods for Assignment to Treatment Groups:

Before the initiation of study run-in at Visit 1, each subject who provides written informed consent will be assigned a screening number. All screening numbers will be assingned in strict numerical sequence at a site and no numbers will skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 and Visit 2 will be assigned a randomization number at the end of Visit 2. The Interactive Web Response System (IWRS) will be used to assign all randomization numbers.

[redacted]

For the non-Japanese subjects, randomization will be further stratified by the following factors and cut-offs:

[redacted]

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). Subjects, Sponsor, CRO, and site personnel will be masked to treatment assignment. To ensure masking, a dedicated unmasked staff member/technician will be delegated to dispense and observe instillation of randomized study drug and collect randomized study drug from a subject for drug accountability. This person cannot perform any other study-related procedures.

8.2 Concurrent Therapies

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

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

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4).

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objectives

Procedures listed below should be performed in the given order. See Appendix 1 for the Schedule of Visits and Measurements Appendix 2 for details on methodologies and grading systems.

8.3.2 Visit 1: Day –14 ± 2 – CAE Screening

All subjects will undergo the following screening assessments:

[redacted]

- Informed Consent/HIPAA
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- [redacted]
- [redacted]
  - [redacted]

[redacted]

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- [redacted]
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- Run-in Instillation at the Study Site: All subjects having a positive response and meeting all other screening eligibility criteria at the end of Visit 1 will receive run-in drops for dosing. [redacted]
- Ora Calibra® Drop Comfort Scale
- Ora Calibra® Drop Comfort Questionnaire
- Run-in (Vehicle) and Diary Dispensation: Prior to discharge from the study site on Day –14, subjects will be dispensed sufficient Run-in supply to last until Visit 2 and will be educated in diary recording and self–administration of vehicle run-in. [redacted]
- AE Query
- Subjects will be scheduled for Visit 2.

8.3.3 Visit 2: Day 1 – CAE Confirmation and Baseline

[redacted]

- Study Diary/Run-in Collection
- [redacted]
- Medical/medication history update
- AE query
- [redacted]
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- Blink Rate
- Tear Osmolarity
- [redacted]
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining

- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- [redacted]
- Randomization
- Study Drug Instillation at the Study Site: All subjects having a positive response and meeting all other screening eligibility criteria at the end of Visit 2 will be randomized to one of four treatment groups utilizing the IWRS system. [redacted]
- Ora Calibra® Drop Comfort Scale
- Ora Calibra® Drop Comfort Questionnaire
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in study drug diary recording and self–administration of study drug. [redacted]
- AE Query
- Subjects will be scheduled for Visit 3.

8.3.4 Visit 3: Day 8 ±1

- Study Drug Diary/Study Drug Collection
- Medical/medication history update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- Blink Rate
- Tear Osmolarity
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 3, subjects will be assigned a new study drug kit via the IWRS system for at-home dosing up to Visit 4. Subjects will again be educated in study drug diary recording and self–administration of study drug. [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- AE Query
- Subjects will be scheduled for Visit 4.

8.3.5 Visit 4: Day 15 ± 2

[redacted]

- Study Drug Diary/Study Drug Collection
- Medical/medication history update
- AE query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- Blink Rate
- Tear Osmolarity
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- [redacted]
- [redacted]
  - [redacted]

[redacted]

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- [redacted]

- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 4, subjects will be assigned a new study drug kit via the IWRS system for at-home dosing up to Visit 5. Subjects will again be educated in study drug diary recording and self–administration of study drug.
-
-
-
- AE Query
- Subjects will be scheduled for Visit 5.

