REVISION HISTORY

Revisions to KX01-AK-002 protocol v2.0_26 Apr 2016 (Amendment 1 protocol)
Current Version and Date: v3.0_26 Sep 2016 (Amendment 2)

Change	Rationale	Affected Protocol Sections
Revised the length of time a female subject must be amenorrheic in the definition of postmenopausal (from 18 months to 12 months). Revised the length of time before study treatment during which a highly effective means of contraception must be used (from 90 days to at least 30 days or 1 menstrual cycle, whichever is longer).	To align with current guidelines. A minimum of 1 menstrual cycle prior to dosing is sufficient for subjects using highly effective contraception.	• Synopsis / Inclusion Criteria • Section 9.3.1
Revised the length of time after which an investigational product was taken in a previous clinical trial as exclusionary in this study (from 14 days to 30 days).	Clinical trial subjects are followed for safety up to 30 days after their last study visit.	• Synopsis / Exclusion Criteria • Section 9.3.2
Specified KX2-391 1% as study drug. Included treatment area borders as part of the application site.	Clarification.	• Section 9.4.2.4 • Section 9.4.4
Added measurement of height as part of the screening physical examination.	BSA may need to be calculated for interpretation of PK data, so height measurement is needed.	• Table 1 • Table 2 • (new) Section 9.5.1.2.4 • Section 9.5.1.5.5
Heading name was revised to remove "…and Exposure to study Drug through Breastfeeding". Specified pregnancies include those occurring in a subject or in the female partner of a male subject. Revised withdrawal from study to discontinuation from treatment.	Correction; section text makes no reference to exposure through breastfeeding. Clarification. Clarification.	• Section 9.5.3.2
Stipulated that pigment-related changes or scarring should be followed until resolution or deemed stabilized by the Investigator.	Additional safety monitoring.	• Section 9.5.1.5.8
Revised language about reporting of significant treatment-emergent laboratory abnormalities.	Clarification.	• Section 9.5.1.5.1 • Section 9.5.1.5.2

Revisions to KX01-AK-002 protocol v2.0_26 Apr 2016 (Amendment 1 protocol)
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Change	Rationale	Affected Protocol Sections
Stipulated that subjects with a history of HIV, chronic hepatitis C, or chronic hepatitis B infection will be excluded from the study.	The effect of KX2-391 ointment on subjects who have these chronic infections for which they are on treatment is unknown.	• Synopsis / Exclusion Criteria • Section 9.3.2
Added additional ECG measurements for Cohort 2.	Additional safety monitoring.	• Table 2 • Section 9.5.1.5.6
Corrected miscellaneous punctuation/grammar errors.	Administrative.	• Throughout protocol

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Added a second cohort with a 3-day dosing regimen.	If the 5-day treatment regimen (Cohort 1) has sufficient activity and safety, a 3-day regimen (Cohort 2) will be evaluated.	• Throughout protocol • Table 1 • (new) Table 2 • List of In-Text Tables
Added a secondary objective.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Objectives • Section 8.2
Made sustained response an exploratory objective; removed it as a primary endpoint and revised exploratory endpoints and analyses to align with it as an exploratory objective; revised wording to describe analysis of recurrence rates.	Sustained response is more appropriate as exploratory because it is assessed post-Day 57; clarification	• Synopsis - Objectives - Statistical Methods / Study Endpoints - Activity Analyses • Section 8.3 • Section 9.7.1.1.1 • Section 9.7.1.1.3 • Section 9.7.1.6
Revised the number of subjects in the study.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Number of subjects • Section 9.1 • Section 9.1.1
Revised PK sampling timepoints.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Pharmacokinetic Assessments • Table 4
Removed reference to a Safety Management Plan; revised text regarding reporting of SAEs, deaths, and life-threatening events, and corresponding follow-up information.	Clarification.	• Section 9.5.3.1
Revised statistical-related text to reflect increased number of subjects based on the addition of Cohort 2; revised text regarding interim analysis.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis - Analysis Sets - Activity Analyses - Safety Analyses - Interim Analysis - Sample Size Rationale • Sections 9.7.1.2 - 9.7.1.6 • Section 9.7.1.8 (entirety) • Section 9.7.2 • Section 9.7.3
Added immunosuppressants and immunomodulators as exclusionary medications.	These medications may affect the intended effects of the study drug.	• Synopsis / Exclusion Criteria • Section 9.3.2
Increased the duration of the study period overall and enrollment	To accommodate addition of a	• Synopsis / Study Period and Phase of Development

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
period.	3-day regimen (Cohort 2).	• Synopsis / Duration of Participation and Treatment
Increased the number of sites conducting the study.	To accommodate increased number of subjects due to addition of Cohort 2; to facilitate enrollment.	• Synopsis / Sites • Section 6
With addition of additional sites, specified that enrollment among sites would be monitored to avoid imbalance.	Clarification.	• Synopsis / Study Design • Section 9.1 • Section 9.4.3
Revised description of study treatment.	Clarification.	• Table 3
Specified "during the Treatment Period" with regard to withdrawal of subjects who become pregnant.	Clarification of timeframe.	• Section 9.5.3.2
Revised text regarding collection and following of adverse events. Removed reference to Screening Disposition CRF/eCRF.	Clarification of timeframe; only study drug-related AEs will be followed. There is no Screening Disposition CRF/eCRF in the study.	• Section 9.5.1.5.1
Removed Appendix 1 and renumbered remaining appendix; added appropriate literature citation for reference.	Investigators are familiar with the method for skin typing; questionnaire and scoring system in Appendix 1 is not validated.	• List of Appendices • Section 9.5.1.2.2 • Section 9.5.1.5.8 • Section 10 • (original) Appendix 1 (deleted)
Revised text regarding removal of subjects from the therapy or assessment; modified some of the reasons for discontinuation.	Clarification.	• Section 9.3.3
Modified text regarding restrictions on the use of concomitant medication/therapies/topical products during the study; referred the reader to an FDA draft guidance.	Per recommendation of the Investigators and subject matter experts; to provide further guidance to the investigators.	• Synopsis / Concomitant Drug/Therapy • Section 9.4.7.3
Revised description of the Final Visit; specified when the Final Visit is for those who do not have complete response at Day 57.	Clarification.	• Table 1 / Footnote c • Section 9.1.3 • Section 9.1.4
Specified that use of sunblock in the treatment area will be recorded in	To be able to evaluate the activity of study drug in the presence and	• Section 9.4.7.2 • Section 9.5.1.5.8

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
the Concomitant Medication CRF. Removed text regarding subjects not changing their use of concomitant medications.	absence of sunblock. Subjects will be able to change concomitant medications per the Investigator's instructions.	
Removed use of body charts for identifying the location and shape of the treatment area.	Not needed; this will be done with the acetate sheets.	• Section 9.1.1 • Section 9.1.2
Specified minimum timeframe during which subjects cannot touch or wet the treatment area after study treatment application; removed information regarding shower times; revised text about instructions to the subjects for care of the treatment area.	Clarification.	• Section 9.4.2.4
Revised description of sun exposure.	Clarification.	• Synopsis / Inclusion Criteria • List of Abbreviations and Definition of Terms • Section 9.3.1
Revised description of Medical History.	Clarification.	• Section 9.5.1.2.1
Revised description of the Final Visit; specified when the Final Visit is for those who do not have complete response at Day 57.	Clarification.	• Table 1 / Footnote c • Section 9.1.3 • Section 9.1.4
Removed exclusionary use of moisturizers or emollients on the face or scalp within 12 hours prior to Visit 1.	Not necessary to exclude before Visit 1.	• Synopsis / Exclusion Criteria • Section 9.3.2
Revised Medical Monitor signatory.	Administrative.	• Protocol Signature page
Specified that scarring, in addition to pigmentation, will be assessed at the visits cited.	Clarification.	• Section 9.5.1.5.8 / Pigmentation and Scarring
Revised description of procedures related to treatment area identification.	Clarification to align with streamlined procedures.	• Section 9.1.1
Revised text to ensure the signing of ICF prior to study procedures.	Clarification.	• Section 5.3
Revised the definition of the Evaluable Set.	Clarification.	• Synopsis / Number of Subjects

