STATISTICAL ANALYSIS PLAN

Study Protocol Number:	KX01-AK-004
Study Protocol Title:	A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp
Date:	04 Jun 2019
Version:	3.0 (Amendement 02)

REVISION HISTORY

Revisions to Version 2.0 Current Version and Date: v3.0 03 Jun 2019 (Amendment 02)		
Change	Rationale	Affected SAP Sections
Re-define study day of the Day 57 Visit in the Recurrence Follow-up Period as Study Day 0	To better define study days in the Recurrence Follow-up Period: the first day of this period should be the day right after the Day 57 visit	Section 11.4.1
Remove summary table for Visit Attendance	Visit attendance is not relevant to AK recurrence analysis	Section 11.6
Remove summary tables for AK history, AK treatment history data, medical history for non-AK conditions	AK history, AK treatment history data, medical history for non-AK conditions are not relevant to AK recurrence analysis	Section 11.8
Remove AK Recurrence Analysis for the Placebo Treatment Group	There are too few subjects in the Placebo Treatment Group	Section 11.10.1
Remove summary table for Kaplan-Meier-based estimation of minimum, quartiles and maximum value of time to recurrence	Kaplan-Meier plot already provides similar information.	Section 11.10.1
Remove subgroup analysis for AK Recurrence	The number of subjects may not be enough in some subgroups for the analysis.	Section 11.10.2
Remove prohibited non-study drug treatment as a censoring factor	To focus on the analysis for the subjects with 100% clearance in the Day 57 Visit in the ITT Population	Section 11.10.3

Revisions to Version 1.0 (Original SAP) Current Version and Date: v2.0 19 Jul 2018 (Amendment 01)		
Change	Rationale	Affected SAP Sections
Add the following sentence: "Any deviations from this randomization plan will be documented and discussed as an appendix of the final version of the SAP."	To clarify the plan to finalize the SAP prior to the first database lock	Section 6
Add 4 listings to the list of outputs for the Blind Data Review Meeting	To update the outputs which are reviewed by the study team in the Blind Data Review Meeting	Section 9
Delete 1 listing from the list of outputs for the Blind Data Review Meeting	To update the outputs which are reviewed by the study team in the Blind Data Review Meeting	Section 9
Add the following sentence: "Subjects with missing AK lesion counts and the associated reasons will be reviewed and supplemented as an appendix of the final version of the SAP."	To clarify the plan to finalize the SAP prior to the first database lock	Section 10.11.4
Revise the wordings for missing data handling and sensitivity analysis	To clarify the data analysis methods based on the real data collected	Section 10.11.5
Add the following sentence "Subjects with missing LSR assessment and the associated reasons will be reviewed and supplemented as an appendix of the final version of the SAP."	To clarify the plan to finalize the SAP prior to the first database lock	Section 10.12.3
Delete the central ECG vendor name "iCardiac"	To make the wording generic	Section 10.12.7
Grey out Section 11 Statistical Evaluation for Data Collected in the Recurrence Follow-up Period	To clarify the current version of SAP is finalized for data collected prior to the Recurrence Follow-up Period.	Section 11
Add Section 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 16.10	To record the decisions made in the Blind Data Review Meeting	Section 16

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AK	actinic keratosis
ADS	analysis data specifications
CI	confidence interval
eCRF	electronic case report form
ITT	Intent-to Treat
LSR	local skin reaction
LOCF	last observation carried forward
PP	Per Protocol
PT	preferred term
RR	recurrence rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

3 STUDY PROTOCOL AND AMENDMENTS

This Statistical Analysis Plan (SAP) is based on the study KX01-AK-004 protocol Amendment 01 (v2.0) dated 18 Feb 2018. This SAP document supersedes the statistical section of the protocol and provides data analysis details for the clinical study report (CSR).

Data collected in the Screening, Treatment, and Response Assessment periods and data collected in the Recurrence Follow-up Period will be discussed and analyzed separately as described in Section 10 and Section 11, respectively.