8.3.6 Visit 5: Day 29 ± 2

- Study Drug Diary/Study Drug Collection
- Medical/medication history update
- AE query
-
-
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Visual Analog Scale (VAS)
-
-
- Conjunctival Redness
- Blink Rate
- Tear Osmolarity
-

- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- [redacted]
- [redacted]
- [redacted]

[redacted]

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- [redacted]
- [redacted]
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- [redacted]
- [redacted]
- [redacted]
- AE Query

8.3.7 Follow-up phone call

- Follow-up phone call (about 7 days after the final day of randomized study drug treatment)
- AE query
- Study exit

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

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

Evaluations that may be conducted at an Unscheduled Visit include:

- [redacted]
- Assessment of AEs
- [redacted]
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visits 1, 2, 3, and 4, and given written instructions. The subject daily diaries, used and unused [redacted] will be collected at each visit from Visit 2 up to and including Visit 5 to assess dosing and symptom assessment compliance. Dosing compliance will be based on the used and [redacted]. If the subject is less than 80% or more than 125% compliant with dosing based on [redacted] then the subject will be deemed non-compliant and a dosing deviation should be recorded.

In the subject daily diary, if more than 20% of Dose boxes are checked "no", left blank, or missing for a diary period, a subject will be deemed non-compliant and a diary deviation will be recorded. If more than 20% of the total diary symptom assessments for that dosing period are missed, these subjects will be deemed non-compliant and a diary symptom assessment deviation will be recorded. These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to [redacted] and/or sponsor and will be clearly documented on the eCRF.

8.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or [redacted] with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 5 visits over approximately a 6-week (~42 days) period (14 days pre-screening, 28 days of treatment) and a follow-up phone call.

8.9 Monitoring and Quality Assurance

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

Regulatory authorities of domestic and foreign agencies, quality assurance and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and

unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning. Exacerbation of conditions related to the signs and symptoms of DED will not be reported as an AE.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- ***Mild*:** Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- ***Moderate*:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- ***Severe*:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- ***Related*:** A reasonable possibility exists that the IP 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 IP 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

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE event include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

The investigator should 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.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening;

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

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours), unless the inpatient admission was pre-planned prior to the signing of the informed consent. For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

  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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Serious Adverse Events

All SAEs and their outcomes, regardless of causality or expectedness, must be reported to [redacted] and the sponsor as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate CRF. Adverse events will be

collected from the time of the signing of the Informed Consent until the follow-up phone call (about 7 days after the final day of randomized study drug treatment).

9.3.1 Reporting a Serious Unexpected Suspected Adverse Reaction

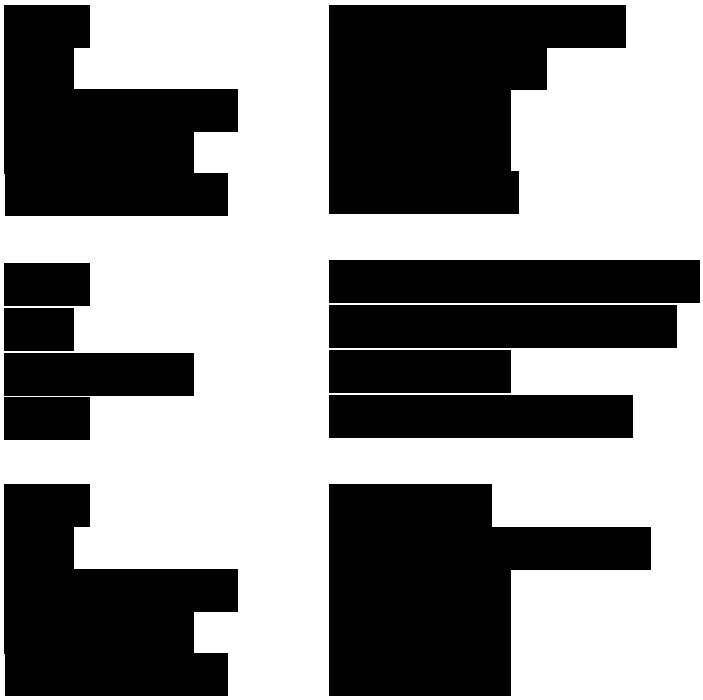
All SAEs that are both 'suspected' and 'unexpected' are also to be reported to the IRB/IEC and the regulatory authorities as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify [redacted] and the sponsor immediately using the contact information below; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] and the sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:



