Kowa Research Institute, Inc.

K-161-3.01

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

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Statistical Analysis Plan

Version 1.0

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Prepared by:

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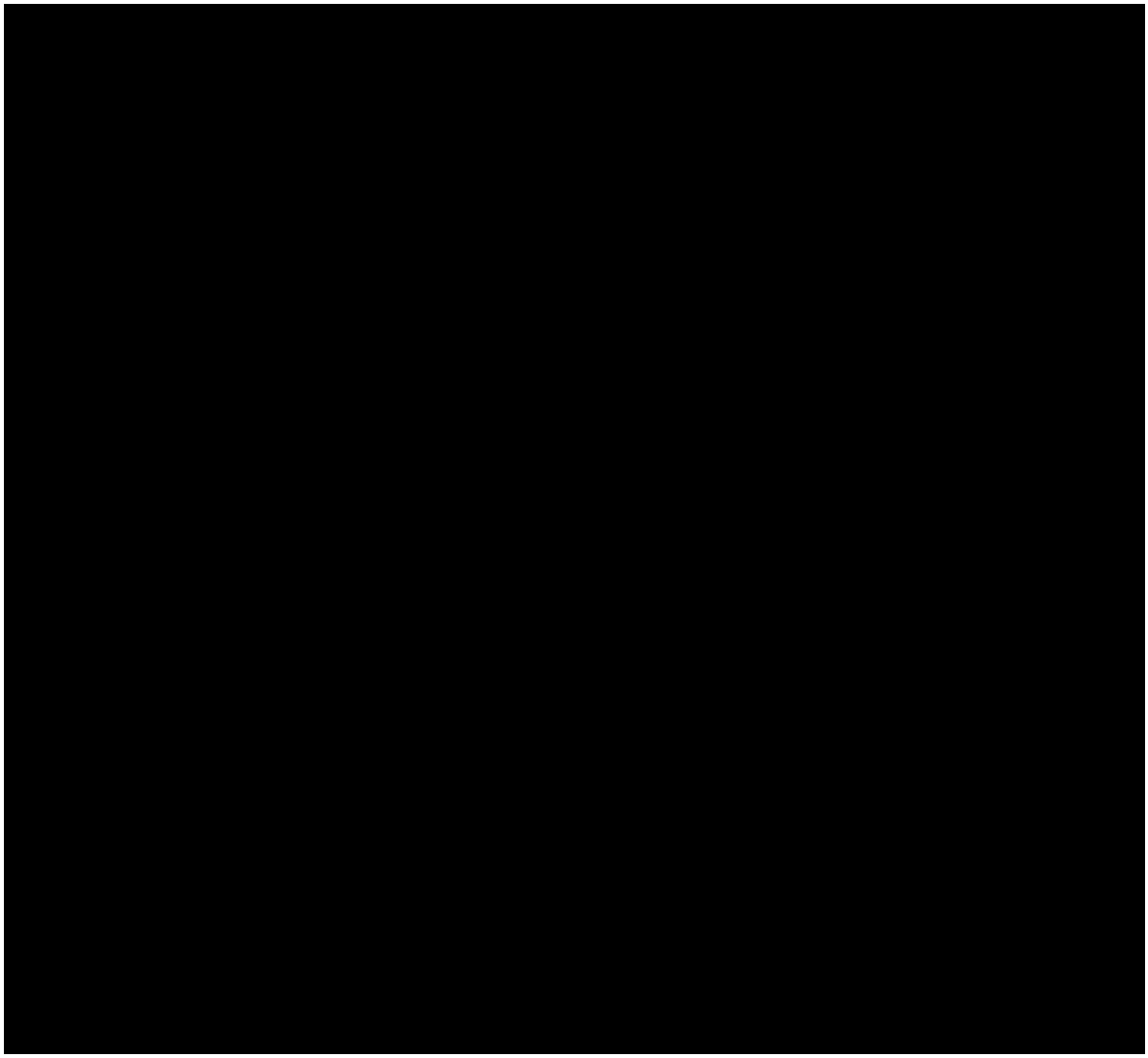

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List of Abbreviations

Abbreviation	Definition
ACMV	available case missing values
AE(s)	adverse event(s)
ATC	anatomical therapeutic chemical
[redacted]	[redacted]
CI	confidence interval
CRO	clinical research organization
CS	clinically significant
DED	dry eye disease
eCRF	electronic case report form
EDC	electronic data capture
EDS	eye dryness score
[redacted]	[redacted]
FAS	full analysis set
FAS12	full analysis set in the 12-week primary period
FAS52	full analysis set in the 52-week overall period
HIPAA	Health Insurance Portability and Accountability Act
ICE(s)	intercurrent event(s)
ICF	informed consent form
IEC	Independent Ethics Committee
[redacted]	[redacted]
IRB	Institutional Review Board
[redacted]	[redacted]
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
[redacted]	[redacted]
MMRM	mixed-model repeated measures
NCS	not clinically significant
NEI	National Eye Institute
OD	oculus dexter; right eye
OS	oculus sinister; left eye
OSDI	Ocular Surface Disease Index
OTC	over-the-counter
OU	oculus uterque; both eyes
PMM	pattern mixture model
PPS	per protocol set
PPS12	per protocol set in the 12-week primary period
PRN	pro re nata (as needed)
PT	preferred term

Q1	quartile 1
Q3	quartile 3
SAE	serious adverse event
SD	standard deviation
SOA	schedule of study site activities
SOC	system organ class
SP	safety population
SP12	safety population in the 12-week primary period
SP52	safety population in the 52-week overall period
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse events
TFBUT	tear film break-up time
[redacted]	[redacted]
US	United States
[redacted]	[redacted]
VAS	visual analog scale
WHO Drug	World Health Organization Drug Dictionary

1. Introduction

[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 dry eye disease (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.

This is a Phase 3, multi-center, randomized, double-masked, vehicle-controlled, parallel group study with up to 52 weeks of treatment.

This statistical analysis plan for K-161-3.01 protocol incorporating Amendment 2 (United States [US]) dated 2022-12-07 will examine efficacy, safety, and tolerability endpoints at planned analysis time points.

2. Objectives

2.1. Primary Objectives

The primary objectives of this study are the following:

- Symptom: To demonstrate the efficacy of K-161 ophthalmic solution [redacted] (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

2.2. 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 (OSDI©) Score
    - 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

2.3. 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

2.4. Exploratory Objectives

[redacted]

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 3, multi-center, 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. The run-in drops will be single-masked for patients. 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 approximately 220 randomized patients (110/arm) will be assigned into the 52-week Overall Period and the rest of study population (approximately 400 [200/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 4. The timing of patient visits and examinations will be consistent throughout the study.

3.2. Study Endpoints

3.2.1. 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.

3.2.2. Key Secondary Efficacy Endpoint

Change from baseline to Day 85 in total eye fluorescein staining score as assessed by expanded NEI scale.

3.2.3. 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.

3.2.4. Safety Endpoints

Safety assessments up to Day 85:

- AEs;
- [redacted]
- Systemic clinical evaluation;
- Clinical laboratory measurement;
- [redacted]

3.2.5. 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

3.2.6. Exploratory Endpoints

[redacted]

3.3. Study Procedures and Baseline

Prior to the implementation of study procedures, patients and persons conducting the consent discussion will be required to sign and date the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved informed consent form (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).