4 STUDY HYPOTHESIS

Treatment with KX2-391 Ointment 1% administered topically once daily for 5 consecutive days will demonstrate a greater complete clearance (defined as 100% clearance of clinically typical and visible actinic keratosis [AK] lesions at Day 57) than vehicle ointment administered topically once daily for 5 consecutive days in adults with AK on the face or scalp.

5 STUDY DESIGN

This is a double-blind, vehicle-controlled, randomized, parallel group, multicenter study to evaluate the efficacy and safety of KX2-391 Ointment 1% administered topically on the face or scalp of adult subjects with AK.

Enrollment will be controlled so that approximately two thirds of subjects enrolled in the study will be treated on the face and approximately one third of subjects enrolled in the study will be treated on the scalp. Eligible subjects will be randomized on Day 1 to treatment in a 1:1 (KX2-391 Ointment 1% or vehicle) ratio in each treatment location subgroup.

Subjects who achieve complete clearance of AK lesions in the treatment area at Day 57 will continue in the Recurrence Follow-up Period to determine recurrence rate (RR) and safety for up to 12 months following the Day 57 visit.

6 RANDOMIZATION

Randomization to treatment (active or vehicle) will be stratified by treatment location (face or scalp) and study site.

For each site, 2 randomization schedules will be created. One schedule with 24 randomization codes is for the subjects in the face subgroup. The other one with 12 randomization codes is for the subjects in the scalp subgroup. Each of the 2 schedules will randomize subjects in a 1:1 ratio to active treatment or vehicle treatment.

Correspondingly, the study kits (active treatment or vehicle control) will be prepared separately for the face subgroup and the scalp subgroup. Each site will receive 24 study kits for the face subgroup and 12 study kits for the scalp subgroup. In this way, study sites will be fully supplied because each site will not be allowed to enroll any more than 20 subjects.

Enrollment into the treatment location subgroups will be controlled at the study level. Once approximately 200 subjects overall have been enrolled into the face subgroup, or 100 subjects have been enrolled into the scalp subgroup, enrollment for that treatment location will be closed.

Any deviations from this randomization plan will be documented and discussed as an appendix of the final version of the SAP.

7 DETERMINATION OF SAMPLE SIZE

The sample size was estimated based on the primary efficacy endpoint, complete clearance (see definition in Section 10.2.1.1) at the Day 57 visit, for the comparison of KX2-391 Ointment 1% and vehicle control. By using a Pearson Chi-square method, a sample size of 100 scalp-treated subjects and 200 face-treated subjects, both of which are with a 1:1 treatment allocation ratio, will give a greater than 90% power to detect a 20% difference (30% for active treatment and 10% for vehicle control) with a two-tailed significant level 0.05.

The 30% response rate for complete clearance at the Day 57 visit for active treatment is assumed based on unpublished results from the 5-day treatment cohort in the Phase 2 study KX01-AK-002.

The 10% response rate of complete clearance at the Day 57 for vehicle control is conservatively assumed per literature reports. For example, in the 2 clinical studies[1] of PEP005 gel 0.015% sponsored by Leo Pharmaceuticals for treatment of AK lesions on face or scalp, vehicle response rates were 2.2% and 5.2%, respectively, for the same primary efficacy endpoint.

8 DATABASE LOCKING

Database lock, randomization code release, and subsequent data analyses will be performed in 2 steps, as follows:

- For the first step, after all dosed subjects have completed the Day 57 Visit or discontinued by the Day 57 Visit, and after all LSRs, hypo- or hyper- pigmentation, scarring, or treatment-related AEs which occur before or on the Day 57 Visit have resolved, returned to baseline, or been deemed stabilized by the Investigators, the data collected before the Recurrence Follow-up Period will be locked and the randomization code will be released to the Sponsor only. The endpoint analyses, except for recurrence rate and AEs in the treatment area after Day 57, will be performed. Any change to the domain data sets after this time will require written authorization, with explanation, by the study statistician.

- For the second step, after the entire study has been completed, the data collected during the Recurrence Follow-up Period will be locked and then analyzed. After the planned analyses are concluded, the randomization code will be released to the study sites.