9.4 Procedures for Unmasking (if applicable)

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment group has been assigned to a subject. When possible (i.e., in non-emergent situations), [redacted] and/or the study sponsor should be notified before unmasking study drug. [redacted] and/or the study sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact [redacted] and/or the medical monitor prior to unmasking the identity of the IP, if possible. [redacted] will ask the site to complete and send them the Unmasking Request Form. [redacted] will notify the sponsor, and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using IWRS. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the TMF. For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study. Unmasked subjects will be followed for safety monitoring until resolution of the adverse event or study completion, whichever occurs last.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to [redacted] within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.
- Per-Protocol Population – The per-protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.
- Safety Population – The safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of efficacy data will be performed for the ITT population and on the PP population as sensitivity analyses.

10.2 Statistical Hypotheses

The following primary hypotheses will be tested against their respective two-sided alternative hypotheses in the order:

H_{01}: There is no difference in the change from baseline in the post-CAE inferior corneal staining score after 28 days of treatment of [redacted] K-161 [redacted] compared to vehicle.

H_{02}: There is no difference in the change from baseline in the post-CAE ocular discomfort score after 28 days of treatment of [redacted] K-161 [redacted] compared to vehicle.

Upon rejecting both H_{01} and H_{02}, the secondary hypotheses will be tested as detailed in Section 10.4.4 in the following order

H_{03}: There is no difference in the change from baseline in the pre-CAE Schirmer's test value after 28 days of treatment of [redacted] K-161 [redacted] compared to vehicle.

H_{04}: There is no difference in the change from baseline in the post-CAE TFBUT after 28 days of treatment of [redacted] K-161 [redacted] compared to vehicle.

These four hypotheses will be tested hierarchically, each at the alpha = 0.05 level to maintain a study-wise Type I error rate at 0.05.

10.3 Sample Size

This study is expected to enroll 240 subjects in a 1:1:1:1 ratio across four treatment arms, or 60 subjects per treatment arm. In addition, randomization will be stratified such that [redacted] will be randomized in each treatment arm.

The standard deviation for change from baseline in post-CAE inferior corneal fluorescein staining ranges between 0.68 and 0.81 units. Assuming a common standard deviation of 0.77, a sample size of 60 subjects per group will have approximately 90% power to detect a difference of 0.46 units between the active treatment group and the vehicle group using a two-sample t-test at a two-sided significance level of 0.05. Again, it is assumed that adjusting for baseline and site will further reduce variability and provide >90% power.

Likewise, the standard deviation for change from baseline scores in the post-CAE ODS at Day 29 is assumed a common standard deviation of 0.82, a sample size of 60 subjects per group will have approximately 90% power to detect a difference of 0.49 units between the active treatment group and the vehicle group using a two-sample t-test at a two-sided significance level of 0.05. It is assumed that adjusting for baseline and site will further reduce variability and provide >90% power.

10.4 Statistical Analysis

10.4.1 General Considerations

Quantitative variables will be summarized descriptively using number of subjects (n), mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

Change from pre-CAE to post-CAE will be calculated as post-CAE value minus pre-CAE value. Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment. Change from baseline will be calculated as follow-up visit value minus baseline value. Treatment comparisons between active and vehicle will be calculated as active minus vehicle.

All analyses will be 2-sided at a significance level of 0.05 unless otherwise specified. For all efficacy analyses, 95% confidence intervals on the difference between each dose of K-161 and vehicle will be provided.

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye, or the "worst eye," as defined by the following:

Worst Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. At least one eye (the right eye or the left eye) must meet all of the criterial. In the case that both eyes are eligible for analysis, the worst eye will be selected as the eye with the worst post-CAE inferior corneal staining at Visit 2. If the post-CAE inferior corneal staining at Visit 2 is the same in both eyes then the eye with the worst post-CAE ODS at Visit 2 will be worst eye. If the post-CAE inferior corneal staining and ocular discomfort are the same in both eyes then the right eye will be selected as the worst eye.

