

STATISTICAL ANALYSIS PLAN

Study Protocol Number: KX01-AK-002

Study Protocol Title: A Phase 2a, Open-Label, Multicenter, Activity and Safety Study of KX2-391 Ointment 1% in Subjects with Actinic Keratosis on the Face or Scalp

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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
LSR	local skin reaction
LOCF	last observation carried forward
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

3 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the protocol for study KX01-AK-002 Amendment 2, v3.0, dated 26SEP2016. This SAP supersedes the statistical section of the protocol and provides data analysis details for the activity and safety data analysis in the clinical study report (CSR). It does not include information regarding the pharmacokinetic (PK) analysis of the study drug, KX2-391 Ointment 1.0%; that information is provided separately.

3.1 Study Objectives

As stated above, objectives related to the PK analysis are not discussed in this document.

3.1.1 Primary Objective

- To evaluate the activity of KX2-391 Ointment 1% administered topically to the face or scalp in subjects with actinic keratosis (AK) by determining complete response rate, defined as 100% clearance at Day 57

3.1.2 Secondary Objectives

- To assess the activity of KX2-391 Ointment 1% during Days 1-57
- To assess the safety and tolerability of KX2-391 Ointment 1% in subjects with AK on the face or scalp
- To assess dose regimens by contrasting 5-day treatment with 3-day treatment in terms of the activity and safety of KX2-391 Ointment 1% in subjects with AK on the face or scalp

3.1.3 Exploratory Objectives

- To determine recurrence rates up to 12 months post-Day 57 for subjects who show response at Day 57
- To determine sustained response rates at 12 months post-Day 57 for subjects who show response at Day 57

3.2 Overall Study Design and Plan

This is an open-label, multicenter, activity, safety, tolerability, and PK study of KX2-391 Ointment 1% administered topically to the face or scalp of subjects with actinic keratosis in 2 sequential cohorts: a 5-day dosing regimen (Cohort 1) and a 3-day dosing regimen (Cohort 2).

The study consists of Screening, Treatment, Follow-up, and Recurrence Follow-up Periods.

In Cohort 1, eligible subjects will receive 5 consecutive days of topical treatment, to be applied at the study site, with 50 mg of KX2-391 Ointment 1% each day. Blood samples for PK analysis will be collected on Day 1 and Day 5. Subjects will return for Follow-up visits until

Day 57. Only Day 57 complete responders will continue Recurrence Follow-up Visits every 3 months for an additional 12 months after Day 57. Activity (lesion counts) and safety evaluations will be performed.

The Sponsor will review accumulating data. If the 5-day regimen (Cohort 1) has sufficient activity and safety to warrant evaluating a 3-day regimen, enrollment of Cohort 2 will start after there are 60 evaluable subjects or up to 80 subjects are enrolled (whichever comes first) in Cohort 1. For the most part, protocol procedures for Cohort 1 will be duplicated for Cohort 2, except PK samples will be collected on Days 1 and 3, and subjects will not return for Visits 5 and 6.

4 DETERMINATION OF SAMPLE SIZE

For either cohort, a sample size of 60 subjects is sufficient to detect a 100% clearance rate at Day 57 greater than 20% with 80% power, based on a two-sided ($\alpha=0.05$) binomial test, assuming a response rate of 35%, and less than a 25% dropout rate. This corresponds to a two-sided 95% confidence interval (CI) with a half-width of less than 15% (ie, lower boundary of the CI above 20%). The sample size of Cohort 2 may be adjusted, depending on the results of Cohort 1.

5 STATISTICAL METHODS

Statistical analyses will be reported using summary tables, graphs and data listings. In general, continuous variables will be summarized with mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized with counts and percentage of subjects in corresponding categories.

5.1 Study Endpoints

5.1.1 Primary Endpoint

- Activity will be evaluated by complete response rate, which is defined as the proportion of subjects achieving 100% clearance of all treated AK lesions on the face or scalp at Day 57.