9 BLIND DATA REVIEW AND RECORDS

Before locking the database and unblinding at the first step, the study statistician will provide the following listings for the study team to review:

- A summary table of subject enrollment and disposition and supporting listings
- A summary table of demographic and baseline characteristic data and supporting listings
- A listing of all primary and key secondary efficacy endpoints available at Day 57
- A listing of prior and concomitant medications (CMs)
- A listing of procedures
- A listing of drug administration records
- A listing of all adverse events (AEs)
- A listing of all non-treatment-emergent adverse events (non-TEAEs)
- A listing of protocol deviations
- A listing of comments

The study team will review these blind data review listings and define the composition of analysis populations and any special data handling methods. The review process and any decisions made as an outcome of review will be documented as an appendix to the final version of the SAP, prior to the first database lock.

10 STATISTICAL EVALUATION FOR DATA COLLECTED IN THE SCREENING, TREATMENT AND RESPONSE ASSESSMENT PERIODS

Data analysis for all efficacy and safety data collected in the Screening, Treatment, and Response Assessment periods will be discussed in this section. Data analysis for the Recurrence Follow-up Period is discussed in Section 11.

10.1 Study Objectives

10.1.1 Primary Objective

- To evaluate the efficacy of topical KX2-391 Ointment 1% once daily for 5 consecutive days compared to vehicle control in terms of 100% clearance at Day 57 in the treatment of adults with AK, when applied to a contiguous area of 25 cm^2 on the face or scalp

10.1.2 Secondary Objectives

- To evaluate the safety of topical KX2-391 Ointment 1% once daily for 5 consecutive days in terms of local skin reactions (LSRs) and other safety evaluations such as AEs and laboratory assessments

- To compare the rates of partial responders defined as ≥75% clearance of AK lesions in the treatment area on the face or scalp at Day 57 between the KX2-391 Ointment 1%-treated group and vehicle-treated group

10.2 Study Endpoints

10.2.1 Efficacy

10.2.1.1 Primary Endpoint

- Complete (100%) clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area

10.2.1.2 Secondary Endpoint

Key Secondary Endpoint:

- Partial clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with a ≥75% reduction in the number of AK lesions identified at Baseline (Day 1 pre-dose) in the treatment area

10.2.2 Safety

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, serious AEs (SAEs), events of special interest, clinical laboratory data, and other safety assessments (vital signs, physical examinations, ECGs, etc.)

10.3 Analysis Populations

The following populations are defined for analysis:

- Intent-To-Treat (ITT) Population: all randomized subjects. This is the primary efficacy population.
- Per-Protocol (PP)/Evaluable Population: all randomized subjects who have received at least 4 of the 5 doses, conformed to the protocol as to entry criteria, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.
- Safety Population: all randomized subjects who have received at least one dose of study treatment.

10.4 General Considerations

10.4.1 Baseline Values

Unless stated otherwise, baseline values are defined as the latest non-missing data collected before or on the first dose date/time, which could come from Screening or the Day 1 visit.

10.4.2 Study Day

Study day will be calculated relative to the first dose date.

10.4.3 Visit Windows

All data will be summarized and analyzed according to the nominal visits.

10.5 Subject Disposition

For screen failure subjects, a listing will be provided to present their screen failure reasons.

Numbers of subjects in each analysis population (ITT, PP/Evaluable and Safety) and for the study overall will be tabulated by treatment group.

Further, the summaries of subject disposition will be performed by treatment group for the ITT population, as follows:

- Subjects randomized
- Subjects dosed
- Subjects who completed Day 57 visit by AK clearance status at Day 57
- Subjects who discontinued before Day 57 visit by the primary discontinuation reason

Summaries by treatment group will also be performed for each study site or each analysis site (see Section 10.11.2 for the definition of analysis site) for the ITT population.

A listing of subjects who discontinued before the Day 57 visit and the associated primary reasons will be presented.

10.6 Subject Attendance

The number of subjects at each visit will be summarized by treatment group for the ITT population and the PP/Evaluable population.