10.4.3 Missing Data

Missing data will be imputed using multiple imputation with a control-based pattern mixture model on the ITT population for the primary analyses, the important secondary, other secondary, and exploratory comparisons.

Sensitivity analyses of the primary analyses and important secondary comparisons will include the following in order to provide a robust understanding of the impact of missing and spurious data:

- Using complete case data (i.e. observed data only) on the ITT population
- Using last observation carried forward (LOCF) on the ITT population
- Multiple imputation under missing at random assumption with Markov Chain Monte Carlo (MCMC) techniques on the ITT population
- Using complete case data on the PP population.

No imputation will be used for safety endpoints.

10.4.4 Multiplicity Consideration

Common factors for multiplicity are multiple arms and multiple endpoints.

1) Multiple arms

The primary treatment comparison will be between the [redacted] K-161 [redacted] treatment arm and the vehicle [redacted] treatment arm. [redacted]

2) Multiple endpoints

The primary and important secondary endpoints will be tested hierarchically to maintain the study-wise Type I error rate of 0.05. First, change from baseline in inferior corneal fluorescein staining will be tested at an alpha level of 0.05. The test for change from baseline scores in the ODS will be conducted at an alpha level of 0.05 only if the previous test demonstrates significance. The test for change from baseline in Schirmer's test will be conducted at an alpha level of 0.05 only if the previous test demonstrates significance. The test for change from baseline in TFBUT will be conducted at an alpha

level of 0.05 only if the previous test demonstrates significance. [redacted]

The hierarchical testing order will be as follows:

Primary comparisons:

1. Comparison of the change from baseline in post-CAE inferior corneal staining at Day 29 ([redacted] K-161 [redacted])
2. Comparison of the change from baseline in post-CAE ocular discomfort at Day 29 ([redacted] K-161 [redacted]

Important Secondary comparisons:

3. Comparison of the change from baseline in pre-CAE Schirmer's test value at Day 29 ([redacted] K-161 [redacted])
4. Comparison of the change from baseline in post-CAE TFBUT at Day 29 ([redacted] K-161 [redacted])

Thus, the study-wise Type I error rate will be maintained at 0.05 by considering only one dose of K-161 as the primary treatment comparison and using a hierarchical testing procedure.

10.4.5 Efficacy Analyses

Primary Efficacy Analyses

The primary comparisons of change from baseline in post-CAE inferior corneal staining and ocular discomfort between the [redacted] K-161 [redacted] group and the vehicle group at Day 29, will be performed using analysis of covariance (ANCOVA) models. The respective baseline post-CAE score will be included as a covariate in each model and site will be included as a fixed effect. Treatment by baseline and treatment by site interactions will be explored in separate models and, if significant, analyses will be performed by baseline stratification and/or site, respectively, to further examine significant interactions. In addition, unadjusted two-sample t-tests and Wilcoxon rank-sum tests will be performed for each comparison as sensitivity analyses. The primary analyses will use the ITT population.

For the primary endpoints, multiple imputation with MCMC techniques will be used. Imputation will be performed by treatment arm with imputation terms for baseline and Day 29 scores.

Secondary Efficacy Analyses

Secondary and exploratory endpoints will be analyzed similarly to the primary analyses on the ITT population. Continuous and ordinal variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, minimum and maximum), and analyzed with ANCOVA models and two-sample two-sided t-tests comparing each K-161 group to the vehicle group. All visit-based data will be analyzed by visit and for each timepoint, if applicable, as well as the change from baseline.

Data collected pre- and post-CAE will also be analyzed for the change from pre- to post-CAE within each visit. Data collected during the CAE will also be analyzed using

repeated measures models including all of the time points from a CAE exposure. Daily subject diary symptom data will be analyzed using each weekly average score from the diaries, as well as using repeated measures models across the diary collection period.