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Revised definition of ICH.	Clarification to align with recent ICH organizational changes.	• Investigator Signature Page • Title Page • List of Abbreviations and Definition of Terms • Section 5.1
Corrected typographical/punctuation/grammar errors.	Administrative.	• Throughout protocol

PROTOCOL SIGNATURE PAGE

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
Investigational Product Name:	KX2-391 Ointment 1%
UTN Number:	U1111-1173-5677

SIGNATURES

Authors:

PPD PPD

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Kinex Pharmaceuticals, Inc.

Date

PPD , PhD
Clinical Pharmacologist
Kinex Pharmaceuticals, Inc.

Date

PPD , PhD
Biostatistician
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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	KX01-AK-002
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Investigational Product Name:	KX2-391 Ointment 1%
UTN Number:	U1111-1173-5677

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name, degree(s)>		
Investigator	Signature	Date

<Name of study site>

Study Site

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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
Sponsor:	United States: Kinex Pharmaceuticals, Inc. 20 Commerce Drive Cranford, New Jersey 07016, US Tel: +1 908-272-0628
Investigational Product Name:	KX2-391 Ointment 1%
Indication:	Actinic keratosis on the face or scalp
Phase:	2a
Approval Date:	v1.0 23 Jan 2016 (original protocol) v2.0 26 Apr 2016 (Amendment 1) v3.0 26 Sep 2016 (Amendment 2)
UTN Number:	U1111-1173-5677
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Kinex Pharmaceuticals, Inc. (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. KX2-391
Name of Active Ingredient: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide
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
Investigators PPD, MD, Lead Principal Investigator
Sites Approximately 8 to 16 sites in the United States
Study Period and Phase of Development First subject in to last subject out, approximately 24 months Phase 2a
Objectives **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 **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 the pharmacokinetics (PK) 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 **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
Study Design This study will be 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, and 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. Thereafter, 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.

The same study sites for the most part of Cohort 1 will be used for Cohort 2. The Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

Number of Subjects

In each cohort, approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set, defined as subjects who complete all planned treatments and most evaluations, including the Day 57 Follow-up visit. Therefore, a total of 160 subjects in 2 cohorts may be enrolled, but the sample size of Cohort 2 may be adjusted, depending on the results of Cohort 1.

Inclusion Criteria

Eligible subjects must have/be:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 30 days or 1 menstrual cycle, whichever is longer, prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device. Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.
8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that the Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities

- clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable

9. Willing to avoid direct sun or ultraviolet (UV) light exposure to the face or scalp
10. Able to comprehend and are willing to sign an informed consent form (ICF)

Exclusion Criteria

Eligible subjects must not have/be:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days
   - immunosuppressants or immunomodulators; 28 days
4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)
   - imiquimod (eg, Aldara; Zyclara)
   - diclofenac with or without hyaluronic acid (eg, Solaraze)
6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy
   - electrodesiccation
   - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
   - chemical peels (eg, tricholoracetic acid)
   - dermabrasion
   - surgical removal (eg, curettage, excision)
7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which

exposes the subject to an unacceptable risk by study participation

10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 30 days or 5 half-lives of the investigational product, whichever is longer, before dosing
13. A known history of human immunodeficiency virus (HIV), chronic hepatitis C, or chronic hepatitis B infection

Study Treatment

50 mg of KX2-391 Ointment 1% will be applied topically once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total).

Duration of Participation and Treatment

- Planned enrollment period for each cohort: approximately 3 months (90 days)
- Planned subject participation is approximately 64 weeks:
  - Screening Period: up to 28 days
  - Treatment Period: For Cohort 1, 5 consecutive treatment days (Days 1-5); for Cohort 2, 3 consecutive treatment days (Days 1-3)
  - Follow-up Period: Visits at Days 8, 15, 29, and 57
  - Recurrence Follow-up Period: only for complete responders at Day 57, visits every 3 months for 12 months after Day 57 (ie, at 3, 6, 9, and 12 months post-Day 57).

Length of stay: On Day 1 (Visit 2, Cohorts 1 and 2) and Day 5 (Visit 6, Cohort 1) or Day 3 (Visit 4, Cohort 2), subjects may stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected.

Concomitant Drug/Therapy

Use of any non-study drug treatment for AK lesions on the treatment area is prohibited until Day 57. Any lesion in the treatment area that is treated during the Recurrence Follow-up Period will be considered as a recurrence.

Assessments

Activity Assessments

The Investigator will perform a count of AK lesions for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

Safety Assessments

Safety will be assessed by recording all adverse events (AEs), serious adverse events (SAEs), laboratory evaluation of hematology, biochemistry, and urinalysis values, measurement of weight and vital signs, evaluation of ECGs, and the performance of physical examinations.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions (LSRs). AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events.

Other Assessments

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst). In addition to LSRs, hypo- and hyper- pigmentation and scarring on the treatment area will be assessed as being present or absent. Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events. All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization. LSRs will be reported separately from AEs.

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Pharmacokinetic Assessments

PK samples will be collected at the following timepoints for Cohort 1:

- Day 1: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose
- Day 5: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose

PK samples will be collected at the following timepoints for Cohort 2:

- Day 1: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose
- Day 3: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Statistical Methods

Study Endpoints

Primary Endpoint

- Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57.

Secondary Endpoints

- Activity: Reduction in lesion counts during Days 1-57
- Safety: Evaluation of AEs and clinical laboratory data; the results of other safety assessments (vital signs, physical examinations, ECGs) will also be evaluated.
- Pharmacokinetic: Determination of C_{max} and where applicable, AUC_t, C_{min}, and accumulation ratio R

Exploratory Endpoints

- Recurrence rate will be defined as the proportion of subjects who achieved 100% complete 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 defined as the proportion of subjects who achieved 100% complete

clearance at Day 57 (Visit 10) without any identified AK lesions on the treatment area at 12 months post-Day 57.

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 evaluation.
- Evaluable Set: the group of subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of treatment and complete most evaluations including the Day 57 Follow-up Visit.
- Safety Analysis/Full Analysis Set: the group of subjects who receive at least one dose of study treatment.
- PK Analysis Set: the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

Activity Analyses

AK lesion counts will be summarized by cohort at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 will be estimated by cohort in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be estimated by timepoint and cohort in the Evaluable Set.

A 95% CI for the sustained response rate at 12 months post-Day 57 will be estimated by cohort in the Evaluable Set.