10.7 Protocol Deviations

Any protocol deviations identified with their corresponding categories during site monitoring will be captured in the eCRF.

The number of subjects with protocol deviations will be summarized by category and treatment group. A listing of protocol deviation details will be presented.

10.8 Demographic and Other Baseline Characteristics

Demographic data, including age (in years), age category (<65, ≥65), gender, race and ethnicity will be summarized by treatment group for the ITT population, the PP/Evaluable population, and the Safety population.

Baseline characteristics, including location of treatment area, AK lesion count, Fitzpatrick skin type, weight, will be summarized by treatment group for the ITT population, the PP/Evaluable population, and the Safety population.

Other baseline data, including AK history, AK treatment history data, medical history for non-AK conditions, will be summarized by treatment group for the ITT population.

The data mentioned above and the data about expanded dermatological examination outside of the treatment area will be presented in data listings for the ITT population.

10.9 Prior and Concomitant Therapy

10.9.1 Prior and Concomitant Medications

Non-study treatment medications will be recorded in the eCRF and are defined as those medications that are taken from 28 days before the first dose until discharge from the study. All verbatim terms collected will be coded with the World Health Organization Drug (WHO Drug) Dictionary published in September 2017.

Prior medications will be defined as medications that stopped before the first dose of study.

Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment. Since it may not be able to determine medication dates relative to the first dose of study treatment due to partial or missing dates, if a medication cannot be determined to be 'prior' (ie, before the first dose of study treatment), it will be considered a concomitant medication.

To identify medications that start before the Recurrence Follow-up Period, start dates will be compared with the actual Day 57 visit date for each subject. If a medication start date cannot be confirmed to fall in the Recurrence Follow-up Period due to missing or partial dates, this medication will be considered to have started before this period.

The number and percentage of the subjects with concomitant medications starting before the Recurrence Follow-up Period will be summarized for the Safety Population:

1) by anatomical therapeutic chemical class, standardized drug name, and treatment group
2) by standardized drug name and treatment group

A listing of all prior and concomitant medications collected for the Safety population will be provided.

10.9.2 Procedures

Procedures that start before the Recurrence Follow-up Period will be identified in the same way as described above.

A listing of all procedures will be provided for the Safety population.

10.10 Treatment Compliance and Extent of Exposure

Study treatment compliance will be defined as the actual number of doses a subject received divided by the number of this subject's planned doses. Study treatment compliance will be summarized by treatment group for the Safety population.

The number of dosed subjects at each visit will be summarized by treatment group for the Safety population.

10.11 Efficacy Analyses

All efficacy endpoints except recurrence rate will be analyzed for the ITT and the PP/Evaluable populations.

10.11.1 Primary Efficacy Analyses

To achieve statistical significance in the study, the Day 57 complete clearance rate will be analyzed using a Cochran-Mantel-Haenszel (CMH) model controlling for treatment location and treatment group. Before applying the CMH method, a Breslow-Day test with a significance level of 10% will be used to explore heterogeneity of the odds ratios across treatment location subgroups.

Further, the Pearson Chi-Square (used to power the study) will be applied to demonstrate basic agreement with the CMH.

The primary efficacy analysis will be performed with the ITT population, and will be repeated with the PP/Evaluable population to support the primary efficacy analysis results.

10.11.2 Pooling of Sites and Additional Analysis Adjusting for Site-to-Site Variability

Low enrollment sites will be pooled to analysis sites with approximately 20 subjects in each pool. For example, the number of subjects enrolled will be graphically displayed by study site and treatment location (face or scalp) from the smallest number to the largest, with bars depicting treatment response. Then, analysis sites will be defined for approximately every 20 subjects pooled from the study sites with the lowest enrollment.

Another CMH test adjusting for treatment group and analysis site will be performed to ensure concordance with the primary efficacy endpoint analyses described above.

To explore heterogeneity of the odds ratios across analysis sites, the Breslow-Day test at a significance level of 10% will be applied. A finding of statistical significance in this test will be followed by exploratory analyses to identify outlier study sites. The outlier sites will be discussed and an exploratory analysis excluding the outlier sites may be carried out to estimate the impact of site-by-treatment interactions. This process will be documented as an appendix to the final version of the SAP, prior to the first database lock.