For the two important secondary endpoints, other secondary, and exploratory endpoints, multiple imputation with MCMC techniques will be used. Imputation will be performed by treatment arm with imputation terms for baseline and Day 29 scores.

[redacted]

10.4.6 Safety Variables

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature 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 will be given of subjects 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 performed for ocular and non-ocular AEs.

[redacted]

Other analyses may be conducted and the details will be included in a separate statistical analysis plan.

[redacted]

[redacted]

10.4.11 Interim Analyses

There will be no interim analyses in this study.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IP in the countries involved will be addressed.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

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

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

11.1.2 Institutional Review Board (IRB) Approval

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

Only an IRB approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

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

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

11.4 Documentation

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

11.4.1 Retention of Documentation

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will

accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

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

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will be entered in eCRF for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.6 Publications

All data derived from the study will be the property of the sponsor and must be kept strictly confidential. The investigator must not submit any of the data from this study for publication without prior consent of the sponsor. The sponsor will have the final decision regarding any manuscript and publication.

12 REFERENCES

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13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Visit 1 Day -14 ± 2		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Follow-up Phone Call (Day 36 ± 2)
	Pre CAE	Post CAE	Pre CAE	Post CAE	Non CAE	Pre CAE	Post CAE	Pre CAE	Post CAE	
Informed Consent / HIPAA	X									
Medical / Medication History and Demographics	X									
[redacted]										
Medical / Medication Update			X		X	X		X		
Adverse Event Query		X	X	X	X	X	X	X	X	X
[redacted]										
Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X	X	X	X	X	
Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X	X	X	X	X	X	
OSDI© Questionnaire	X		X		X	X		X		
Visual Analog Scale	X	X	X	X	X	X	X	X	X	
[redacted]										
Conjunctival Redness	X	X	X	X	X	X	X	X	X	
Tear Osmolarity			X		X	X		X		
[redacted]										
TFBUT	X	X	X	X	X	X	X	X	X	
Fluorescein Staining	X	X	X	X	X	X	X	X	X	
Lissamine Green Staining	X	X	X	X	X	X	X	X	X	
Schirmer's Test	X		X		X	X		X		
Blink Rate			X		X	X		X		

Procedure	Visit 1 Day -14 ± 2		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Follow-up Phone Call (Day 36 ± 2)
	Pre CAE	Post CAE	Pre CAE	Post CAE	Non CAE	Pre CAE	Post CAE	Pre CAE	Post CAE	
[redacted]										
Vehicle Run-In Dispensation		X								
Vehicle Run-In Instillation		X								
Vehicle Run-in Collection			X							
Randomization				X						
Study Drug Dispensation				X	X		X			
[redacted]										
Study Drug Collection					X	X		X		
Diary Dispensation		X		X	X		X			
Diary Collection			X		X	X		X		
Exit Subject from Study										X