Worst Eye (Study) Eye: For efficacy analyses, 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. **The investigator will select the study eye**.

Day 1 (Visit 2) is when randomization occurs and is the day when the first dose of double-masked study drug is administered.

Baseline is defined as the last non-missing measurement including unscheduled assessments prior to the administration of first dose of double-masked study drug. The most recent ocular measurement for each eye will be used as a baseline value. Change from baseline is defined as the post-baseline value minus the baseline value for the given assessment. Note that the Visit 2 [redacted] is taken after study drug, so Visit 1 measurement likely serves as baseline in most cases.

Treatment ends either at Day 85 (Visit 6) for patients in the 12-week Primary Period or Day 365 (Visit 9) for patients in the 52-week Overall Period, or whenever the patient is prematurely discontinued/withdrawn from study drug administration.

Patients will have two weeks of untreated follow-up that ends either at Day 99 (Visit 6.5) for patients in the 12-week Primary Period or Day 379 (Visit 10) for patients in the 52-week Overall Period.

The schedule of study site activities (SOA) is presented in Section 12.

3.4. Treatments

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. The run-in drops will be single-masked for patients. Those who qualify at Visit 2 (Day 1) will administer either [redacted] K-161 or vehicle [redacted] in a double-masked fashion.

Patients in the 52-week Overall Period (the first approximately 220 patients) will receive K-161 [redacted] or Vehicle [redacted] for 52 weeks. There will be 2 weeks of untreated follow-up.

Patients in the 12-week Primary Period (the remaining approximately 400 patients) will receive K-161 [redacted] or Vehicle [redacted] for 12 weeks. There will be 2 weeks of untreated follow-up.

Randomization will be performed in a 1:1 ratio [redacted]. To preserve masking, all patients will self-administer assigned study drug [redacted] from [redacted]

Study drug is administered as [redacted] Patients will be instructed to administer study drug in the morning and in the evening. 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.

4. General Statistical Considerations

Statistical analysis will be performed using SAS software (Version 9.4, SAS/STAT 15.2). Continuous variables will be summarized using the mean, the standard deviation (SD), median, Quartile 1 (Q1), Quartile 3 (Q3), minimum value, and maximum value. Categorical variables will be summarized using frequency and percentages. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Selected ordinal data may be summarized using both descriptive statistics and frequencies and percentages of participants in each category, as appropriate. Data will be listed in data listings.

All statistical tests will be 2-sided and performed using a 0.05 significance level, leading to 95% (2-sided) Confidence Intervals (CIs). P-values less than 0.0001 will be presented as '<0.0001' and p-values = 1 will be presented as '>0.9999' in all tables.

Number of patients, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, and quartiles will be calculated to one more decimal place than the source data. SDs, standard errors, and CIs will be calculated to two more decimals than the source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%).

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. 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.

The investigator will select the study eye, and this selection will be used in the final analysis even if the fellow eye is found to qualify and be worst.

All efficacy analyses will only be presented for the study eye.

Numeric data may be recorded at limits of detection (with a '<' or '>' sign, i.e. < 0.1 or > 0.1). To summarize the data, the original value below a limit of detection will be converted to one half of the reported limit if it is a biological molecule, 0 otherwise. Values above a limit of detection will be reported at the limit. The actual values will be presented in the data listings.

4.1. Sample Size

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:

Table 1: Intercurrent Event Estimates

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.

4.2. 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 conjunctival sum fluorescein staining score and EDS (VAS) including measurements after ICEs (i.e., treatment policy strategy). Potential ICEs of the study are as follows:

- Discontinuation of the study treatment due to an AE
- Discontinuation of the study treatment due to lack of efficacy

Population-level Summary

Difference in means between the two treatment conditions.

4.3. Randomization, [redacted] and Masking

Patients in the 52-week Overall Period (the first approximately 240 patients) will receive K-161 [redacted] Oculus Uterque (OU) or Vehicle [redacted] OU for 52 weeks.

Patients in the 12-week Primary Period (the remaining approximately 380 patients) will receive K-161 [redacted] OU or Vehicle [redacted] OU for 12 weeks.

Randomization will be performed in a 1:1 ratio [redacted]. To preserve masking, all patients will self-administer assigned study drug [redacted] from [redacted] All arms will be double-masked.

All study drugs will be supplied in identical packaging, color, smell, and appearance to enable double-masked conditions. K-161 and matching vehicle will be provided in identical packaging so that all investigators, study site staff, patients, and clinical monitors will remain masked throughout the study. The electronic data capture (EDC) system will assign study drug to patients at the time of randomization. Only personnel in randomization and clinical supplies will be unmasked and will have access to treatment assignments; all other parties involved in the study will be fully masked.

Labeling and packaging for the run-in period will be identical to those for the double-masked treatment periods. The run-in drops (vehicle) will be single-masked for patients.

4.4. Analysis Sets

4.4.1. Full Analysis Set in the 12-week Primary Period

Full Analysis Set (FAS) in the 12-week Primary Period (FAS12) will include all randomized patients who received at least 1 dose of double-masked 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.

4.4.2. Per Protocol Set in the 12-week Primary Period

Per Protocol Set (PPS) in the 12-week Period (PPS12) 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. Analyses will be presented by actual treatment received.

4.4.3. Safety Population in the 12-week Primary Period

Safety Population (SP) in the 12-week Primary Period (SP12) will include all randomized patients who have received at least 1 dose of double-masked study treatment. Analyses will be presented by actual treatment received.

4.4.4. Full Analysis Set in the 52-week Overall Period

FAS in the 52-week Overall Period (FAS52) will include the randomized patients who are assigned into the 52-week Overall Period and received at least 1 dose of double-masked study treatment. Patients will be analysed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment.

4.4.5. Safety Population in the 52-week Overall Period

SP in the 52-week Period (SP52) will include randomized patients for the 52-week Overall Period and who had at least 1 dose of double-masked study treatment. Analyses will be presented by actual treatment received.

4.5. Assessment Windows and Time Periods

4.5.1. Study Day

When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of assessment - Day 1 +1, if date of assessment ≥ Day 1.
- study day = date of assessment - Day 1, if date of assessment < Day 1.

Note that the day before Day 1 is Day -1 (for analysis, there is no Day 0 for study day).

4.5.2. Visit Windows for Analysis

Visit windows will be defined for by-visit summary and analysis purposes. Summary data (such as AEs and concomitant medications) that are not reported by visit will not use visit windows.

Scheduled, unscheduled, and early termination visits will be considered as valid assessments for analysis. Visit labels will be assigned to each post-baseline record based on the windows for study day relative to the date of first dose of double-masked study drug. If an assessment at Day 1 is missing, the closest visit with non-missing assessment on or before the date of first dose of double-masked study drug will be used as baseline. All analyses will be based on the analysis visit windows in Table 2. If there are multiple valid assessments within a time window, the assessment which occurs closest to the target day will be used in the

analysis. If there are multiple valid assessments with the same difference from the target day, the latest assessment will be used in the analysis.