10.11.3 Secondary Efficacy Analyses

- Key Secondary Efficacy Endpoint:

Partial clearance rate will be analyzed in the same way as the primary efficacy endpoint (complete clearance rate).

However, to control for multiplicity, partial clearance rate as the key secondary efficacy endpoint will be examined using a step-down gatekeeping testing strategy for the overall type I error rate. In other words, the primary endpoint will serve as a gatekeeper for the key secondary endpoint. The complete clearance rate will be tested initially; if, and only if it is statistically significant at the 0.05 significance level, then the partial clearance rate will be statistically tested at the same significance level.

10.11.4 Additional AK Lesion Count Analysis:

Moreover, the number of AK lesions and the change from baseline in lesion count at each visit will be summarized using descriptive statistics (ie, mean, standard deviation (SD), median, minimum and maximum) by treatment location (face or scalp) and treatment group for the ITT population.

Subjects with missing AK lesion counts and the associated reasons will be reviewed and supplemented as an appendix of the final version of the SAP.

10.11.5 Missing Data Handling and Sensitivity Analysis

Because no subjects discontinued prior to Day 57 visit, no sensitivity analyses for the primary and the key secondary efficacy endpoints will be performed.

10.11.6 Subgroup Analysis

To indicate concordance with the overall results, the primary and the key secondary efficacy endpoints will be tabulated and displayed graphically in subgroups such as treatment location (face or scalp), gender, age (<65 or ≥65 years), baseline AK lesion count (4, 5, 6 or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/ VI). Outliers will be clinically explained in the clinical study report.

Similarly, a Clopper-Pearson Exact 95% confidence interval (CI) will be provided for each estimation. But no statistical test will be performed between subgroups.

10.12 Safety Analyses

For data locked at the first step (see Section 8), safety variables will be analyzed in the Safety population.

10.12.1 Adverse Events

All AE verbatim terms will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA version 18.1 or higher).

For all subjects, AEs, regardless of relationship to study treatment, will be collected from the time the subject signs ICF through Day 57.

Treatment-emergent AEs (TEAEs) will be identified as:

- Either those AEs with an onset on or after the date of the first dose of study treatment or
- Those pre-existing AEs that worsen after the date of the first dose of study treatment

If an AE cannot be determined by the definition above for partial dates or missing dates, it will be considered as a TEAE unless it is confirmed to stop before the first dose date/time of study treatment.

An overall summary table of AEs will include the number of subjects with the following events for each treatment group.

- Any AEs
- Any TEAEs
- Any AEs that are at least possibly related to study treatment, including those definitely related, probably related, and possibly related, or those with missing relationship
- Any serious AEs
- Any severe AEs
- Any AEs leading study discontinuation
- Any AEs that are associated with death

In addition, summaries of the number of subjects with the following AEs will be displayed for each treatment group:

- All TEAEs by SOC and PT
- All TEAEs by PT

- All TEAEs by PT and maximum severity (mild, moderate, or severe)
- All AEs that are at least possibly related to study treatment by SOC and PT
- All AEs that are at least possibly related to study treatment by PT
- All AEs that are at least possibly related to study treatment by PT and maximum severity (mild, moderate or severe)

Moreover, the following listings will be provided:

- Severe AEs
- Serious AEs
- AEs leading to treatment discontinuation will also be listed.
- Death

All AEs will be presented in a subject data listing.

10.12.2 Events of Special Interest

During the Treatment and Response Assessment periods, events of special interest, including overdose of study drug, pregnancy, ocular exposures to study drug and all skin cancers, will be reported and presented in a listing.

10.12.3 Local Skin Reactions

LSRs will be assessed by using a 4-point (0 - 3) grading criteria for the following signs: Erythema, Flaking/Scaling, Crusting, Swelling, Vesiculation/Pustulation, Erosion/Ulceration in treatment area at visits Day 1, Day 5, Day 8, Day 15, Day 29, Day 57 or Early Termination.