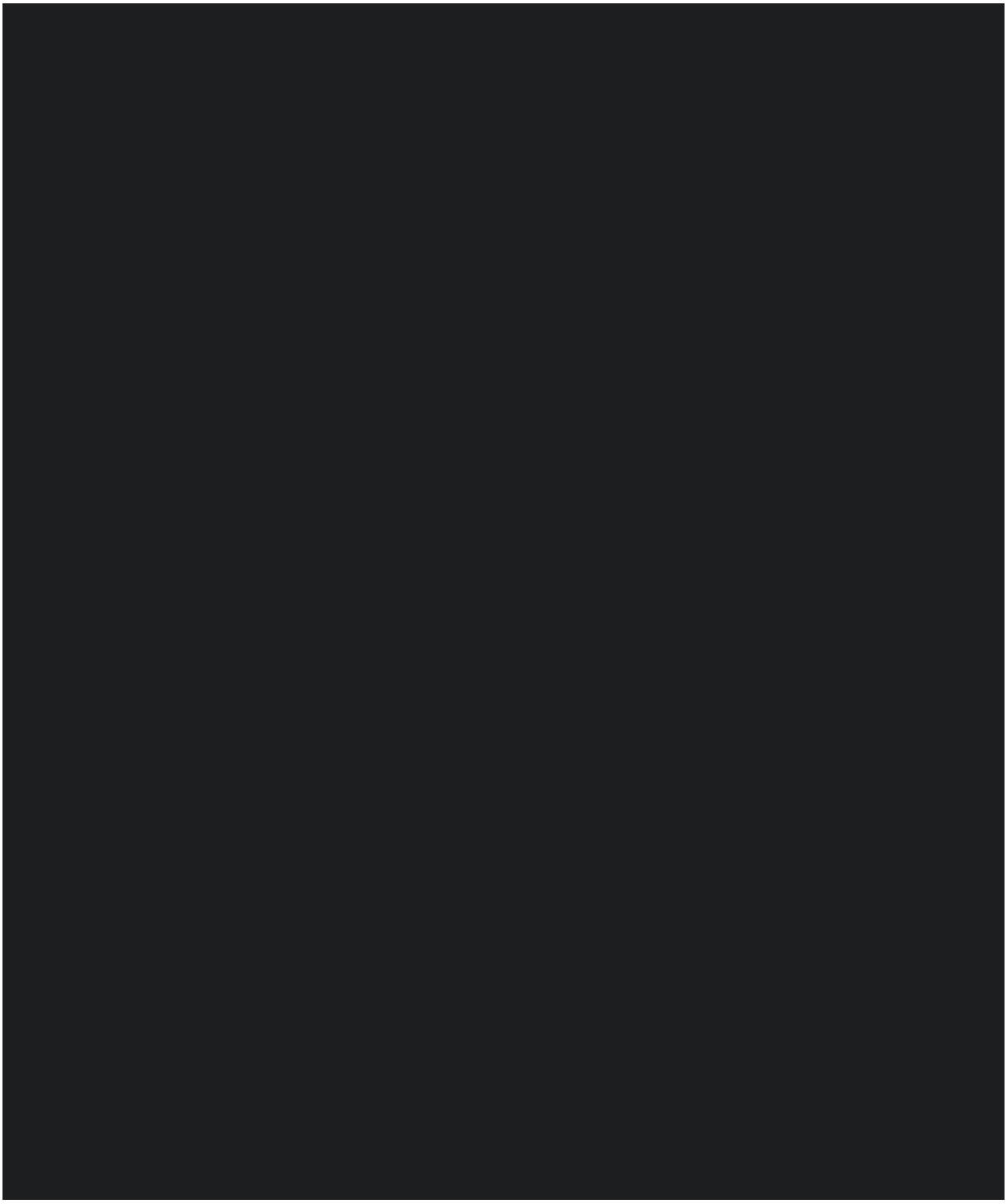
[redacted]