Table 2: Analysis Visit Windows

	Analysis Visit Window	
Analysis Visit	12-week Primary Period Patients / Total Patients	52-week Overall Period Patients
Day -14	Nominal Visit	Nominal Visit
Day 1	Nominal Visit	Nominal Visit
Baseline	Most recent measurement up to and including day 1	Most recent measurement up to and including day 1
Day 15	2 to 22 Days	2 to 22 Days
Day 29	23 to 43 Days	23 to 43 Days
Day 57	44 to 71 Days	44 to 71 Days
Day 85	72 to 92 Days	72 to 127 Days
Day 99	93 to 105 Days	N/A
Day 169	N/A	128 to 211 Days
Day 253	N/A	212 to 309 Days
Day 365	N/A	310 to 372 Days
Day 379	N/A	373 to 385 Days

4.5.3. Time Periods

Data may be summarized for different time periods according to whether 12-week Primary Period Patients, 52-week Overall Period Patients, or Total patients are summarized. For data collected at the study sites for individual assessments and summarized for FAS12, PPS12, or SP12, data will be summarized through the Day 85 window. For FAS52 or SP52, data for assessments will be summarized through the Day 379 window.

Event data will not be summarized according to the data windows above. This includes data for protocol deviations, concomitant medications and procedures, ICEs, and AEs. Data summarized for FAS12, PPS12, or SP12 will be summarized for the following period:

- 12-week Primary Period
  - Through study day 85 for 52-week Overall Period Patients;
  - Through the end of the study for 12-week Primary Period Patients (including data at and after Day 99 visit, if appropriate).

For FAS52 or SP52, data will be summarized according to 3 different time periods:

- 52-week Overall Period, through the end of the study (including all available data);

- 12-week Primary Period, through study day 85;
- 40-week Extension Period, from study day 86 through the end of the study (including all available data).

Periods for event data will be labeled for analysis populations FAS52 or SP52 in the analyses. The single period for event data will not be labeled beyond the labels used for FAS12, PPS12, or SP12.

Windowing for study drug dosing and compliance is discussed in Section 7.7.

5. Patient Disposition

5.1. Disposition

Enrollment by site and country will be presented for 52-week Overall Period Patients, 12-week Primary Period Patients, and All Patients.

Disposition will be summarized by treatment for 52-week Overall Period Patients, 12-week Primary Period Patients, and All Patients. The counts and percentages of patients who receive study treatment will be presented. The study completion status of patients will be presented and the reasons for withdrawal from the study will be presented for patients who withdraw. Study completion status for 52-week Overall Period Patients will also be presented by Primary and Extension Periods. Primary Period includes visits through Visit 6 and Extension Period includes visits after Visit 6. Withdrawals will be summarized to the period in which they occur. Patients are assumed to be ongoing in the Primary Period if they did not withdraw. Patients are assumed to be ongoing unless they complete or withdraw the study in the Extension Period. The treatment completion status of patients will be presented and the reasons for study drug discontinuation will be presented for patients who do not complete treatment. The counts and percentages of patients who attend each study visit will be summarized. All percentages within the patient disposition summary will be based on the number of patients randomized in each treatment group within the appropriate patient population or overall. All percentages within the treatment disposition summary will be based on number of patients randomized who received at least 1 dose of double-masked study therapy. For reason for study withdrawal, percentages will be based on the number of patients who withdrew from the study. For treatment completion status, percentages are based on number of patients randomized who received at least one dose of double-masked study therapy. For reason for study drug discontinuation, percentages are based on the number of patients who discontinued study drug.

The count and percentage of patients who screen failed will be summarized out of patients who consented to the study. Reasons for screen failure will be presented for patients who screen failed.

Patient and treatment disposition data will be listed. Screen failures will also be listed in the data listing.

5.2. Protocol Deviations

Protocol deviations will be tracked by the clinical team on an ongoing basis and will be recorded within the EDC.

Patients with protocol deviations will be tabulated for each treatment group and overall for the 12-week Primary Period for FAS12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for FAS52. All percentages will be based on the number of patients in each treatment group or overall. All deviations will be listed by patient. Protocol deviations will be finalized prior to database lock.

5.3. Intercurrent Events

Patients with protocol deviations will be tabulated for each treatment group and overall for the 12-week Primary Period for FAS12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for FAS52. Possible ICEs include:

- Discontinuation of the study treatment due to an AE, whether by investigator (e.g., "Adverse event, in the opinion of the investigator") or the patient (e.g., "Patient request, Adverse event");
- Discontinuation of the study treatment due to lack of efficacy, whether by the investigator (e.g., "Lack of efficacy, as judged by the investigator") or the patient (e.g., "Patient request, Lack of efficacy").

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information and baseline characteristics collected at Screening will be summarized for the FAS12, PPS12, FAS52, SP12, and SP52. Continuous variables include age (years) will be summarized using descriptive statistics for each treatment group and overall. The following categorical variables will be summarized by reporting the number and percentage of patients in each category for each treatment group and overall.

- Sex (Male, Female)
- Age (<65, ≥65) and (<65, 65-84, ≥85)
- Sex × Age (Male <65, Male ≥65, Female <65, Female ≥65)
- Ethnicity (Hispanic, Latino/a, or Spanish origin, Not Hispanic, Latino/a, or Spanish origin, Not Reported, Unknown)

- Hispanic, Latino/a, or Spanish Origin (Mexican, Mexican American, Chicana/o; Puerto Rican; Cuban; Other; Multiple)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander, Not Reported, Unknown, Other, and Multiple)
- Iris color of study eye (Brown, Blue, Hazel, Grey, Green, Black, Other)
- Study eye [Oculus Dexter (OD) or Oculus Sinister (OS)]
- Status of Smoking (Never, Current, Former)
- Status of Vaping (Never, Current, Former)
- Alcohol Use Occurrence (Never, Current, Former)

Percentages will be based on the total number of patients in the FAS12, FAS52, SP12, and SP52. Percentages of individual ethnicities are out of patients of Hispanic, Latino/a, or Spanish Origin.

All demographic and baseline characteristics will be listed.

6.2. Dry Eye, Medical, and Surgical History

6.2.1. Dry Eye History

Dry eye history is captured in the electronic case report form (eCRF). Duration of dry eye years will be summarized descriptively using SP12 and SP52. The frequency and percentage of patients with specific features of dry eye will be summarized by treatment group and overall using the SP12 and SP52.

Dry Eye duration will be calculated in years as (consent date – start date + 1) / 365.25.

In case of a partial start date of DED:

- If the start date is missing entirely, it will be left missing.
- If the year is present and the month is missing, then the month will be set to January.
- If the month and year are present and the day is missing, then the day will be set to the first day of month.

6.2.2. Medical History

Ocular and non-ocular medical histories will be captured in the eCRF. The investigator will record the verbatim term, start date, and stop date (or continuing). For ocular medical history, the investigator will also record the eye [right eye (OD), left eye (OS), both eyes

(OU)]. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

The frequency and percentage of patients with any medical history will be summarized by treatment group and overall using SP12 and SP52. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-161 [redacted]
- Descending frequency within vehicle;
- PT in alphabetical order.

Medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical histories will be summarized separately. Ocular and non-ocular medical histories will be identified according to whether eye is specified or not. Ocular medical history will be summarized for either eye.

6.2.3. Surgical History

Ocular and non-ocular surgical histories are captured in the eCRF. The investigator will record the verbatim term and surgical date. For ocular surgical history, the investigator will also record the eye (OD, OS, OU). Surgical history will be coded using the MedDRA Version 25.0.