For each LSR sign, the number and percentage of subjects with LSRs will be summarized by grade and treatment group at each visit. The total number of subjects with non-missing assessments at each visit will be used as the denominator. In addition, LSR grades will be regarded as continuous values and be summarized using descriptive statistics by treatment group at each visit.

Further, the incidence of the worst post-baseline LSR grades will be compared with corresponding baseline grades and then tabulated by treatment group for each LSR sign.

Shifts from baseline to the worst post-baseline grade and to the Day 57 grade will be provided for each LSR sign by treatment group.

Furthermore, a composite LSR score will be constructed by summing the non-missing grades for the 6 individual LSR signs described above at each visit. If any one of the grades from the 6 sign is missing, the composite score will be considered as missing.

This composite score and change from baseline will be summarized by treatment group at each visit using descriptive statistics. Further, the composite score mean plus/minus SD at each visit will be plotted against visit to visualize the change over time. Subjects with missing composite score will not be included in the calculation for descriptive statistics.

All LSR grades, including the composite score, and any associated comments will be displayed in a data listing.

Subjects with missing LSR assessment and the associated reasons will be reviewed and supplemented as an appendix of the final version of the SAP.

10.12.4 Pigmentation and Scarring

Absence or presence of pigmentation and scarring in the treatment area will be assessed at the following visits: Day 1, Day 5, Day 8, Day 15, Day 29, Day 57, or Early Termination.

The incidence of pigmentation (ie, hypopigmentation and hyperpigmentation) and scarring will be summarized by treatment group at each visit. In addition, shifts from baseline to Day 57 will be summarized by treatment group.

All pigmentation and scarring records will be presented in a data listing.

10.12.5 Laboratory Data – Hematology, Blood Chemistry, and Urinalysis

Laboratory assessments for hematology, blood chemistry and urinalysis (mainly dipstick but microscopic test is possible) will be performed at Screening, Day 8, and Day 15.

The following laboratory parameters will be analyzed:

Hematology

Red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils

Chemistry

Electrolytes: chloride, potassium, sodium, bicarbonate (HCO_3)

Liver function tests: alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), direct bilirubin, total bilirubin

Renal function tests: blood urea/blood urea nitrogen, creatinine

Other: Albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, uric acid

Urinalysis (dipstick)

Hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood

Actual values, changes from baseline and percentage changes from baseline will be summarized for the following laboratory parameters using descriptive statistics by treatment group at each visit:

- Hematology: all numeric parameters
- Blood Chemistry: all numeric parameters

Hematology and blood chemistry laboratory data will also be tabulated using shift tables by post-baseline visit (Day 8 and Day 15) and treatment group. For this purpose, all numeric hematology and blood chemistry laboratory values will be flagged with "LOW", "NORMAL", "HIGH" or "UNKNOWN" based on normal ranges provided by the central lab (PPD).

In these shift tables, entries will be numbers of subjects shift to low (or high) divided by numbers of subjects with non-missing baseline and post-baseline assessments followed by corresponding percentages.

Listings of all hematology, blood chemistry and urinalysis values will be provided with abnormalities flagged.

10.12.6 Vital Signs

Vital signs (systolic/diastolic blood pressures, pulse rate, respiratory rate and body temperature) will be assessed at the following scheduled visits: Screening, Day 1, Day 5, Day 57, or Early Termination.

Actual values, changes from baseline and percentage changes from baseline of each vital sign parameter will be summarized using descriptive statistics by treatment group at each visit (Baseline, Day 5, and Day 57).

A listing of vital sign values will be provided.

10.12.7 12-Lead Electrocardiograms

Assessment of 12-lead ECG will be performed at Screening, Day 1, Day 5, and Day 15 and the data will be listed.

ECG data from the studies KX01-AK-004 and KX01-AK-004 will be combined for a separate cardiac parameter analysis conducted by the central ECG vendor. A separate plan for this analysis will be provided by the central ECG vendor.