5.1.2 Secondary Endpoints

- Activity: Reduction in lesion counts during Days 1-57
- Safety: Evaluation of adverse events (AEs), local skin reactions (LSRs) and clinical laboratory data; the results of other safety assessments (vital signs, physical examinations, ECGs) will also be evaluated

5.1.3 Exploratory Endpoints

- Recurrence rate will be estimated with a Kaplan-Meier method for subjects who achieved 100% clearance at Day 57 (Visit 10) with any identified AK lesions on the treatment area at 3, 6, 9, and 12 months post-Day 57.
- Sustained response rate will be estimated with the same Kaplan-Meier method for subjects who achieved 100% clearance at Day 57 (Visit 10) without any identified AK lesions on the treatment area at 12 months post-Day 57.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

- Per-Protocol Set: the group of protocol-eligible subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of study treatment and complete at least one scheduled post-treatment AK lesion evaluation
- Evaluable Set: the group of protocol-eligible subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of treatment and complete Day 1 and Day 57 AK lesion evaluations
- Safety Analysis/Full Analysis Set: the group of subjects who receive at least one dose of study treatment
- Recurrence Follow-up Set: the group of subjects who achieve complete clearance at Day 57

5.2.2 Subject Disposition

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

The number of subjects in each analysis set (Safety/Full Analysis, Per-Protocol, Evaluable, and Recurrence Follow-up) will be tabulated by cohort.

For the Safety/Full Analysis Set, subject disposition will be summarized by cohort for:

- Subjects dosed
- Subjects who completed the Day 57 visit
- Subjects who achieved 100% AK clearance at the Day 57 visit
- Subjects who discontinued before the Day 57 visit and their primary reason for discontinuation

In addition, the number of subjects dosed and the number of subjects who completed the Day 57 visit will be summarized by study site and cohort.

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

For the Recurrence Follow-up Set, the recorded discontinuation reasons will be reviewed and subjects who discontinued early due to AK recurrence will be assigned “AK Recurrence” as the new primary reason for discontinuation.

Subject disposition will be summarized by cohort for:

- Subjects who entered the Recurrence Follow-up Period
- Subjects who completed the Recurrence Follow-up Period
- Subjects who discontinued during the Recurrence Follow-up Period and their primary reason for discontinuation

Subjects who discontinued during the Recurrence Follow-up Period will also be listed.

5.2.3 Protocol Deviations

Any protocol deviations identified during site monitoring will be captured on the eCRF. A listing with protocol deviation details will be presented.

5.2.4 Demographic and Other Baseline Characteristics

Demographic data and baseline characteristics will be analyzed for the Safety/Full Analysis Set, the Per-Protocol Set, the Evaluable Set, the Recurrence Follow-up Set, the subjects with recurrence in the Recurrence Follow-up Set and the subjects without recurrence at 12 Months Post-Day 57 Visit in the Recurrence Follow-up Set.

Demographic data, including age (in years), age category (<65, ≥65), sex, race, and ethnicity will be summarized by cohort.

Baseline characteristics, including location of treatment area (face or scalp), Fitzpatrick skin type, baseline weight, primary diagnosis of treatment area, and baseline AK lesion count will be summarized by cohort.

Demographic and baseline characteristic data mentioned above will be presented in data listings for the Safety/Full Analysis Set only.

Other baseline data, including AK history, AK treatment history, medical history for non-AK conditions, and surgical history for non-AK conditions will be listed for the Safety/Full Analysis Set.

5.2.5 Prior and Concomitant Therapy

5.2.5.1 Prior and Concomitant Medications

Non-study treatment medications will be recorded on the eCRF from 28 days before Day 1 through the final study visit. All verbatim terms collected will be coded with the World Health Organization Drug Dictionary (WHO-DD) March 1, 2017.

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

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.

Furthermore, 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/Full Analysis Set:

- 1) by anatomical therapeutic chemical class, standardized drug name, and cohort
- 2) by standardized drug name and cohort

The incidence of concomitant medications in the Recurrence Follow-up Period (i.e. those start after Day 57 visit) will be summarized in the same way, but separately.

In addition, a listing of all prior and concomitant medications collected throughout the entire study will be provided.

5.2.5.2 Procedures

All procedures collected on the eCRF will be presented in a data listing.