The frequency and percentage of patients with any surgical history will be summarized by treatment group using SP12 and SP52. SOC will be sorted alphabetically, and PT within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-161 [redacted]
- Descending frequency within vehicle;
- PT in alphabetical order.

Surgical history will include both the ocular and the general (non-ocular) history. Ocular surgical history and general (non-ocular) surgical history will be summarized separately. Ocular and non-ocular surgical history are identified according to whether eye is specified or not. Ocular surgical history will be summarized for either eye.

6.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented in a data listing. A summary table of inclusion and exclusion criteria that were not met will be presented for screen failures.

7. Treatments and Medications

7.1. Prior Medications and Concomitant Medications

The investigator must record the use of all concomitant medications and any historical use of [redacted] before Visit 1, both dispensed and over-the-counter (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.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) (B3 WHO Drug Global Mar 2022 or later) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of patients with coded medications will be summarized by treatment group using SP12 and SP52. Coded medications will be tabulated separately for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52. A patient who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup will be sorted alphabetically, and preferred name will be sorted by descending frequency overall within each Level 3 term according to:

1. Descending frequency within K-161 [redacted]
2. Descending frequency within vehicle;
3. PT in alphabetical order.

Prior medications are defined as any medications that started and stopped prior to the first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the first dose of double-masked study drug. Medications taken after a patient's last visit or withdrawal from the study are not considered concomitant.

Partial or missing medication stop dates for medications that are not ongoing will be handled as follows:

- Partial stop dates of prior and concomitant medications and procedures will be assumed to be the latest possible date consistent with the partial date.
- If the year is present and the month is missing, then the month is set to December.
- If the month and year are present and the day is missing, then the day is set to the last day of month.
- For patients who are treated, if the year is missing and the month or day are not missing, then the year will be assumed to be the year part of the patient's last recorded study visit date.
- For patients who are not treated, if the year is missing and the month or day is not missing, then the year will be assumed to be the year part of the patient's discontinuation date.
- If the complete stop date is missing, the stop date will be considered to be either the patient's last recorded visit date for treated patients or the patient's discontinuation date for non-treated patients.

The above imputations are for tabulations of study data. Data will be presented as obtained in listings. Prior and concomitant medications will be summarized separately. Ocular and non-ocular medications are identified according to whether eye is specified or not and will be summarized separately. Ocular prior and concomitant medications will be summarized for either eye.

7.2. Rescue Medications

The subset of concomitant medications that are determined to be rescue medications for the signs and symptoms of DED will be summarized in a manner similar to concomitant medications.

7.3. [redacted]

The subset of concomitant medications that are determined to be [redacted] will be summarized in a manner similar to concomitant medications.

The proportion of patients with any prior [redacted] will be summarized for SP12 and SP52. The number of doses and days of prior [redacted] use will be summarized by arm. Prior [redacted] is before the first dose of double-masked study treatment. If the dose frequency is recorded as pro re nata (PRN), one dose will be assumed per day. Other dosing frequencies will be reviewed prior to database lock.

7.4. Concomitant Surgeries/Procedures

Concomitant surgeries/procedures will be captured in the EDC in a similar manner to what is described in 6.2.3 Surgical History. Concomitant surgeries/procedures are defined as any

surgery/procedure that starts at or after the first dose of double-masked study drug. Date imputation will be performed in a manner consistent with what was described in 7.1 Prior Medications and Concomitant Medications. Concomitant surgeries/procedures will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52.

7.5. Rescue Surgeries/Procedures

The subset of surgeries/procedures that are determined to be rescue surgeries/procedures for the signs and symptoms of DED will be summarized in a manner similar to surgeries/procedures.

7.6. Concomitant Devices

Concomitant devices will be presented in a listing. Rescue status for the signs and symptoms of DED will be listed.

7.7. Study Treatments

7.7.1. Extent of Exposure

Descriptive statistics for the study treatment exposure (number of instillations and duration of treatment) and compliance will be provided by treatment group and overall and tabulated separately for the 12-week Primary Period for SP12 and the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52. Duration of exposure will be calculated in days as the (date of last dose – date of first dose + 1). For exposure for the 12-week Primary Period, 52-week Overall Period Patients will use the Visit 6 date – 1 as their last dose date if they have not already discontinued study drug. Duration for the 40-week Extension Period will be computed as last dose date minus Visit 6 date + 1 for 52-week Overall Period Patients.

Frequency and percentages of patients in the following exposure categories will be summarized for SP12:

- <1 week
- 1 to ≤ 4 weeks
- >4 to ≤ 8 weeks
- >8 to ≤ 12 weeks
- >12 weeks
- Overall
    - 1 to ≤ 12 weeks.

Frequency and percentages of patients in the following exposure categories will be summarized for SP52:

- <1 week
- 1 to ≤ 4 weeks
- >4 to ≤ 8 weeks
- >8 to ≤ 12 weeks
- >12 to ≤ 24 weeks
- >24 to ≤ 36 weeks
- >36 to ≤ 52 weeks
- >52 weeks
- Overall
    - 1 to ≤ 12 weeks
    - >12 to ≤ 52 weeks
    - 1 to ≤ 52 weeks.

7.7.2. Treatment Compliance and Modifications

Percent compliance will be calculated as:

$$\frac{\text{total assumed number of study drug instillations}}{\text{planned number of instillations}} \times 100$$

for SP12 and SP52.

To calculate the planned number of instillations, the following scenarios are considered:

- For all study days, the total number of study drug instillations is the number of dispensed vials minus the number of unused vials reported on the Study Drug Dispensation and Accountability eCRF.
- For all study days, the number of planned instillations will be 2 doses.
- 12-week Primary Period Patients will not be dosed on Day 85 (Visit 6). Duration of exposure for patients who complete this phase will generally be (Visit 6 date – 1) – Visit 2 date + 1.
- 52-week Overall Period Patients will not be dosed on Day 365 (Visit 9). Duration of exposure for patients who complete this phase will generally be (Visit 9 date – 1) – Visit 2 date + 1.
- Patients who discontinue dosing early (dates do not correspond to Visit 6 or 9) will include both doses in the planned number of doses on the last date of dosing.
- Patients will be considered compliant with study treatment if the calculated percent compliance is between 80% and 125%, inclusive.

Summaries for run-in medication will be similarly presented, except that exposure categories will not be included. Compliance for run-in medication will be calculated in a similar manner as above. Patients are expected to dose [redacted] daily from Visit 1 (inclusive) up to the date prior to Visit 2 (inclusive). Duration will generally be calculated as Visit 2 – Visit 1.

A by-patient listing will be presented for the study treatment exposure and compliance, as well as drug accountability.

8. Efficacy Analysis

The FAS12 will be the primary analysis set for efficacy analyses. Separate efficacy analyses will be presented by the FAS52 if appropriate. Efficacy analyses will only be presented for the study eye. Primary efficacy endpoints will also be analyzed using PPS12.

Summary statistics will be calculated for the observed values and change from baseline for the primary endpoints through Day 85 for FAS12 and through Day 365 for FAS52. The changes from baseline will be analyzed using MMRM models. This analysis will also be performed using PPS12. Imputation methods are described below.