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

Safety Analyses

All subjects who receive at least one dose of KX2-391 Ointment 1% will be included in the safety analyses. Treatment-emergent AEs (TEAEs) are defined as either those AEs with an onset after dosing or those pre-existing AEs that worsen after dosing. For AEs, verbatim terms on the case report form/electronic case report form (CRF/eCRF) will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; v 16.0 or higher). Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized by cohort. Adverse events will also be summarized by severity, relationship to study drug, and cohort. Subject incidence of SAEs will also be displayed by cohort. Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by cohort. Changes from baseline will also be summarized by cohort. In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up in each cohort.

Local skin reactions, pigmentation, and scarring as reported by the Investigator, will be displayed and summarized by visit and cohort for all subjects.

Similar to the activity analyses, any contrast between the 2 cohorts will mainly be noninferential in the safety analyses.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

Plasma concentrations for KX2-391 will be analyzed to determine applicable PK parameters.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

Interim Analysis

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. The decision to open Cohort 2 will be documented.

Statistical Methods

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.

Sample Size Rationale

For either cohort, a sample size of 60 subjects is sufficient to detect a 100% complete 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% 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.

FINAL v3.0_26 Sep 2016

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 1)

Period	Screening	Treatment					Follow-up				Recurrence Follow-up [a]
Visit	1	2	3	4	5	6	7	8	9	10 [b]/ Early Term	11, 12, 13, 14 [a]
Day	-28 to -1	1	2	3	4	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Visit time window (days)	None	None	None	None	None	None	±2	±2	±2	±2	±14
Informed consent	X										
Inclusion & exclusion criteria	X	X[d]									
Demographics	X										
Medical/surgical history	X										
AK history/AK treatment history	X										
Fitzpatrick skin-type scale	X										
Vital signs[e]	X					X	X	X	X	X	
Prior and concomitant medications/therapies	X	X[d]	X	X	X	X	X	X	X	X	X
Physical examination, including weight and height[f]	X									X	
Treatment area identification	X	X[d]									
AK lesion count	X	X[d]					X	X	X	X	X
ECG[g]	X						X			X	
Clinical chemistry, hematology, and urinalysis[h]	X						X			X	
Pregnancy test	X	X[d,i]					X			X	
PK blood samples		X[j]				X[j]					
Study medication application		X	X	X	X	X					
AEs[k]	X	X	X	X	X	X	X	X	X	X	X[l]
LSRs		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Pigmentation and scarring		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Standardized photography	X	X[d]					X			X	X

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 1)

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; PK = pharmacokinetic; Term = Termination.

a For Day 57 complete responders only.

b For subjects who do not have complete response at Day 57, Day 57 is the Final Visit.

c For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

d Assessment performed before study medication application. Day 1 evaluation will serve as baseline for these assessments.

e Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.

f A complete PE will include weight and an assessment of HEENT, integumentary, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height will be measured at Screening only.

g Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

h Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments.

i For females of childbearing potential; urine pregnancy test on Day 1 before study medication application. All other pregnancy tests are performed with serum.

j PK assessments on Day 1 and Day 5 at 0 hour (just before study medication application) and at 0.5 (±5 min), 1 and 4 hours (±10 min) after study drug application.

k Before LSR assessment, subjects will be queried for spontaneously reported AEs.

l Only AEs in the selected treatment area will be recorded.

Table 2 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 2)

Period	Screening	Treatment					Follow-up				Recurrence Follow-up [a]
Visit	1	2	3	4	5 [b]	6 [b]	7	8	9	10[c]/ Early Term	11, 12, 13, 14 [a]
Day	-28 to -1	1	2	3	4	5	8	15	29	57[c]	3, 6, 9, 12 Months Post-Day 57[d]
Visit time window (days)	None	None	None	None			±2	±2	±2	±2	±14
Informed consent	X										
Inclusion & exclusion criteria	X	X[e]									
Demographics	X										
Medical/surgical history	X										
AK history/AK treatment history	X										
Fitzpatrick skin-type scale	X										
Vital signs[f]	X			X			X	X	X	X	
Prior and concomitant medications/therapies	X	X[e]	X	X			X	X	X	X	X
Physical examination, including weight and height[g]	X									X	
Treatment area identification	X	X[e]									
AK lesion count	X	X[e]					X	X	X	X	X
ECG[h]	X	X[h]		X[h]			X			X	
Clinical chemistry, hematology, and urinalysis[i]	X						X			X	
Pregnancy test	X	X[e,j]					X			X	
PK blood samples		X[k]		X[k]							
Study medication application		X	X	X							
AEs[l]	X	X	X	X			X	X	X	X	X[m]
LSRs		X[e]	X[e]	X[e]			X	X	X	X	
Pigmentation and scarring		X[e]	X[e]	X[e]			X	X	X	X	
Standardized photography	X	X[e]					X			X	X

Table 2 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 2)

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; PK = pharmacokinetic; Term = Termination.

a For Day 57 complete responders only.

b These visits are not required for Cohort 2 subjects.

c For subjects who do not have complete response at Day 57, Day 57 is the Final Visit.

d For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

e Assessment performed before study medication application. Day 1 evaluation will serve as baseline for these assessments.

f Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.

g A complete PE will include weight and an assessment of HEENT, integumentary, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height will be measured at Screening only.

h Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. On Days 1 and 3, ECGs will be performed 4 hours postdose.

i Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments.

j For females of childbearing potential; urine pregnancy test on Day 1 before study medication application. All other pregnancy tests are performed with serum.

k PK assessments on Day 1 and Day 3 at 0 hour (just before study medication application) and at 0.5 (±5 min), 1 and 4 hours (±10 min) after study drug application.

l Before LSR assessment, subjects will be queried for spontaneously reported AEs.

m Only AEs in the selected treatment area will be recorded.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Terms
AE	adverse event
AK	actinic keratosis
AUC	area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum (trough) plasma concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetics
PT	preferred term
R	accumulation ratio
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
US	United States
UV	ultraviolet (light)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, any protocol amendments, informed consent form (ICF), and appropriate related documents must be reviewed and approved before subjects are screened for entry by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice [GCP][1]), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [CFR] Part 56). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the Principal Investigator (PI) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)
- ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.
- Title 21 of the United States CFR (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it, and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject provides verbal consent to the subject's participation in the study and has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF and all authorizations required by local law (eg, Protected Health Information in North America) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Kinex Pharmaceuticals, Inc. at approximately 8 to 16 investigational sites in the United States (US).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of any contract research organizations (CROs) will be listed in the Regulatory Binder provided to the site.

7 INTRODUCTION

7.1 Indication

In this study, the activity, safety, and pharmacokinetics (PK) of KX2-391 Ointment 1% will be evaluated in adult subjects with a clinical diagnosis of stable, clinically typical actinic keratosis (AK) on the face or scalp.

7.1.1 Mechanism of Action

KX2-391 (also referred to as KX01) is a synthetic and highly selective inhibitor of Src tyrosine kinase signaling and tubulin polymerization. KX2-391 ointment is being developed as a topical treatment for actinic keratosis. KX2-391 is also being developed as an oral agent for oncology indications. In defining its pharmacological activity in tumor cells, both in vitro and in vivo, KX2-391 has been shown to have potent activity against a wide range of solid tumors as well as leukemia cell lines, including cell lines that are resistant to commonly used cancer drugs. Clinically, the safety, tolerability and pharmacokinetics of KX2-391 have been studied in approximately 120 patients in both solid and liquid tumors using either once or twice daily dosing. The best overall response in these early studies has been 'stable disease' in 25-30% of patients.