10.12.8 Physical Examination

Physical examination findings at Screening, Day 57, or the Early Termination Visit will be listed for each subject.

10.12.9 Weight

Weight will be measured at Screening, Day 57, or the Early Termination Visit. Weight actual values, changes from baseline, and percentage changes from baseline will be summarized by treatment group at each visit.

10.12.10 Pregnancy Test

Results of pregnancy tests will be listed for subjects if applicable.

10.13 Comments

During the study, Investigators may provide extra information as comments for a specific visit, assessment or for the whole study. Investigator comments will be listed.

11 STATISTICAL EVALUATION FOR DATA COLLECTED IN THE RECURRENCE FOLLOW-UP PERIOD

Data analysis for AK recurrence and safety data collected in the Recurrence Follow-up Period will be discussed in this section.

It is expected that few subjects in the Vehicle treatment group will enter the Recurrence Follow-up Period. Therefore, no comparison between treatment groups will be performed for the Recurrence Follow-up Population defined in Section 11.3.

11.1 Objectives

- To determine the recurrence of AK in the treatment area up to 12 months post-Day 57 in subjects who had complete clearance at Day 57 after 5 consecutive days of treatment with KX2-391 Ointment 1%
- To evaluate the safety of topical KX2-391 Ointment 1% within the treatment area during the Recurrence Follow-up Period

11.2 Endpoints

Recurrence Rate

- Recurrence rate of AK lesions in subjects who achieved complete clearance at Day 57

Safety

- AEs within the treatment area after Day 57 and up to 12 months post-Day 57

11.3 Analysis Population

Recurrence Follow-up population: all subjects in the ITT Population who achieved complete clearance at the Day 57 visit.

All recurrence and safety data collected in the Recurrence Follow-up Period will be analyzed for the Recurrence Follow-up population only.

11.4 General Consideration

11.4.1 Definition of Study Day

Study day in the Recurrence Follow-up Period will be calculated relative to the Day 57 visit, which is considered as study day 0.

11.5 Subject Disposition

The following disposition events will be tabulated by treatment group for the Recurrence Follow-up population:

- Subjects in the Recurrence Follow-up Population
- Subjects who completed the Recurrence Follow-up Period
- Subjects who discontinued during the Recurrence Follow-up Period by the primary discontinuation reason

A listing of subjects who discontinued during the Recurrence Follow-up Period and the associated primary discontinuation reasons will be provided.

11.6 Protocol Deviation

Protocol deviation data captured during the Recurrence Follow-up Period will be listed only.

11.7 Demographic and Baseline Characteristics

Demographic data and other baseline characteristics, including age (in years), age category (<65, ≥65), gender, race, ethnicity, treatment location, number of baseline AK lesions, baseline weight and Fitzpatrick skin type will be summarized by treatment group for the Recurrence Follow-up Population.

11.8 Medications and Procedures

Medications with start dates after the Day 57 visit date will be analyzed. Medications will be summarized by anatomical therapeutic chemical class, standard name of those medications and treatment group. Those medications will be provided in listings as well.

Similarly, procedures with dates after the Day 57 visit date will be identified. Those procedures will be provided in listings.

11.9 AK Recurrence Results

11.9.1 Analysis of Recurrence

Recurrence will be defined as appearance of any AK lesions in the treatment area, including those recurred or newly identified. Recurrence rates will be estimated based on a Kaplan-Meier method at each post-Day 57 analysis visit. Subjects with missing AK assessments in the Recurrence Follow-up Period will be considered as censored at their last AK assessment.

Analysis visits will be defined based on the time interval between the actual visit date and the Day 57 visit date:

Analysis Visit	Time Interval in Days (Actual Visit Date - Day 57 Visit Date)
0 Month Post-Day 57	NA[(a)]
3 Months Post-Day 57	[1, 140]
6 Months Post-Day 57	[141, 225]
9 Months Post-Day 57	[226, 320]
12 Months Post-Day 57	=<321

(a) Subjects who did not enter the Recurrence Follow-up Period or were lost to follow-up right after Day 57 visit are considered as censored at 0 Month Post-Day 57.