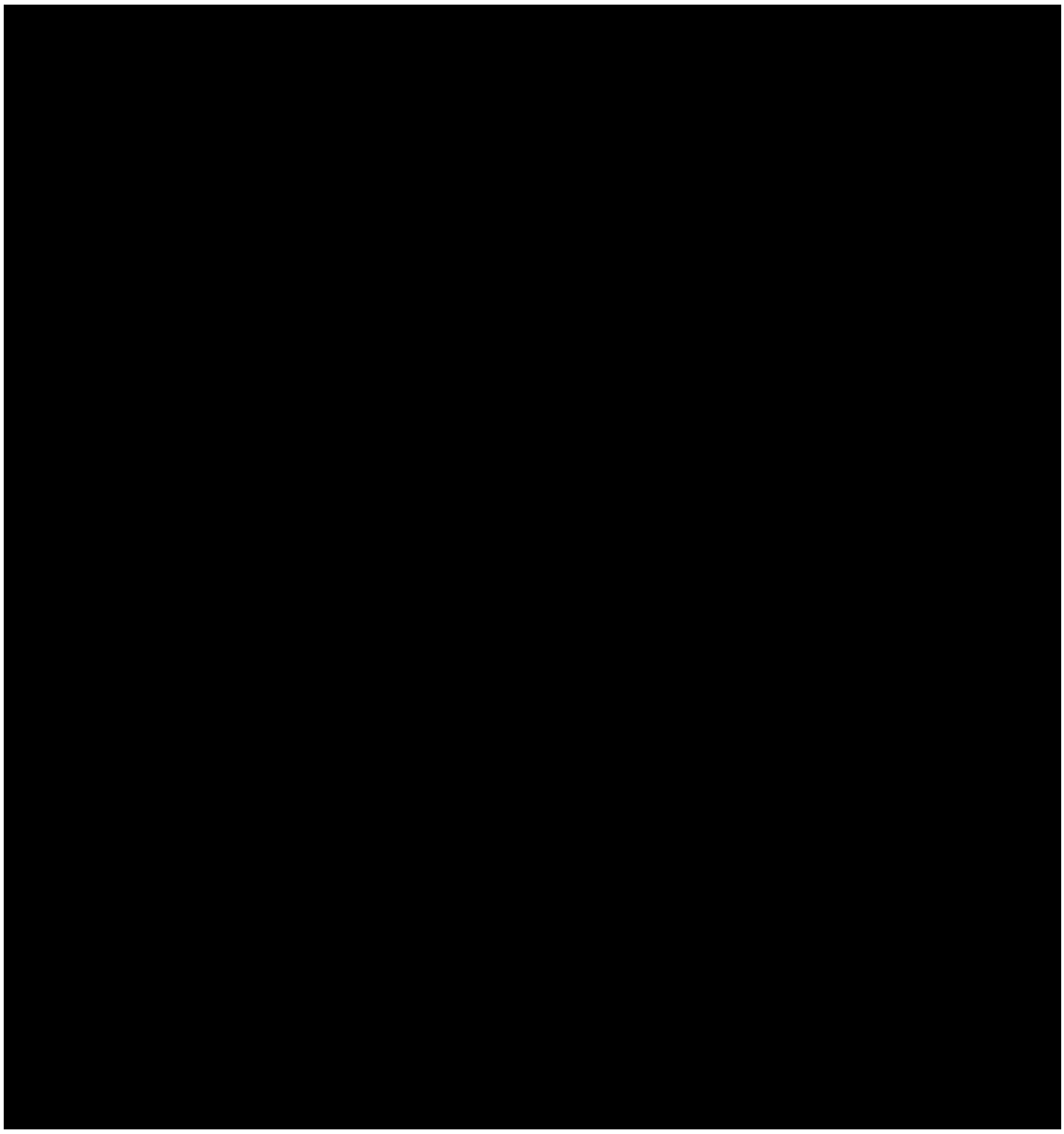
[redacted]

[redacted]

[redacted]

[redacted]





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APPENDIX 3: PROTOCOL AMENDMENT SUMMARY

Not Applicable.

APPENDIX 4: SPONSOR AND [redacted] APPROVALS

Protocol Title: A Phase 2, Prospective, Double-Masked, Randomized, Multi-Center, Vehicle-Controlled, Parallel-group, 4-week Administration Study Assessing the Safety, Efficacy, and Optimum Dosage of K-161 in non-Japanese/Japanese Adult Subjects with Moderate to Severe Dry Eye Disease Both in Environmental and Controlled Adverse Environmental (CAE) Settings

Protocol Number: K-161-2.01US

Final Date:

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

[redacted]

APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title: A Phase 2, Prospective, Double-Masked, Randomized, Multi-Center, Vehicle-Controlled, Parallel-group, 4-week Administration Study Assessing the Safety, Efficacy, and Optimum Dosage of K-161 in non-Japanese/Japanese Adult Subjects with Moderate to Severe Dry Eye Disease Both in Environmental and Controlled Adverse Environmental (CAE) Settings

Protocol Number: K-161-2.01US

Final Date:

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

[redacted]