KX2-391 promotes the induction of p53, G2/M arrest of proliferating cell populations and subsequent apoptosis via the stimulation of Caspase-3 and PARP cleavage. Data from pre-clinical dermatology studies coupled with an understanding of the mechanism of action of KX2-391 suggests that this compound will have clinical activity in dermatology indications such as actinic keratosis. Potent inhibition of the growth of primary human keratinocytes and several melanoma cell lines in vitro (50% growth inhibition [GI_{50} values] $\leq$50 nM), suggests that KX2-391 has the potential to inhibit the proliferative expansion and promote apoptosis of abnormally proliferating cells in the epidermal and dermal layers upon topical application. KX2-391 has also been observed to inhibit T cell migration and endothelial tubule formation in vitro, suggesting additional potential therapeutic benefits for conditions where pathology is supported by lymphocyte infiltration, inflammation, and/or angiogenesis.

Information regarding KX2-391 nonclinical studies is provided in the Investigator's Brochure.

7.1.2 Clinical Experience with KX2-391

KX2-391 Ointment 1% has been administered to humans in ongoing study KX01-AK-01-US. Based on preliminary PK data from this study in AK lesions on the forearm, the systemic exposure to KX2-391 following topical administration is limited, and is considerably lower than observed in previous clinical studies of oral KX2-391. Patients should be monitored for the occurrence of application site reactions and systemic toxicity.

KX2-391 has been administered orally to approximately 120 patients with malignancy.

The Kinex studies of oral KX2-391 are as follows:

KX2-391 was evaluated in a Phase I clinical trial, Study No. KX01-01-07, entitled "A Combined Rising Single-Dose (RSD) and Rising Multiple-Dose (RMD) Phase I Study to Evaluate Safety, Tolerability, and Pharmacokinetics of KX2-391 in Patients with Advanced Malignancies That Are Refractory to Conventional Therapies".

KX2-391 has been evaluated in Study No. KX01-002-09, entitled "A Phase II, Open-Label, Single-Arm Study Evaluating the Safety, Efficacy and Pharmacokinetics of KX2-391 in

Patients with Bone-Metastatic, Castration-Resistant Prostate Cancer Who Have Not Received Prior Chemotherapy."

KX2-391 was evaluated in Study No, KX01-03-11, "A Phase 1b Rising Multiple-Dose Clinical Study to Evaluate Safety, Tolerability and Activity of Oral Monotherapy with KX2-391 in Elderly Subjects with Acute Myeloid Leukemia (AML) Who Are Refractory to or Have Declined Standard Induction Therapy".

7.2 Study Rationale

Actinic keratoses represent the initial intra-epidermal manifestation of abnormal keratinocyte proliferation having the potential to progress to squamous cell carcinoma (SCC). Squamous cell carcinoma is the second leading cause of skin cancer deaths in the US, with up to 65% of SCC arising from pre-existing actinic keratoses.[2,3] The risk of progression has been determined to be between 0.025% and 16% per year,[2,4] and the calculated lifetime risk of malignant transformation for a patient with AKs followed up for 10 years is between 6.1% and 10.2%.[5] The rationale behind treating every AK is based on the difficulty in predicting which single AK will progress to squamous cell carcinoma.[6,7] Suchniak et al[8] reported 36% of lesions previously diagnosed clinically as AKs being in fact SCC, with 14% being in situ SCC. Ehrig et al[9] showed that 4% of AKs clinically diagnosed by board-certified dermatologists were in fact SCC and 5% were considered occult early stage of cutaneous malignancy. Spontaneous regression has been reported in up to 25.9% of AKs over a 12-month period, although 15% later reappeared.[10,11,12] The goals of treatment are to completely eliminate AKs, minimizing their risk of progression to invasive SCC, reducing the potential to metastasize and cause death, while obtaining the best cosmetically acceptable outcomes. Current approved/marketed treatment has shown up to approximately 60% efficacy, with a recurrence rate of approximately 35%.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is:

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

8.2 Secondary Objectives

The secondary objectives of the study are:

- 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 the PK 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

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- 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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be 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, and Follow-up Periods.

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. Thereafter, 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.

Cohort 2:
Eligible subjects will receive 3 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 3. Subjects will return for Follow-up visits until Day 57. Thereafter, 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.

For both cohorts, subjects may stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected on Days 1 and 5 (Cohort 1) or Days 1 and 3 (Cohort 2).

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.

The same study sites for the most part of Cohort 1 will be used for Cohort 2. The Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

In each cohort, approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set, defined as subjects who complete all planned treatments and most evaluations, including the Day 57 Follow-up visit. Therefore, a total of 160 subjects in 2 cohorts may be enrolled, but the sample size of Cohort 2 may be adjusted, depending on the results of Cohort 1.

9.1.1 Screening Period

The Screening Period may last up to 28 days for each cohort.

Subject eligibility will be established during the Screening Period. Subjects will be screened within 28 days of the first dose of study drug. All screening assessments/evaluations, as presented in Table 1 and Table 2 will be performed after the subject provides informed consent and eligibility criteria are met.

Treatment Area Identification

At Screening (Visit 1), the Investigator will select a continuous treatment area affected with AK on the face or scalp for each subject that:

- measures 25 cm^2
- contains 4 to 8 AK lesions that are clinically typical

The location and approximate shape of the treatment area will be recorded on an acetate transparency sheet.

At Visit 1, the Investigator and an investigational center staff member will identify the treatment area by:

- Examining the face or scalp and locating each AK with a dot of removable marker.
- Using an 8 x 11 acetate transparency sheet with 1x1 cm squares.
- Mapping at least 2 anatomical landmarks on the acetate sheet. Example of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
- Indicating the location of AK lesions with permanent marker dots on the acetate transparency sheet.

- Outlining the treatment area on the transparency sheet with the permanent marker.
- Removing marker dots on the face/scalp with alcohol swabs or water (after taking the screening photo).

9.1.2 Treatment Period

The inclusion/exclusion criteria will be reviewed again prior to treatment on Day 1, to re-confirm subjects' eligibility to participate in the study.

Subjects in Cohort 1 will be treated for 5 consecutive days (Days 1-5 [Visits 2-6]) during the Treatment Period. Visits 2 through 6 should be scheduled to occur at approximately the same time each day.

Subjects in Cohort 2 will be treated for 3 consecutive days (Days 1-3 [Visits 2-4]) during the Treatment Period. Subjects will not return on Day 4 (Visit 5) or Day 5 (Visit 6). Visits 2 through 4 should be scheduled to occur at approximately the same time each day.

At Visit 2 (Day 1), prior to study drug application, the Investigator and any appropriate investigational staff member(s) (Investigator-trained designee) will confirm the location of the treatment area using the Visit 1 acetate sheet. The Investigator should re-mark the treatment area borders as needed so the study evaluations may be effectively completed.

Once the treatment area has been re-identified at Visit 2, photographs will be taken (Section 9.5.1.5.8). 50 mg of KX2-391 Ointment 1% will be applied topically once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total). See Section 9.4.2.4 for a detailed description of study medication application.

Pharmacokinetic blood sampling, activity, safety assessments, and local skin reaction (LSR) assessments (see Section 9.5 for details) will be performed (Table 1 and Table 2). Pigmentation and scarring in the treatment area also will be assessed by the Investigator (or a trained designee).

Standardized photography will be performed at designated visits throughout the study (Table 1 and Table 2).

9.1.3 Follow-up Period

After the Treatment Period for both cohorts, there will be Follow-up Visits at Days 8, 15, 29, and 57 to assess safety, activity, LSRs, pigmentation, and scarring.