8.1. Primary Efficacy Endpoints

8.1.1. Notation

i Patient ($i = 1, \ldots, n_j$)
j Treatment group ($j = 1, \ldots, J$)
k ICE status ($k = 1, \ldots, K$)
n_j The number of patients for treatment group j
t Time point ($t = 1, \ldots, T$)
y_{ijt} Response variable for patient i within treatment group j at time point t
d_{ijt} Change from baseline to time point t for patient i within treatment group j ($d_{ijt} = y_{ijt} - y_{ij0}$ where y_{ij0} is baseline value)
$\mathbf{x}_{ij}$ Covariates (vector) for patient i within treatment group j
R_{ijt} Missingness status ($R_{ijt} = 0$ if observed, $R_{ijt} = 1$ if missing) for patient i within treatment group j at time point t

K-161-3.01 study has $J = 2$ treatments, $K = 3$ different ICE statuses and $T = 3$ time points as follows:

Indicator
Treatment Group

$j = 1$	Vehicle [redacted]
$j = 2$	K-161 [redacted]
Intercurrent Event Status	
$k = 1$	Not occurred.
$k = 2$	Discontinuation of the study treatment due to an AE.
$k = 3$	Discontinuation of the study treatment due to lack of efficacy.
Time Points	
$t = 1$	Day 29
$t = 2$	Day 57
$t = 3$	Day 85

8.1.2. Pattern Mixture Model with Multiple Imputation

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.

As for the primary analysis, y_{ijT} refers to either EDS (VAS) or conjunctival sum fluorescein staining score to be measured at Day 85, whose observed values are used regardless of whether or not the following ICEs occur: discontinuation of the study treatment due to an AE ($k = 2$) or lack of efficacy ($k = 3$). In other words, the treatment policy strategy is utilized for those two ICEs. If missing values occurred, however, those values are imputed using the pattern mixture model (PMM) with multiple imputation (MI). In this analysis framework, patterns are defined on the basis of ICE status (k) and missingness status (R) in each treatment group (j) at the last time point ($t = T$). Suppose that, here,

$$f\left(y_{ij}\middle|\mathbf{x}_{ij}, j = p, k = q, t = T, \underline{R_{ij} = 1}\right) = f\left(y_{ij}\middle|\mathbf{x}_{ij}, j = p, k = q, t = T, \underline{R_{ij} = 0}\right)$$

where $f(\cdot)$ is a probability density function. Then, missing values will be imputed using SAS® MI procedure:

MI Step 1

```
PROC MI DATA= input1 OUT= output1 NIMPUTE= 100
        MINIMUM= . . 0 MAXIMUM= . . 100 ROUND= . . 1 ;
    WHERE ICEN IN (2, 3) ;
    BY TRTPN TRTP ICEN ICE ;
    CLASS SEX;
```

```
    VAR SEX BASE AVAL3 ;
    FCS ;
RUN ;
```

Note: The numbers specified in MINIMUM, MAXIMUM and ROUND options are utilized only for EDS (VAS). As for conjunctival sum fluorescein staining score, the following numbers are specified:

```
MINIMUM= . . 0 MAXIMUM= . . 24 ROUND= . . 0.5
```

The following is an example of datasets to be used:

SUBJID	TRTP	TRTPN	AGE	SEX	SEXN	BASE	AVAL1	AVAL2	AVAL3	ICE	ICEN
0001	Vehicle	1	48	F	1	76	51	49	60	Not Occurred	1
0002	K-161	2	32	F	1	70	60			Not Occurred	1
0003	K-161	2	39	F	1	55	58	41		LOE	3
0004	Vehicle	1	21	M	0	60	72	76	55	AE	2
…	…	…	…	…	…	…	…	…	…	…	…

SUBJID: Patient Identifier, TRTP: Planned Treatment, TRTPN: Planned Treatment (N), AGE: Age, SEX: Sex, SEXN: Sex (N), BASE: Baseline Value, AVAL1: Analysis Value at Day 29, AVAL2: Analysis Value at Day 57, AVAL3: Analysis Value at Day 85, ICE: Intercurrent Event Status, ICE: Intercurrent Event Status (N)

With regard to the other ICE status ($k = 1$), y_{ijT} will be imputed under the Missing At Random (MAR) assumption if it is not observed. Let $\mathbf{R}_{ij} = \left(R_{ij1}, R_{ij2}, \ldots, R_{ijT}\right)'$. When there is a patient whose values were observed at time points $t < T$ but not observed at the last time point $t = T$, for example, the MAR assumption implies that

$$f\left(y_{ijT}\middle|\mathbf{x}_{ij}, j = p, y_{ij1}, \ldots, y_{ij(T-1)}, \mathbf{R}'_{ij} = \left(0, \ldots, 0, \underline{1}\right)\right)$$
$$= f\left(y_{ijT}\middle|\mathbf{x}_{ij}, j = p, y_{ij1}, \ldots, y_{ij(T-1)}, \mathbf{R}'_{ij} = \left(0, \ldots, 0, \underline{0}\right)\right).$$

Actually, not only the last time point also but the other intermediate time points will be imputed in turn on the basis of the Available Case Missing Values (ACMV) restriction if there exists “not-observed” values. Thus, “not-observed” values will be imputed using SAS® MI procedure (Step 2A and 2B):

MI Step 2A

```
/*First, MCMC is used to complete input data to monotone pattern*/
PROC MI DATA= input1 OUT= output2 NIMPUTE= 100
        MINIMUM= . . 0 0 0 MAXIMUM= . . 100 100 100
         ROUND= . . 1 1 1 ;
   WHERE ICEN IN (1) ;
   BY TRTPN TRTP ;
```

```
   VAR SEXN BASE AVAL1 AVAL2 AVAL3 ;
   MCMC IMPUTE= MONOTONE ;
RUN ;
```

Note: The SEXN is the numeric variable for sex which was coded as 1 = female and 0 = male. The numbers specified in MINIMUM, MAXIMUM and ROUND options are utilized only for EDS (VAS). As for conjunctival sum fluorescein staining score, the following numbers are specified:

```
MINIMUM= . . 0 0 0 MAXIMUM= . . 24 24 24
 ROUND= . . 0.5 0.5 0.5
```

MI Step 2B

```
/*Then, single imputation is performed in order for the data to be full*/
PROC MI DATA= output2 OUT= output3 NIMPUTE= 1
      MINIMUM= . . 0 0 0 MAXIMUM= . . 100 100 100
       ROUND= . . 1 1 1 ;
   BY TRTPN TRTP _Imputation_ ;
   CLASS SEX ;
   VAR SEX BASE AVAL1 AVAL2 AVAL3 ;
   MONOTONE REG ;
RUN ;
```

Note: The numbers specified in MINIMUM, MAXIMUM and ROUND options are utilized only for EDS (VAS). As for conjunctival sum fluorescein staining score, the following numbers are specified:

```
MINIMUM= . . 0 0 0 MAXIMUM= . . 24 24 24
 ROUND= . . 0.5 0.5 0.5
```