5.2.6 Treatment Compliance and Extent of Exposure

5.2.6.1 Extent of Exposure

In general, subjects in each cohort at each dosing schedule received study drug in the range of 30 to 70 mg with 50 mg being the most common dose, as planned in the protocol. However, one subject from Cohort 1 and two subjects from Cohort 2 received 500 mg of study drug for each daily dose during their treatment period. In addition, dosing amount of another two subjects from Cohort 1 at Day 1 is missing because the site personnel inadvertently did not record the amount dosed after applying the study treatment on the subjects. Compared with other subjects, these overdosed or dose-missing subjects showed similar safety and activity profiles. Thus, they are still considered as protocol-eligible subjects.

The number of doses each subject received will be summarized as a continuous variable by cohort at each visit.

5.2.6.2 Treatment Compliance

Study treatment compliance will be defined as the actual number of doses a subject received divided by the planned number of doses, 5 (Cohort 1) or 3 (Cohort 2). Study treatment compliance will be summarized by cohort.

5.3 Data Analysis General Considerations

Both cohorts will be analyzed with the same statistical methods. Since this is not a dose regimen-randomized study, contrast between the 2 cohorts may be performed, but would mainly be noninferential, and consist of listings and descriptive statistics.

5.4 Activity Analyses

5.4.1 Primary Activity Analyses

The proportion of subjects with 100% clearance of all treated AK lesions at Day 57 will be considered to follow a binomial distribution. Based on the number of subjects who achieved 100% clearance at Day 57, the complete response rate and its corresponding 95% Clopper-Pearson Exact CI will be estimated in the Evaluable Set.

5.4.2 Secondary Activity Analyses

The number of AK lesions at the Screening, Day 1, Day 8, Day 15, Day 29, and Day 57 visits and actual/percentage lesion number change from baseline will be summarized by cohort at each visit in the Per-Protocol Set. Baseline values are defined as the assessments at Day 1.

5.4.3 Other Activity Analyses

The number of subjects with partial clearance ($\geq 75\%$) of treated AK lesions at Day 57 will be analyzed in the same way as the primary activity endpoint.

5.4.4 Exploratory Analyses

Analysis visits in the Recurrence Follow-up Period will be mapped based on the actual days relative to the Day 57 visit of each subject:

Actual Visit Date - Day 57 Visit Date	Analysis Visit
Between 1 and 136 (inclusive)	3 MONTHS POST-DAY 57
Between 137 and 226 (inclusive)	6 MONTHS POST-DAY 57
Between 227 and 316 (inclusive)	9 MONTHS POST-DAY 57
317 and Beyond	12 MONTHS POST-DAY 57

Recurrence rates and the associated 95% CIs will be evaluated with a Kaplan-Meier method at each post-Day 57 analysis visit:

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

where

j: Visit j

RR_j: Recurrence rate at visit j

S_j: Sustained response rate at visit j

R_j: Number of subjects with AK lesion recurrence at visit j

N_j: Number of subjects at risk at visit j

Early-discontinued subjects with no AK recurrence will be considered as censored at the last visit with AK lesion assessment. Completed subjects with no AK recurrence will be considered as censored at 12 Months post-Day 57 visit. The number of subjects at risk for visit j will be calculated as $N_{j-1} - R_{j-1} - C_{j-1}$, where N_{j-1} is the number of subjects at risk at the visit j-1. R_{j-1} is the number of subjects with recurrence at the visit j-1 and C_{j-1} is the number of subjects censored at visit j-1.

The recurrence rates and their associated 95% CIs will be presented by analysis visit, treatment location, and cohort for the Recurrence Follow-up Set.

Similarly, the sustained response rate and its 95% CI at 12 Months Post-Day 57 will be estimated by treatment location and cohort for the Recurrence Follow-up Set.

A listing of subjects who is included in the Kaplan-Meier analysis will be presented to provide their event or censoring details.

5.4.5 Subgroup Analysis

Complete clearance rate at Day 57, partial clearance rate at Day 57, sustained response rate at 12 Months Post-Day 57 will be analyzed by cohort in the following subgroups: age (<65, ≥65), sex (female, male), baseline AK lesion count (4, 5, 6, 7 and 8), baseline weight (< 200 and ≥200 lbs), skin type group (each skin type), study site (each study site).

5.5 Safety Analyses

All safety variables will be analyzed in the Safety/Full Analysis Set.