For subjects who do not have complete response at Day 57, Day 57 is their Final Visit.

9.1.4 Recurrence Follow-up Period

For both cohorts, only for subjects who show complete response at Day 57, there will be additional visits every 3 months up to 12 months post-Day 57 (ie, at 3, 6, 9, and 12 months

post-Day 57) to assess recurrence of AK lesions. These subjects will continue to undergo scheduled activity and safety assessments (Table 1 and Table 2).

For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is a nonrandomized, open-label study. No control group has been included.

9.3 Selection of Study Population

Eligible subjects will be adults (≥18 years of age) with a clinical diagnosis of stable, clinically typical AK on the face or scalp.

9.3.1 Inclusion Criteria

Inclusion criteria will be reviewed at Screening (Visit 1).

Subjects must meet all of the following criteria to be included in this study:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 30 days or 1 menstrual cycle, whichever is longer, prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device. Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.

8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that the Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities
   - clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable
9. Willing to avoid direct sun or ultraviolet (UV) light exposure to the face or scalp
10. Able to comprehend and are willing to sign an informed consent form

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days
   - immunosuppressants or immunomodulators; 28 days
4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)
   - imiquimod (eg, Aldara; Zyclara)
   - diclofenac with or without hyaluronic acid (eg, Solaraze)
6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy

- electrodesiccation
- laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
- chemical peels (eg, tricholoracetic acid)
- dermabrasion
- surgical removal (eg, curettage, excision)

7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the subject to an unacceptable risk by study participation
10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 30 days or 5 half-lives of the investigational product, whichever is longer, before dosing
13. A known history of human immunodeficiency virus (HIV), chronic hepatitis C, or chronic hepatitis B infection

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

The Investigator will document the reason for discontinuing a subject from treatment or from the study.

The Investigator may discontinue treatment or discontinue a subject from the study for any of the reasons listed below:

- Occurrence of AEs
- Occurrence of pregnancy

- Use of a prohibited concomitant medication or treatment (see Section 9.4.7.3)
- Conditions that, in the opinion of the Investigator, would make the subject's continued participation in the study inadvisable (actual condition must be documented)
- Noncompliance (Investigator must describe)
- Withdrawal of consent (subject asked, but not required to give a reason)
- Other (Investigator must describe)

If the study is terminated by the Sponsor, the Investigator will promptly explain to the subject involved that the study will be discontinued and provide appropriate medical treatment and other necessary measures for the subject.

9.4 Treatments

The investigational product in the study is KX2-391 Ointment 1%.

9.4.1 Treatment Administered

Information regarding study treatment is provided in Table 3.

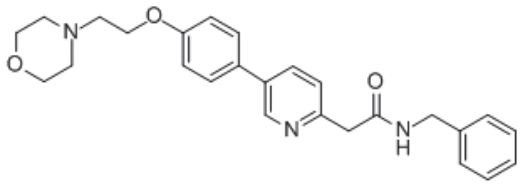
Table 3 Treatment Administered in KX01-AK-002

Investigational Product	Strength	Size of Treatment Area	Quantity study medication/ KX2-391	Number Applications and Frequency	Study Days Administered
KX2-391 Ointment 1%	1%	25 cm^2	50 mg of study drug = 0.5 mg of KX2-391	1 application daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2)	Days 1-5 (Cohort 1) Days 1-3 (Cohort 2)

9.4.2 Identity of Investigational Products

9.4.2.1 Chemical Name and Structural Formula of KX2-391

- Study drug code: KX2-391 Ointment 1%
- Drug Product: KX2-391 free base ointment formulated with glyceryl monostearate and propylene glycol
- Chemical name: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide
- Molecular formula: $C_{26}H_{29}N_3O_3$
- Molecular weight: 431.53 g/mole
- Structural formula:



9.4.2.2 Labeling for Study Drug

Investigational product will be packaged and labeled in a manner consistent with the study and will be designed by:

Kinex Pharmaceuticals, Inc.
1001 Main Street
Suite 600
Buffalo, NY 14203

Labels will be nonremovable in nature.

Labels for the investigational product will be in accordance with US regulations and will include (but will not be limited to) the following information:

- For clinical study use only
- Name and address of the Sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.3 Storage Conditions

Study drug will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.2.4 Administration of Investigational Products

The study medication is for external topical use on the treatment area. An investigational center staff member will perform the study medication applications. The staff member must wash her/his hands before and after each study medication application.

50 mg of KX2-391 Ointment 1% will be applied topically to a 25 cm^2 treatment area. This amount contains a total of 0.5 mg KX2-391 free base. KX2-391 Ointment 1% will be applied once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) (see Table 3).

The staff member will weigh the appropriate amount of study medication into a weighing boat (or equivalent) using a calibrated scale. The amount of study medication applied will be calculated by determining the difference of the weight of the weighing boat with study medication before and after application. The amount of study medication weighed will be as close to the intended dose as possible.

A study staff member will perform and document a scale accuracy check at least every day before weighing study medication.

KX2-391 Ointment 1% will be applied to the subject's treatment area using a fingertip protected with a powder-free finger cot or examination glove. The study medication will be gently and evenly rubbed over the treatment area, including its borders, until no visible accumulation is evident. The time when the study medication application is completed (Application Completion Time) will be recorded.

The study medication should remain on the treatment area. Subjects must avoid touching or wetting the treatment area for at least 12 hours from time of last application and are not allowed to apply any topical products to the treatment area (see Section 9.4.7.3). Instructions will be sent home with the subject clarifying on how to care for the treatment area.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study with 2 sequential cohorts. Each site will enroll subjects for Cohort 1 (5-day regimen) first, and will not assign any subjects to Cohort 2 (3-day regimen) until being notified. The Sponsor will review accumulating data on Cohort 1 to decide if, when, and where to start Cohort 2. In addition, the Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

9.4.4 Selection of Doses in the Study

The dose of 50 mg of KX2-391 Ointment 1% applied to a 25 cm^2 area on the face or scalp for 5 or 3 consecutive days is based on a previous study using the same dose regimen for the treatment of AK on the forearm (study KX01-AK-01-US). Preliminary data show that this regimen had an acceptable LSR and safety profile, with efficacy outcomes considered to warrant further investigation.

9.4.5 Selection and Timing of Dose for Each Subject

Section 9.4.2.4 provides detailed instructions for administering KX2-391 Ointment 1% in this study. Study medication should be applied at about the same time each day.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Prior Therapy

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies including radiotherapy taken 28 days before Day 1 through the final study visit must be recorded in the case report form/electronic case report form (CRF/eCRF). A complete AK treatment history will be recorded on the AK Treatment History CRF/eCRF (see Section 9.5.1.2.1).

9.4.7.2 Concomitant Medication/Therapy

Concomitant medication/therapies are any new or existing therapy received by the subject after signing the ICF until discharge from the study.

Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication CRF/eCRF.

Use of sunblock or any topical products in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication CRF/eCRF.

The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Subjects will refrain from receipt of any therapy in accordance with the inclusion/exclusion criteria.

9.4.7.3 Prohibited Medication/Therapy

Use of any non-study drug treatment for AK lesions on the treatment area is prohibited until Day 57. AK lesions located outside the treatment area may be treated by lesion-directed treatment only, eg, cryotherapy or biopsy, as determined by the Investigator. A list of prohibited medications follows.