Two output datasets *output1* and *output3* are combined, which is named as *input2*, and then change from baseline to each time point (d_{ijt}) is calculated, whose variable names are CHG1, CHG2 and CHG3, respectively. The dataset *input2* is analyzed using SAS® MIXED procedure in each imputation after sorted by the variable _Imputation_. The following analysis model is assumed:

$$d_{ijT} = \boldsymbol{\beta}'\mathbf{x}_{ij} + \tau_j + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2)$$

where τ_j is effect of treatment group j. The estimator of interest is $\left(\hat{\tau}_2 + \hat{\boldsymbol{\beta}}'\bar{\mathbf{x}}\right) - \left(\hat{\tau}_1 + \hat{\boldsymbol{\beta}}'\bar{\mathbf{x}}\right) = \hat{\tau}_2 - \hat{\tau}_1$, which is the difference of least squares means between K-161 [redacted] vs. Vehicle [redacted]

```
PROC MIXED DATA= input2 ;
  BY _Imputation_ ;
  CLASS SEX TRTP ;
  MODEL CHG3 = BASE SEX TRTP ;
  LSMEANS TRTP / OM DIFF= CONTROL('Vehicle') CL ;
  ODS OUTPUT Diffs= output4 ;
RUN ;
```

The output dataset *output4* will have one hundred estimates of treatment difference (Estimate) and the corresponding standard errors (StdErr). They are combined using Rubin's rule (Rubin 1987). The SAS® code is as follows:

```
PROC MIANALYZE DATA= output4 ;
  MODELEFFECTS Estimate ;
  STDERR StdErr ;
RUN ;
```

8.1.3. Sensitivity Analysis

A tipping point analysis based on the delta adjustment is performed by each ICE status. The following MNAR statement is added to MI procedure (MI Step 1' or 2B'):

MI Step 1' or 2B'

```
PROC MI DATA= inputX OUT= outputX NIMPUTE= 100
  ...
  MNAR ADJUST(AVAL3 / DELTA= δ ) ;
RUN ;
```

A tipping point $\delta = \delta_t$, at which the primary analysis result turns out to be not-significant, is examined in each ICE status.

Appropriate ranges of values for δ will be determined prior to database lock.

8.1.4. Alternative Approach for the Primary Analysis

Regarding the MI Step 1 in the primary analysis, the control-based mean imputation proposed by Mehrotra et al. (2017) will be applied instead of the PMM with MI if there are not enough patients to develop the imputation model in either pattern. That is, it applies when the total number of observed values at Day 85 for at least one of the ICEs is less than 20 in the pooled treatment group under the masking condition.

Note that observed values after any of the ICEs occurred are not used in this approach, that is, those values are considered as "not-observed". In this approach, first, a separate Mixed Model for Repeated Measures (MMRM) analysis for each treatment group is performed using all randomized patients under the MAR assumption:

Step 1

```
PROC MIXED DATA= input1 ;
   BY TRTPN TRTP ;
   CLASS SUBJID AVISIT ;
   MODEL CHG = BASE SEXN AVISIT BASE*AVISIT / DDFM= KR ;
   REPEATED AVISIT / SUBJECT= SUBJID TYPE= UN ;
   LSMEANS AVISIT / AT (BASE SEXN)= (&BASE_Mean &SEXN_Mean) ;
   ODS OUTPUT LSMeans= output1 ;
RUN ;
```

Note: The SEXN is the numeric variable for sex which was coded as 1 = female and 0 = male. The &BASE_Mean and & SEXN_Mean are an overall mean of baseline and an overall proportion of female patients values, respectively, in all study patients in the appropriate analysis population, FAS12 or PPS12.

The following is an example of datasets to be used:

SUBJID	TRTP	TRTPN	AGE	SEX	SEXN	AVISIT	AVISITN	BASE	CHG	ICE	ICEN
0001	Vehicle	1	48	F	1	Day 29	1	76	-25	Not Occurred	1
0001	Vehicle	1	48	F	1	Day 57	2	76	-27	Not Occurred	1
0001	Vehicle	1	48	F	1	Day 85	3	76	-16	Not Occurred	1
0002	K-161	2	32	F	1	Day 29	1	70	-10	Not Occurred	1
0002	K-161	2	32	F	1	Day 57	2	70		Not Occurred	1
0002	K-161	2	32	F	1	Day 85	3	70		Not Occurred	1
0003	K-161	2	39	F	1	Day 29	1	55	3	LOE	3
…	…	…	…	…	…	…	…			…	…

SUBJID: Patient Identifier, TRTP: Planned Treatment, TRTPN: Planned Treatment (N), AGE: Age, SEX: Sex, SEXN: Sex (N), AVISIT: Analysis Visit, AVISITN: Analysis Visit (N), BASE: Baseline Value, CHG: Change from Baseline, ICE: Intercurrent Event Status, ICE: Intercurrent Event Status (N)

Second, the by-treatment MMRM analysis is repeated using only patients in whom any ICEs didn't occur ($k = 1$):

Step 2

```
PROC MIXED DATA= input1 ;
   WHERE ICEN = 1 ;
   BY TRTPN TRTP ;
   CLASS SUBJID AVISIT ;
   MODEL CHG = BASE SEXN AVISIT BASE*AVISIT / DDFM= KR ;
   REPEATED AVISIT / SUBJECT= SUBJID TYPE= UN ;
```

```
    LSMEANS AVISIT / AT (BASE SEXN)= (&BASE_Mean &SEXN_Mean) ;
    ODS OUTPUT LSMeans= output2;
RUN ;
```

When $\hat{\mu}_{j,MAR}$ and $\hat{\mu}_j^{k=1}$ denote LS-Means at week 12 for treatment group j from the Step 1 and 2, respectively, the estimator of effect for active treatment (i.e., K-161 [redacted] $j = 2$) proposed by Mehrotra et al. (2017) is as follows:

$$\hat{\mu}_{2,new}[c] \equiv f_2^{k=1}\hat{\mu}_2^{k=1} + f_2^{k\neq 1}\left(\hat{\mu}_{1,MAR} + c\right)$$

where $f_j^{k=1}$ and $f_j^{k\neq 1}$ are the proportions of patients with $k = 1$ or $k \neq 1$ in treatment group j, that is, $f_j^{k\neq 1} = 1 - f_j^{k=1}$. As for the primary analysis, suppose that $c = 0$, which implies that an average of active group's patients in whom any of ICEs occurred is equal to one of vehicle group's patients. Thus, the proposed estimator of treatment difference and its variance are as follows:

$$\hat{\delta}_{new}[c] = \hat{\mu}_{2,new}[c] - \hat{\mu}_{1,MAR} = f_2^{k=1}\left(\hat{\mu}_2^{k=1} - \hat{\mu}_{1,MAR} - c\right) + c$$

and

$$\hat{V}\left(\hat{\delta}_{new}[c]\right) = \left[A_2 + \left(f_2^{k=1}\right)^2\right]\left(\hat{V}_2^{k=1} + \hat{V}_{1,MAR}\right) + \left[A_2\left(\hat{\mu}_2^{k=1} - \hat{\mu}_{1,MAR} - c\right)^2\right]$$

where $A_2 = f_2^{k=1}\left(1 - f_2^{k=1}\right)n_2^{-1}$. $\hat{V}_2^{k=1}$ and $\hat{V}_{1,MAR}$ are the estimated variances of $\hat{\mu}_2^{k=1}$ and $\hat{\mu}_{1,MAR}$, respectively, with corresponding Kenward-Roger type degrees of freedom $\lambda_2^{k=1}$ and $\lambda_{1,MAR}$. Therefore, the statistic

$$t_{new}[c] = \frac{\hat{\delta}_{new}[c]}{\sqrt{\hat{V}\left(\hat{\delta}_{new}[c]\right)}}$$

is tested using t-distribution with the degree of freedom

$$\lambda[c] = \frac{\left[\hat{V}\left(\hat{\delta}_{new}[c]\right)\right]^2}{\frac{\left(\hat{V}_2^{k=1}\right)^2}{\lambda_2^{k=1}} + \frac{\left(\hat{V}_{1,MAR}\right)^2}{\lambda_{1,MAR}}}$$

In order to calculate the above statistics, the following values are extracted from the two output datasets *output1* and *output2*, and aggregated into one dataset *output3* with underlined variables.