5.5.1 Adverse Events

All AEs, regardless of relationship to study treatment, will be collected from the time the subject signs the informed consent form through the final contact in the Follow-up Period at Day 57. In addition, treatment-related AEs/SAEs may be followed after the Day 57 visit to resolution, or if resolution is unlikely, to stabilization. For subjects participating in the Recurrence Follow-up Period, all spontaneously reported AEs will be collected whether they occurred at the treatment area or not.

For AEs, verbatim terms on the eCRF will be mapped to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Treatment-emergent AEs (TEAEs) will be identified, and are defined as:

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

If an AE cannot be determined to be treatment-emergent according to the definition above due to partial or missing dates, it will be considered as a TEAE unless it is confirmed to have stopped before the first dose date/time of study treatment.

Furthermore, to identify TEAEs that start before the Recurrence Follow-up Period, AE start dates will be determined relative to the actual Day 57 visit date for the corresponding subject. In such cases, if an AE start date cannot be confirmed to fall within the Recurrence Follow-up Period due to partial or missing dates, that AE will be considered to have started before that period.

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

- 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 to 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 cohort:

- 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)

Severe or serious AEs, whether treatment-emergent or not, will be presented in listings. AEs leading to treatment discontinuation will also be listed.

AEs that are collected during the Recurrence Follow-up Period (i.e. those with start dates after Day 57 visit) will be summarized and listed in the same way, but separately, for the Recurrence Follow-up Set.

Moreover, all AEs will be reviewed manually by the study Medical Monitor to identify any skin cancer-related records. Those event records will be displayed in a separate listing.

All AEs collected during the entire study including the Recurrence Follow-up Period will be presented in a subject data listing.

5.5.2 Local Skin Reactions

LSRs will be assessed using a 5-point grading scale ranging from 0 (Not Present) to 4 (Worst) for such signs as Erythema, Flaking/Scaling, Crusting, Swelling, Vesiculation/Pustulation, Erosion/Ulceration on the treatment area at the following visits: Day 1, Day 2, Day 3, Day 4 (Cohort 1 only), Day 5 (Cohort 1 only), Day 8, Day 15, Day 29, and Day 57. In addition, LSRs may be followed after the Day 57 visit to resolution, or if resolution is unlikely, to stabilization.

LSR baseline grades are defined as the LSR grades recorded at Day 1 (either pre-dose or post-dose).

The incidence of LSRs will be summarized by grade and cohort at each visit for each sign. In addition, LSR grades will be regarded as continuous values and will be summarized using descriptive statistics by cohort at each visit for each sign. Similarly, grades for each LSR sign will be visually presented in bar graphs by cohort at each visit.

Further, the incidence of the worst post-baseline LSR grade will be summarized by LSR grade and cohort for each sign.

The number of subjects with shift from baseline to the worst post-baseline grade and to the Day 57 grade will be summarized by cohort for each sign.

Furthermore, a composite LSR score will be constructed by summing the individual LSR grades for each sign at each visit. This composite score and change from baseline will be summarized by cohort at each visit using descriptive statistics. In addition, this score will be presented graphically by cohort in a line plot.

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

5.5.3 Pigmentation and Scarring

Presence or absence of pigmentation (including hypo-pigmentation and hyper-pigmentation) and scarring will be assessed on the treatment area at the following visits: Day 1, Day 2, Day 3

Day 4 (Cohort 1 only), Day 5 (Cohort 1 only), Day 8, Day 15, Day 29, and Day 57. In addition, pigmentation and scarring may be followed after the Day 57 visit to resolution, or if resolution is unlikely, to stabilization.

Results will be summarized by cohort at each visit. The number of subjects with shift from baseline to Day 57 will be summarized by cohort.

All pigmentation and scarring records with comments will be presented in data listings.

5.5.4 Laboratory Data – Hematology and Blood Chemistry

Laboratory assessments for hematology and blood chemistry will be performed at Screening, Day 8, and Day 57.

Actual values, changes from baseline, and percentage change from baseline for the following laboratory parameters will be summarized by cohort at each visit using descriptive statistics.