Prohibited drug products and treatments that might influence or mask the effects of treatment until Day 57 include: immunomodulators or immunosuppressive therapies, cytotoxic drugs, interferon/interferon inducers, topical or systemic steroids, 5-FU, ingenol mebutate, imiquimod, diclofenac, topical or systemic retinoids, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, acid-containing therapeutic products, benzoyl peroxide, chemodestruction, medicated/therapeutic topical salves or topical steroids, photodynamic therapy, psoralen plus UVA or UVB therapy, artificial tanner, excessive or prolonged exposure to UV light source.[13]

During the Recurrence Follow-up Period, lesion-directed treatment such as cryotherapy or biopsy, and topical treatment is allowed for treatment of AK lesions emerging in any part of the body. Any lesion in the treatment area that is treated during the Recurrence Follow-up Period will be considered as a recurrence.

Subjects are prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments to the treatment area up until the end of Visit 10 (Day 57), except when those medications are prescribed by the Investigator for the management of local skin reactions. All other routinely used topical products can be used on the treatment area from Day 57 onward, at the discretion of the Investigator.

All subjects should be reminded to avoid direct sun or UV exposure to the treatment area throughout the study. From Day 15 onward, if a subject is unable to avoid direct sun or UV exposure to the treatment area, the Investigator may allow the use of sunblock only.

Subjects have unrestricted use of nonmedicated topical products on areas outside of the treatment area during the study. After Day 57, all routinely used topical products can be used.

Any subjects who start systemic therapies for the treatment of AK will be withdrawn from the study.

Any subjects who start topical therapies for AK on the treatment area will be withdrawn from the study.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration.

9.4.8 Prohibitions and Restrictions during Study Period

Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments (see Section 9.5.1.5.3); otherwise there are no food, water, beverage, or physical activity restrictions during the study.

9.4.9 Treatment Compliance

Records of treatment administration for each subject will be kept during the study. The clinical research associates (CRAs) will review treatment administration throughout the course of the study.

9.4.10 Drug Supplies and Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to GCP guidelines, as well as national requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies and dispensing of study drug to the subject must be maintained. This includes, but is not limited to:

- documentation of receipt of clinical supplies
- study drugs dispensing/return reconciliation log, including amount and date of dispensing
- study drugs accountability log
- all shipping service receipts
- documentation of study drug returned to the Sponsor

All forms will be provided by the Sponsor (or its designee). Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. A copy of the drug accountability record must be provided to the Sponsor at the end of the study.

The supplies and inventory records must be made available, on request, for inspection by the Sponsor (or its designee) or a representative of a health authority. If applicable, all unused study drugs and empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor at the conclusion of the study unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. On completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, study drug that is to be returned to the Sponsor, if necessary must be boxed and sealed and shipped back to the Sponsor following all local regulatory requirements.

The CRA(s) will review drug accountability during monitoring site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

All assessments and timing of the assessments should be performed according to the Schedule of Procedures and Assessments (Table 1 and Table 2).

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical/Surgical and Actinic Keratosis History

Medical and surgical history and current medical conditions will be recorded at Screening (Visit 1). All pertinent medical history must be noted in the CRF/eCRF. A complete AK medical history will also be recorded.

Medical history will include:

- Significant medical and surgical history; childhood diseases and common colds are not required unless it is ongoing at Screening
- A complete AK history from the time of initial diagnosis
- A complete AK treatment history including all commercial and investigational products, including medical therapies and surgical modalities, and other prescribed and nonprescription therapies dating back to the initial diagnosis.

9.5.1.2.2 Fitzpatrick Skin-Type Classification

The Fitzpatrick Skin-Type is a skin classification system[14] which measures 2 components (genetic disposition and reaction to sun exposure). Skin-types range from very fair (Type I) to very dark (Type VI).

Subjects' skin will be typed using this classification system at Screening (Visit 1).

9.5.1.2.3 PRIOR MEDICATIONS

Prior medications taken within 28 days before Day 1, including nonprescription remedies, vitamins, etc, will be recorded at Screening (Visit 1).

9.5.1.2.4 HEIGHT

Height will be measured only during the screening physical examination.

9.5.1.3 Activity Assessments

9.5.1.3.1 ACTINIC KERATOSIS LESION COUNT

The Investigator will perform a count of AK lesions (lesion count) for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

The AK lesion count is the Investigator's assessment of the number of AK lesions in the treatment area. A subject must have 4 to 8 AK lesions in the treatment area to be eligible to continue in the study at Visit 1.

For this assessment, an AK lesion is considered to be on the treatment area, and should be counted if it is completely inside the treatment area or is touching any of the borders of the treatment area. These lesions will be treated during the study medication application process.

The Investigator must NOT refer to any other evaluation to assist with the AK lesion count. This is not a comparison with the AK lesion count at any other timepoint.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (3 mL at each timepoint) for PK analysis of KX2-391 will be collected at the following timepoints (Table 4):

Table 4 Blood Sample Collection Times for Pharmacokinetic Analyses

Application Day	**Time (hours)**			
	0 predose	**0.5 postdose**	**1 postdose**	**4 postdose**
Window		±5 minutes	±10 minutes	±10 minutes
Both cohorts: Day 1 (Visit 2)	X[a]	X	X	X
Cohort 1: Day 5 (Visit 6)	X[a]	X	X	X
Cohort 2: Day 3 (Visit 4)	X[a]	X	X	X

a Prior to application of study treatment.

Approximately 24 mL will be collected for measurement of plasma concentrations of KX2-391.

The actual times of PK sampling will be recorded.

A description of collection, handling, and shipping procedures for PK samples will be provided to the sites.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will include recording all AEs and serious adverse events (SAEs).

Safety assessments also include laboratory evaluation of hematology, biochemistry, and urinalyses; periodic measurement of weight, vital signs, ECGs, and performance of PEs, as detailed in the sections below and shown in Table 1 and Table 2.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions. AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events. Treatments administered for LSRs will be recorded on the Concomitant Medications CRF.

9.5.1.5.1 ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is KX2-391 Ointment 1%.

Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing conditions that worsen after dosing

The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- any new disease or exacerbation of an existing disease
- any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- recurrence of an intermittent medical condition (eg, headache) not present at baseline

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the final contact in the Follow-up Period on Day 57. For subjects participating in the Recurrence Follow-up Period, only AEs at the treatment area will be collected.

Subjects with study drug-related AEs will be followed until resolution, resolved with sequelae, or under medical care. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

All AEs observed during the study will be reported on the CRF/eCRF.

Laboratory Adverse Events

A treatment-emergent abnormal laboratory test result should be considered as a treatment-emergent AE (TEAE) if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

An abnormal laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study drug
- results in withholding of study drug pending some investigational outcome
- results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- increases in severity compared with baseline

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF/eCRF.

For significant treatment-emergent laboratory abnormalities meeting criteria as SAEs, the study site must submit an SAE report to the Sponsor or designee using the SAE reporting procedures described in Section 9.5.3.1. However, if a significant treatment-emergent laboratory abnormality is accompanied by, and is part of the syndrome of, a serious clinical event or diagnosis, it is the clinical event/diagnosis that should be reported as the SAE and not the significant treatment-emergent laboratory abnormality.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs. An ECG abnormality in a subject with symptoms may meet the criteria for an AE as described in this protocol. In these instances, the AE corresponding to the symptomatic ECG abnormality will be recorded on the Adverse Events CRF/eCRF.