Basically, a Kaplan-Meier plot will be created for the recurrence rate in the KX2-391 Ointment 1% group. The algorithm is described as below:

The number of subjects at risk at each analysis visit will be expressed as:

$$N_j = N_{j-1} - R_{j-1} - C_{j-1}$$

where

j: Sequence number of analysis visits (j=1 for 3 Month Post-Day 57, 2 for 6 Month Post-Day 57,
3 for 9 Month Post-Day 57 and 4 for 12 Month Post-Day 57)

N_j: Number of subjects at risk during the current analysis visit

N_{j-1}: Number of subjects at risk during the previous analysis visit

R_{j-1}: Number of subjects with AK recurrence during the previous analysis visit

C_{j-1}: Number of subjects considered as censored with missing AK lesion assessment results due to early study discontinuation, protocol violation or other reasons

Then, the recurrence rate (RR) estimate will be calculated at the analysis visit j as:

$$RR_j = 100*[1 - S_j], \text{ with } S_j = S_{j-1}*[1 - R_j/N_j] \text{ for } j>0 \text{ and } S_0=1$$

Recurrence-free rate at 12 Month Post-Day 57 visit is defined as $100*S_j$ when j=4. This rate and the associated 95% CI will be presented by treatment location in the KX2-391 Ointment 1% group.

The number of subjects at risk, the number of subjects with recurrence and the number of censored subjects will be presented at each analysis visit by treatment location in the KX2-391 Ointment 1% group.

Listing of subject status for the Kaplan-Meier analysis in the Recurrence Follow-up Period will be provided.

11.9.2 Handling of Missing or Censored Data

Missing data will not be imputed. Subjects with missing AK lesion assessments due to early termination will be considered as censored on the analysis visit at which they discontinued.

11.9.3 AK Lesion Counts

A listing will be provided for AK lesion count at each assessment.

11.10 Safety Results

11.10.1 Adverse Events

The protocol specifies AEs within the treatment area would be collected during the Recurrence Follow-up Period. However, spontaneous reports of AEs not in the treatment area were also collected. All AEs, regardless of treatment area AEs or not, will be analyzed.

An overall summary table of AEs will include the number of subjects with the following events for each treatment group.

- Any AEs
- Any AEs that are at least possibly related to study treatment, including those definitely related, probably related, and possibly related, or those with missing relationship
- Any serious AEs
- Any severe AEs
- Any AEs leading study discontinuation
- Any AEs that are associated with death

In addition, summaries of the number of subjects with the following AEs will be displayed for each treatment group:

- All AEs by SOC and PT
- All AEs by PT and maximum severity (mild, moderate, or severe)

SAEs, severe AEs, AE-leading to discontinuation and death will be presented in listings, respectively.

All AEs collected in this period will be listed as well.

11.10.2 Events of Special Interest

During the Recurrence Follow-up Period, only pregnancy and skin cancers in the treatment area will be reported. These records will be presented in listings.

11.11 Comments

During the study, Investigators may provide extra information as comments for a specific visit, assessment or for the whole study. Investigator comments will be listed.

12 INTERIM ANALYSES

No interim analyses have been planned.

13 CHANGES IN THE PLANNED ANALYSES

Prior to locking the database and unblinding the study, any changes in the planned analyses based on data review will be documented in the final SAP.

Per the discussion of the Blind Data Review Meeting prior to the first database lock, the primary and the key secondary endpoint analyses will be based on the Non-Responder Imputation approach for missing data handling. In addition, no sensitivity analyses will be performed as no subjects are missing the AK lesion count data at the Day 57 visit.

14 PROGRAMMING SPECIFICATIONS

Analysis dataset specifications will be provided in a stand-alone document.

15 STATISTICAL SOFTWARE

Statistical software SAS® v9.4 will be used for all summaries and statistical analyses.

16 APPENDICES

16.1 Schedule of Procedures and Assessments

SIGNATURE PAGE

Author:

PPD

Study Statistician

PPD

Date/Time

Approval:

PPD

Study Medical Monitor

PPD

Date/Time