$\hat{\mu}_2^{k=1}$ Value of variable Estimate where TRTPN = 2 AND AVISIT = 'Day 85' in dataset *output2*: mu2_k1.

$\hat{\mu}_{1,MAR}$ Value of variable Estimate where TRTPN = 1 AND AVISIT = 'Day 85' in dataset *output1*: mu1_MAR.

$\hat{V}_2^{k=1}$ Squared value of variable StdErr where TRTPN = 2 AND AVISIT = 'Day 85' in dataset *output2*: V2_k1.

$\hat{V}_{1,MAR}$ Squared value of variable StdErr where TRTPN = 1 AND AVISIT = 'Day 85' in dataset *output1*: V1_MAR.

$\lambda_2^{k=1}$ Value of variable DF where TRTPN = 2 AND AVISIT = 'Day 85' in dataset *output2*: lambda2_k1.

$\lambda_{1,MAR}$ Value of variable DF where TRTPN = 1 AND AVISIT = 'Day 85' in dataset *output1*: lambda1_MAR.

Besides, $f_2^{k=1}$ the proportion of treated group patients with $k = 1$ and n_2 the sample size in study treatment group in FAS (i.e., K-161 [redacted] $j = 2$) are added to the dataset.

With regard to the primary analysis, p-value (Probt) and two-sided 95% CI (Lower and Upper) are calculated as follows:

```
DATA output4 ;
    SET output3 ;
    c= 0 ;
    delta_new_c= f2_k1*(mu2_k1 - mu1_MAR - c) + c ;
    A2= f2_k1*(1 - f2_k1)/n2 ;
    V_delta_new_c= (A2 + (f2_k1)**2)*(V2_k1 + V1_MAR)
                + (A2*(mu2_k1 + mu1_MAR - c)**2) ;
    t_new_c= delta_new_c/sqrt(V_delta_new_c) ;
    lambda_c= V_delta_new_c**2/
              (V2_k1**2/lambda2_k1 + V1_MAR**2/lambda1_MAR) ;
    Probt= 2*(1 - cdf('T', abs(t_new_c), lambda_c)) ;
    Lower= delta_new_c -
           quantile('T', .975, lambda_c)*sqrt(V_delta_new_c) ;
    Upper= delta_new_c +
           quantile('T', .975, lambda_c)*sqrt(V_delta_new_c) ;
RUN ;
```

8.1.5. Subgroup Analysis

Week 12 observed and change from baseline for the primary endpoints will also be presented by the following subgroups:

- Baseline EDS VAS (≤ or > median);
- Baseline conjunctival sum fluorescein staining score (≤ or > median);
- Baseline total eye fluorescein staining score (≤ or > median);
- Baseline corneal sum fluorescein staining score (≤ or > median);
- Baseline Schirmer score (≤ 5 mm or > 5 mm).

8.1.6. Sensitivity Analysis

A tipping point $c = c_t$, at which the primary analysis result turns out to be not-significant, is examined.

An appropriate range of values for c_t will be determined prior to database lock.

8.2. Key Secondary Efficacy Endpoint

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

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

Week 12 observed and change from baseline for the key secondary efficacy endpoint will also be presented by the subgroups defined for the primary endpoint.

Summary statistics will be calculated for the observed values and change from baseline for the key secondary endpoint through Day 85 for FAS12 and through Day 365 for FAS52. Changes from baseline will also be analyzed using MMRM models. The MMRM analysis will also be performed using PPS12. Note that efficacy analyses using MMRM only summarize and analyze data that occur prior to ICEs.

8.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are the change from baseline to Day 85 for:

- Corneal sum fluorescein staining score as assessed by expanded NEI scale, study eye;
- OSDI© Score;
- Schirmer's test (unanesthetized), study eye;
- TFBUT, study eye.

The secondary endpoints will be analyzed in a similar manner as performed for primary endpoint. The key secondary efficacy endpoint will be tested at alpha=0.05 (two-sided) if primary endpoints are both significant at alpha=0.05.

Week 12 observed and change from baseline for corneal sum fluorescein staining score will also be presented by the subgroups defined for the primary endpoint.

Summary statistics will be calculated for the observed values and change from baseline for secondary endpoints through Day 85 for FAS12 and through Day 365 for FAS52. Changes from baseline will also be analyzed using MMRM models. The MMRM analysis will also be performed using PPS12. Note that efficacy analyses using MMRM only summarize and analyze data that occur prior to ICEs.

Note that $\text{OSDI} = \frac{(\text{sum of scores for all questions answered}) \times 25}{(\text{total number of questions answered})}$.

8.4. Exploratory Efficacy Endpoints

[redacted]

Summary statistics will be calculated for the observed values and change from baseline for continuous exploratory endpoints through Day 85 for FAS12 and through Day 365 for FAS52. Change from baseline will also be analyzed using MMRM models. Note that efficacy analyses using MMRM only summarize and analyze data that occur prior to ICEs.

Note that for OSDI Subtotal score B (questions 6, 7, 8, 9) = $\frac{\text{(sum of scores for all questions answered 6,7,8,9)} \times 25}{\text{(total number of questions answered out of questions 6,7,8,9)}}$.

Frequencies and percentages for [redacted] will be presented by visit through Day 85 for FAS12 and through Day 365 for FAS52. The [redacted] and will be analyzed as described above for other continuous endpoints using the MMRM. Note that efficacy analyses using MMRM only summarize and analyze data that occur prior to ICEs.

[redacted]

The [redacted] will be compared between arms using Wilcoxon Rank Sum Test. The proportion of patients with [redacted] will be compared using Fisher's exact test. Prior [redacted] is before first dose of

double-masked study treatment. Otherwise, [redacted] on or after first dose of double-masked study treatment through the end of the study. If the dose frequency is recorded as pro re nata (PRN), one dose will be assumed per day. Other dosing frequencies will be reviewed prior to database lock. The proportion of patients with prior usage and [redacted] will be compared using Fisher's exact test. The number of doses and [redacted] will be summarized in a listing. Similar analyses will be provided for Rescue medications, though number of doses will not be summarized.

[redacted] will not be summarized as part of the clinical study report. Whether [redacted] were collected will be summarized by treatment.

[redacted] was previously performed in earlier versions of the protocol. Available data will be summarized in a table and listed.

9. Safety Analysis

Safety assessments include AEs, [redacted] systemic clinical evaluation, clinical laboratory measurements, [redacted]

In general, safety data will be summarized and listed with no statistical hypothesis testing performed. However, continuous summaries of laboratory measurements will compare arms using Wilcoxon rank sum test with signed-rank tests testing non-zero change from baseline measurements. No safety endpoints will be imputed.