For symptomatic ECG abnormalities meeting criteria as SAEs, the study site must submit an SAE report, including the ECG report to the Sponsor, or designee, using the SAE reporting procedures (Section 9.5.3.1).

Assessing Severity of Adverse Events

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.

Adverse events will be graded for severity as follows:

Mild	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that is sufficiently discomforting to interfere with everyday activities

Severe An event that prevents normal everyday activities

Investigators will assess severity for all AEs (for both increasing and decreasing severity). The criteria for assessing severity are different from those used for seriousness (see Section 9.5.1.5.2).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- temporal relationship of the onset of the event to the initiation of the study treatment
- the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- whether the event is known to be associated with the study treatment or with other similar treatments
- the presence of risk factors in the study subject known to increase the occurrence of the event
- the presence of nonstudy treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF/eCRF using the following criteria:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent or underlying disease or other drugs or conditions

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, conditions or concurrent or underlying disease provide plausible explanations

9.5.1.5.2 Serious Adverse Events and Other Events of Interest

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

- results in death

- is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest, which include pregnancy and overdose, are to be captured using the SAE procedures described in Section 9.5.3.1, but are to be considered as SAEs only if they met one of the above criteria. All events of these types are to be reported on the Adverse Events CRF/eCRF whether or not they meet the criteria for SAEs.

The following hospitalization is not considered to be an SAE because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

9.5.1.5.3 LABORATORY MEASUREMENTS

Blood will be collected for clinical laboratory tests at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2). Collection of blood and urine (including samples for pregnancy testing, where applicable) will be conducted at the clinic site. Approximately 20 mL of blood will be collected for clinical laboratory testing, including pregnancy testing, when required. Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments. Fasting status must be documented for all laboratory samples.

Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator. When conducted, microscopic urinalysis results will be recorded on the CRF/eCRF.

The clinical laboratory tests to be measured during the study are provided in Table 5.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW)
Chemistry	
Electrolytes	chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), 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)[a]	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
Pregnancy Testing	serum pregnancy test, urine pregnancy test (where applicable)

a Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF/eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5.2), the site must electronically transmit the SAE report including the laboratory report to the Sponsor using the SAE form (see Section 9.5.3.1).

9.5.1.5.4 VITAL SIGNS

Vital sign (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) measurements will be taken after the subject has been seated for at least 5 minutes at Screening (Visit 1), Day 5 (Visit 6) for Cohort 1 or Day 3 (Visit 4) for Cohort 2, Day 8 (Visit 7), Day 15 (Visit 8), Day 29 (Visit 9), and Day 57 (Visit 10) (Table 1 and Table 2). Serial vital signs may be obtained to confirm accurate readings.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete PE will be performed at Screening (Visit 1) and Day 57 (Visit 10) (Table 1 and Table 2).

A complete PE will include weight and an assessment of head, eyes, ears, nose, and throat (HEENT), integumentary, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems.

Height will be measured only during the screening physical examination.

Documentation of the PE will be included in the source documentation at the site. Only changes from screening PE findings that meet the definition of an AE will be recorded on the Adverse Events CRF/eCRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

A 12-lead ECG will be completed at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2), at a convenient time during the visit. ECGs will also be performed in Cohort 2 subjects at 4 hours postdose on Day 1 (Visit 2) and Day 3 (Visit 4). Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. The ECG data recorded on the CRF/eCRF must include rate, rhythm, intervals, and QTc/QTcF.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs.

9.5.1.5.7 PREGNANCY TESTING

Serum pregnancy tests will be obtained in females of childbearing potential at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2).

A urine pregnancy test will be performed on females of childbearing potential before study medication application on Day 1 (Visit 2). Visit 1 and Visit 2 test results must be reviewed before dosing.

9.5.1.5.8 OTHER ASSESSMENTS

Concomitant Medications

Concomitant medications will be assessed at all clinic visits (Table 1 and Table 2). Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication CRF/eCRF. The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Use of sunblock or any topical products in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication CRF/eCRF.

Local Skin Reactions

At every post-Screening clinic visit through Day 57 (Visit 10), the Investigator or trained designee will assess any LSR on the treatment area for signs:

- Before study medication application (on dosing days)
- After the assessment of adverse events

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling,

vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst) (Table 6).

Table 6 Local Skin Reaction Grading Criteria

	Grading Criteria				
Local Skin Response	**0**	**1**	**2**	**3**	**4**
Erythema	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking / Scaling	Not present	Isolated scale, specific to lesion	Scale <50%	Scale >50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation / Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles <50%	Transudate or pustules, with or without vesicles >50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion / Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

Examples of LSR signs are shown in photographs in Appendix 1.[15]

Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events.

All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization.

Treatment for any LSR or interruption/discontinuation of study treatment for an LSR will be recorded on the CRF/eCRF.

LSRs will be reported separately from adverse events.

Pigmentation and Scarring

Hypo- and hyper- pigmentation and scarring on the treatment area will be assessed by the Investigator (or a trained designee) as being present or absent.

Pigmentation and scarring will be assessed at every post-Screening clinic visit through Day 57 (Visit 10) (Table 1 and Table 2). Pigment-related changes or scarring should be followed until resolution or deemed stabilized by the Investigator.

Standardized Photography

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Care must be taken to ensure the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph. Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

The photographs are to document the appearance of the subjects' treatment area and to assist with the identification and confirmation of the location of the treatment area throughout the study (Section 9.1.1).

Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

9.5.2 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in dermatology studies as well as in the routine clinical care of patients with actinic keratosis.

9.5.3 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.3.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event. SAE reporting requirements will be provided in the Investigator File.

All SAEs, regardless of causality assessment, must be collected through the last subject contact and followed to resolution or, if resolution is unlikely, to stabilization. SAEs reported to the site from the time of the last subject contact up to 30 days after the last contact, will be collected (ie, Day 57 plus 30 days). During the Recurrence Follow-up Period, all AEs, including SAEs in the treatment area will be collected until the last subject

contact. These SAEs will be discussed in the clinical study report. Any SAE event judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Deaths and life-threatening events should be reported immediately by telephone. The initial report must be submitted within 1 business day by electronically transmitting the completed SAE form.

The detailed contact information for reporting of SAEs will be provided in the Investigator File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. All supporting documents should be sent de-identified and should contain the assigned subject number. Only supporting documents directly related to the event should be sent.

Any follow-up information received on SAEs should be forwarded as soon as possible. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

9.5.3.2 Reporting of Pregnancy

Any pregnancy, whether occurring in a subject or in the female partner of a male subject, for which the estimated date of conception was either before the last visit or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs (see Section 9.5.3.1).

Pregnancies must be reported by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies is provided in the Investigator File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant during the Treatment Period must be discontinued from treatment but continue to participate in the study per the protocol.

9.5.3.3 Reporting of Other Events of Interest

9.5.3.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied.

Any study drug overdose should be noted on the Study Medication CRF/eCRF.

All AEs associated with overdose, or medication error should be captured on the Adverse Event CRF/eCRF and also reported using the procedures detailed in Section 9.5.3.1 even if the AEs do not meet serious criteria. If the AE associated with an overdose or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner, but should be noted as nonserious on the SAE form and the Adverse Event CRF/eCRF.

9.5.3.4 Expedited Reporting

The Sponsor (or its designee) must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

In determining what SAEs meet criteria for expedited reporting, the current version of the Investigator's Brochure will be used for reference safety information.