- Hematology:

Red Blood Cells, Hemoglobin, Hematocrit, Platelets, White Blood Cells, Neutrophils (Absolute Count), Neutrophils (%), Lymphocytes (Absolute Count), Lymphocytes (%), Monocytes (Absolute Count), Monocytes (%), Eosinophils (Absolute Count), Eosinophils (%), Basophils (Absolute Count), Basophils (%), Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Blood Cell Distribution Width

- Blood Chemistry:

Electrolyte: Sodium, Potassium, Chloride, Carbon Dioxide

Liver Function: Alkaline Phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma-glutamyl Transferase (GGT), Bilirubin (Total), Bilirubin (Direct)

Renal Function: Blood Urea/Blood Urea Nitrogen, Creatinine

Other: Glucose, Calcium, Albumin, Cholesterol, Triglycerides, Phosphorus, Lactate Dehydrogenase (LDH), Total Protein, Uric Acid

These laboratory parameters will also be analyzed using shift tables by post-baseline visit (Day 8 and Day 57) and cohort.

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

5.5.5 Laboratory Data – Urinalysis

Urinalysis assessment will be performed at Screening, Day 8 and Day 57. All parameter values will be provided in a data listing with abnormalities flagged.

5.5.6 Vital Signs

Vital signs (systolic/diastolic blood pressures, pulse rate, respiratory rate and body temperature) will be assessed at the following visits: Screening, Day 3 (Cohort 2 only), Day 5 (Cohort 1 only), Day 8, Day 15, Day 29, and Day 57.

Actual values, change from baseline, and percentage change from baseline for each vital sign parameter will be summarized using descriptive statistics by cohort at each visit.

A listing of vital sign values will be provided with flags for those outside (above or below) the reference range (see Section 12.2).

5.5.7 12-Lead Electrocardiograms

A 12-lead ECG will be completed at Screening, Day 1 (4 hours postdose, Cohort 2 only), Day 3 (4 hours postdose, Cohort 2 only), Day 8, and Day 57 to assess rhythm, heart rate, and intervals (PR, QRS, QT, and QTcF).

QTc will be collected. Study sites may have applied different formulae for calculation of QTc, therefore, this parameter will be reported in a data listing, but will not be analyzed.

For heart rate and ECG intervals, actual values, changes from baseline, and percentage change from baseline will be summarized using descriptive statistics by cohort at each visit.

Additionally, a listing of subjects with clinically significant abnormal ECG results will be presented.

All 12-lead ECG data, including details of abnormal findings from investigators, will be provided in a subject listing.

5.5.8 Other Safety Analyses

Physical examination findings at Screening and Day 57 will be listed for each subject.

Weight will be measured at Screening and Day 57. Actual values, change from baseline, and percentage change from baseline will be summarized by cohort and visit.

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

6 ONGOING ANALYSES

A formal interim analysis is not planned. Since this is an open-label study, after each group of approximately 20 subjects, ongoing analyses will be performed with tabulation of activity, LSRs, and adverse events.

7 CHANGES IN THE PLANNED ANALYSES

Definition of the Evaluable Set is updated to include Day 1 and Day 57 AK lesion evaluations only.

The Recurrence Follow-up Set is defined in this document to analyze data collected during the Recurrence Follow-up Period.

AK recurrence is not listed as a discontinuation event on CRF. The Sponsor reviewed all collected disposition event details and recategorized the subjects who discontinued due to AK recurrence in the Recurrence Follow-up Period into a new category of primary reason for discontinuation - "AK recurrence" (See Section 12.3).

The recurrence rates and the sustained response rate will be estimated with a Kaplan-Meier method to consider censored subjects who discontinued due to non-AK recurrence reasons.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Baseline Values

Unless stated otherwise, baseline values are defined as the last non-missing data collected before or on the first dose date/time, which would be either, the Screening or Day 1 visit.

8.2 Adverse Event Relationship to Study Drug

If an adverse event relationship to study drug is missing, it will be considered as related to study drug.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

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

11 MOCK TABLES, LISTINGS, AND GRAPHS

Mock tables, listings, and graphs will be provided as standalone documents.

12 APPENDICES

12.1 Schedule of Procedures and Assessments

SIGNATURE PAGE

Author:	
_____ PPD Study Statistician	_____ PPD Date
Approval:	
_____ Study Medical Monitor	_____ Date

SIGNATURE PAGE

Author:	
_____	_____
Study Statistician	Date
Approval:	
PPD _____	PPD _____
Study Medical Monitor PPD	PP Date