Safety analyses will be presented through Day 99 for SP12 and through Day 379 for SP52.

9.1. Adverse Events

AEs will be coded using the MedDRA Version 25.0.

In general, all AEs will be listed and all TEAEs and treatment-emergent serious AEs (TESAEs) will be summarized.

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

TEAEs and TESAEs will be summarized separately for ocular events at the patient level and non-ocular TEAEs/TESAEs.

SOC will be sorted alphabetically, and PT within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-161 [redacted]
- Descending frequency within vehicle;
- PT in alphabetical order.

Patients are counted only once for each SOC and PT. The percentages are calculated based on the number of patients in each treatment group.

Partial dates on AE start dates will be handled as follows:

- If the onset date is completely missing and the AE end date is not prior to the date of first dose of double-masked study drug, onset date will be set to the date of first dose.
- If the year is present and the month is missing, then the month will be set to January. If the year is the same as the year of the date of first dose of double-masked study drug and the AE end date is not prior to the date of first dose of double-masked study drug, then onset date will be set to the date of first dose of double-masked study drug.
- If the month and year are present and the day is missing, then the day will be set to the 1st day of month. If the month and year are the same as the month and year of the date of first dose and the AE end date is not prior to the date of first dose of double-masked study drug, then onset date will be set to the date of first dose of double-masked study drug.
- If the AE end date is present, then the imputed start date will be no later than the end date.

9.1.1. Overview of Adverse Events

Overall summaries of TEAEs by treatment will include:

- the number of TEAEs and TESAEs reported;
- the number of study-drug related TEAEs and TESAEs reported;
- the number and percentage of patients who experienced any TEAE or TESAE;
- the number and percentage of patients who experienced any study-drug related TEAE or TESAE;
- the number and percentage of patients with specific reasons for seriousness for TESAE;
- the number and percentage of patients with TEAE or TESAE leading to study drug discontinuation;
- the number and percentage of patients with TEAE or TESAE leading to study withdrawal;

- the number and percentage of patients with any TEAE or TESAE by worst severity.

The above quantities will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52 for total, ocular, and non-ocular events.

9.1.2. Incidence of Adverse Events

Both ocular and non-ocular TEAEs will be summarized by treatment group or overall. The total number of TEAEs and the number and percentage of patients with at least one TEAE in each SOC and having each individual TEAE based on the PT will be presented. The number of events overall will also be presented. All AEs will be listed.

The above analyses will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52 for ocular and non-ocular events.

9.1.3. Severity of Adverse Event

A summary of TEAEs by maximum severity will be presented in a table by total number of patients with incidence of TEAE occurrence. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are "Mild," "Moderate," and "Severe." If a patient reported multiple occurrences of the same TEAE, only the most severe will be presented in the incidence count. TEAEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity. The percentages are calculated based on the number of patients in each treatment group and overall. The number of events overall by severity will also be presented.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.2. The above analyses will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52 for ocular and non-ocular events.

9.1.4. Adverse Events Related to Study Drug

The relationship or association of the study drug in causing or contributing to the TEAE will be characterized as related or not related. A summary of TEAEs related to study drug will be presented in a table by total number of patients with incidence of TEAE occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. TEAEs that are missing a relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship. The percentages are

calculated based on the number of patients in each treatment group or overall. The number of events overall will also be presented.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.2.

Summaries based on maximum relationship will be conducted in a manner similar to analyses for severity described in Section 9.1.3.

The above analyses will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52 for ocular and non-ocular events.

9.1.5. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

TEAEs leading to study drug discontinuation will be identified as TEAEs on the AE eCRF page, where the action taken with study drug is "Study Drug Discontinued". The TEAEs leading to study drug discontinuation will be categorized and presented by SOC and PT in a manner similar to Section 9.1.2 that described in. All TEAEs leading to study drug discontinuation will be listed in a data listing.

9.1.6. Treatment-Emergent Adverse Events Leading to Study Withdrawal

TEAEs leading to study withdrawal will be identified as such if the study completion page lists reason for discontinuation is AE, in the opinion of the patient with the AE listed. The TEAEs leading to study withdrawal will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.2. All TEAEs leading to study withdrawal will be listed in a data listing.

9.1.7. Serious Adverse Events

The TESAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.2. The TESAE data will be presented by SOC, PT, and severity as described in Section 9.1.3. The TESAE data will be presented by SOC, PT, and relationship as described in Section 9.1.4. The TESAE leading to treatment discontinuation and study withdrawal will be categorized and presented by SOC and PT in a manner similar to Sections 9.1.5 and 9.1.6. For all TESAE summaries, the number of events under each SOC and PT will also be presented. All SAE data will be listed in a data listing.

The above analyses will be tabulated for each treatment group and overall for the 12-week Primary Period for SP12 and for the 52-week Overall Period, 12-week Primary Period, and 40-week Extension Period for SP52 for ocular and non-ocular events.

9.1.8. Death

Deaths will be identified as AEs on the AE eCRF page. Patient deaths will be identified as AEs where the outcome is "Death". All deaths will be listed in a data listing.

9.2. Systemic Clinical Evaluation

Systemic clinical evaluation will be conducted by investigator at baseline, Day 85, and Day 365 and will include a review of the patient's medical and medication history and subsequent evaluation of relevant body system complaints. In case of abnormal findings, full evaluation of the condition should be conducted by a physician in accordance with local standard of care. The findings will be documented in the patient's medical records and eCRF. Clinically significant (CS) abnormal findings should be recorded as AEs.

Whether these evaluations were performed will be listed.

9.3. Clinical Laboratory Measurements

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)

Descriptive summaries of the observed test results at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for hematology, serum chemistry, and a subset of urinalysis labs (specific gravity, pH, urobilinogen). The frequency and percentage of the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for labs. The frequency and percentage of patients with observed values for categorical urinalysis laboratory measurements will be tabulated at each scheduled visit. All laboratory data will be listed.

[redacted]

[redacted]

[redacted]

10. Interim Analysis

No interim analysis is planned for this study. Planned analyses at Day 85 including the primary and secondary analyses will be performed by an unmasked team not involved in the conduct of the study once all patient data through Day 85 are obtained in a fashion to protect the masking of the patients who will be followed in the extension. 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. Details on this unmasking plan will be summarized in a separate memo to file prior to this Day 85 analysis. The results will be delivered in accordance with the unmasking plan.

11. References

[redacted]

Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979;6:65–70.

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Mehrotra DV, Liu F, Permutt T. Missing data in clinical trials: control-based mean imputation and sensitivity analysis. Pharm Stat. 2017;16(5):378-392.

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Rubin, D.B. (1987) Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons Inc., New York.

[redacted]

12. Appendix I: Time and Event Table

Table 4: Schedule of Study Site Activities

	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]	

	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]**
Fluorescein Staining Scoring	X	X		X	X	X	X	X	X	
VAS	X	X		X	X	X	X	X	X	
[redacted]										
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		X				X			X	
Clinical Laboratory Measurement	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]**
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 110 patients of each arm, approximate total 220 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 [redacted] will be collected and the [redacted] will be returned to patients at Visit 4 and Visit 5.

[redacted]