9.5.3.5 Breaking the Blind

Not applicable

9.5.3.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.4 Completion/Discontinuation of Subjects

A subject may elect to discontinue from the study at any time for any reason. See Section 9.3.3 for reasons why Investigators may discontinue subjects from the study. Investigators must document the actual reason(s) why they decided to discontinue subjects, or why subjects withdrew consent, as applicable. Study disposition information will be collected on the Disposition CRF/eCRF.

Subjects who withdraw from study treatment (with the exception of death or withdrawal of consent) will be encouraged to complete the Early Termination assessments at the time of withdrawal as indicated in Table 1 and Table 2. A subject who has ceased to return for visits

will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF/eCRF.

9.5.5 Abuse or Diversion of Study Drug

Not applicable

9.5.6 Confirmation of Medical Care by another Physician

The Investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be documented in the subject source documentation, collected on the CRF/eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. A CRF/eCRF or a select CRF/eCRF page may be used as a source document. CRF/eCRFs used as source documents will be listed in the Data Management Plan. As defined by ICH E6 guidelines (Section 1.11), the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject. In this study, the CRF may refer to either a paper (CRF) or electronic data collection form (eCRF), or both.

Data collected on the CRF/eCRF must be completed following the instructions described in the CRF/eCRF Completion Guidelines, which will be based on the Data Management Plan. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF/eCRF. The PI must sign the CRF/eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs/eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

Responsible site personnel will enter the information required by the protocol onto the CRF/eCRFs in accordance with the CRF/eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to review the CRF/eCRFs for completeness and accuracy against the source documents. They will identify any discrepancies and ensure that appropriate site personnel address the discrepancies.

The original CRFs/eCRFs will be maintained at the site in a central document repository. If used, a copy of the CRF will be forwarded to the Sponsor.

At the end of the study an electronic copy of the database along with appropriate system version will be archived.

Uniform procedures will be discussed at the Investigator meetings or at site initiation and/or will be documented in the CRF/eCRF Completion Guidelines.

9.6.2 Clinical Data Management

All data, both CRF/eCRF and external data, will be loaded into a clinical system as specified in the Data Management Plan.

Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

9.7 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked. Statistical analyses will be performed using Phoenix WinNonlin and SAS software or other validated statistical software as required.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.

For all analyses, study Day 1 will be defined as the date of the first dose of study drug.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

The primary endpoint is activity.

Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57.

9.7.1.1.2 SECONDARY ENDPOINTS

Activity

Reduction in lesion counts at each visit during Days 1-57 will be assessed as the secondary endpoint for activity.

Safety

Safety will be evaluated primarily by assessment of AEs and clinical laboratory data. The results of other safety assessments (vital signs, PEs, ECGs) will also be evaluated.

Pharmacokinetic

Secondary endpoints include the following PK parameters derived by noncompartmental analysis using the plasma concentration-time data of KX2-391: C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

9.7.1.1.3 EXPLORATORY ENDPOINTS

Exploratory endpoints include recurrence and sustained response rates.

Recurrence rate will be defined as the proportion of subjects who achieved 100% complete 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 defined as the proportion of subjects who achieved 100% complete clearance at Day 57 (Visit 10) without any identified AK lesions on the treatment area at 12 months post-Day 57.

9.7.1.2 Definitions of Analysis Sets

The Per-Protocol Set is 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 evaluation.

The Evaluable Set is the group of subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of treatment and complete most evaluations including the Day 57 Follow-up Visit.

The Safety Analysis/Full Analysis Set is the group of subjects who receive at least one dose of study treatment.

The PK Analysis Set is the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

9.7.1.3 Subject Disposition

All subjects will be tabulated by cohort as to study discontinuation and the reasons for discontinuation as described in Section 9.3.3.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort. For continuous demographic variables, results will be summarized by cohort as well, and presented as N, mean, SD, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be used in each cohort. No statistical testing will be performed.

9.7.1.5 Prior and Concomitant Therapy

All Investigator terms for medications recorded in the CRF/eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary drug codes.

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

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. Prior and concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of prior and concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All medications will be presented by cohort in subject data listings.

9.7.1.6 Activity Analyses

AK lesion counts will be summarized by cohort at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 will be estimated by cohort in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be estimated by timepoint and cohort in the Evaluable Set.

A 95% CI for the sustained response rate at 12 months post-Day 57 will be estimated by cohort in the Evaluable Set.

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

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

PK analyses will be performed on the PK Analysis Set.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable

9.7.1.8 Safety Analyses

All subjects in the Safety Analysis Set will be included in the safety analyses.

Safety data will be summarized by cohort using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters, weight, vital signs, 12-lead ECG results, and physical examination findings.

Similar to the activity analyses, any contrast between the 2 cohorts will mainly be noninferential in the safety analyses.

9.7.1.8.1 EXTENT OF EXPOSURE

The actual number of doses for each subject will be summarized by cohort.

9.7.1.8.2 ADVERSE EVENTS

For AEs, verbatim terms on the CRFs/eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0 or higher). Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized by cohort. Adverse events will also be summarized by severity, relationship to study drug, and cohort. Subject incidence of SAEs will also be displayed by cohort.

Only those AEs that were treatment-emergent will be included in summary tables. Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing AEs that worsen after dosing

All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC, PT, and cohort. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC, PT, and cohort. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by cohort. Changes from baseline will also be summarized by cohort.

In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up in each cohort.

9.7.1.8.4 VITAL SIGNS

Vital sign values will be evaluated by cohort on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG data will be tabulated by cohort for each individual subject.

9.7.1.8.6 PHYSICAL EXAMINATIONS

Physical examination findings will be listed by cohort for each subject.

9.7.1.8.7 PREGNANCY TESTS

Results of pregnancy tests will be listed by cohort for all subjects, as applicable.

9.7.1.8.8 OTHER ANALYSES

Local Skin Reactions

Local skin reactions as reported by the Investigator will be displayed and summarized by visit and cohort for all subjects.

Pigmentation and Scarring

Pigmentation and scarring as reported by the Investigator will be displayed and summarized by visit and cohort for all subjects.

9.7.2 Determination of Sample Size

For either cohort, a sample size of 60 subjects is sufficient to detect a 100% complete 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% 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.

9.7.3 Interim Analysis

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. The decision to open Cohort 2 will be documented.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the prespecified plans need to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.

2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1(8589):795-7.

3. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115(11):2523-30.

4. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000;42(1 Pt 2):23-4.

5. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42(1 Pt 2):4-7.

6. Guidelines for the Management of Actinic Keratoses. 2004/2005 European Dermatology Forum. Available from: http://www.euroderm.org [Accessed 02 July 2012].

7. Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for actinic keratoses. Committee on Guidelines of Care. J Am Acad Dermatol 1995;32(1):95-8.

8. Suchniak JM, Baer S, Goldberg LH. High rate of malignant transformation in hyperkeratotic actinic keratoses. J Am Acad Dermatol 1997;37(3 Pt 1):392-4.

9. Ehrig T, Cockerell C, Piacquadio D, et al. Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg 2006;32(10):1261-5.

10. Berman B, Bienstock L, Kuritzky L, et al. Primary Care Education Consortium; Texas Academy of Family Physicians. Actinic keratoses: sequelae and treatments. Recommendations from a consensus panel. J Fam Pract 2006;55(5 Suppl):1-8.

11. Quaedvlieg PJ, Tirsi E, Thissen MR, et al. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol 2006;16(4):335-9.

12. Marks R, Foley P, Goodman G, et al. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115(6):649-55.

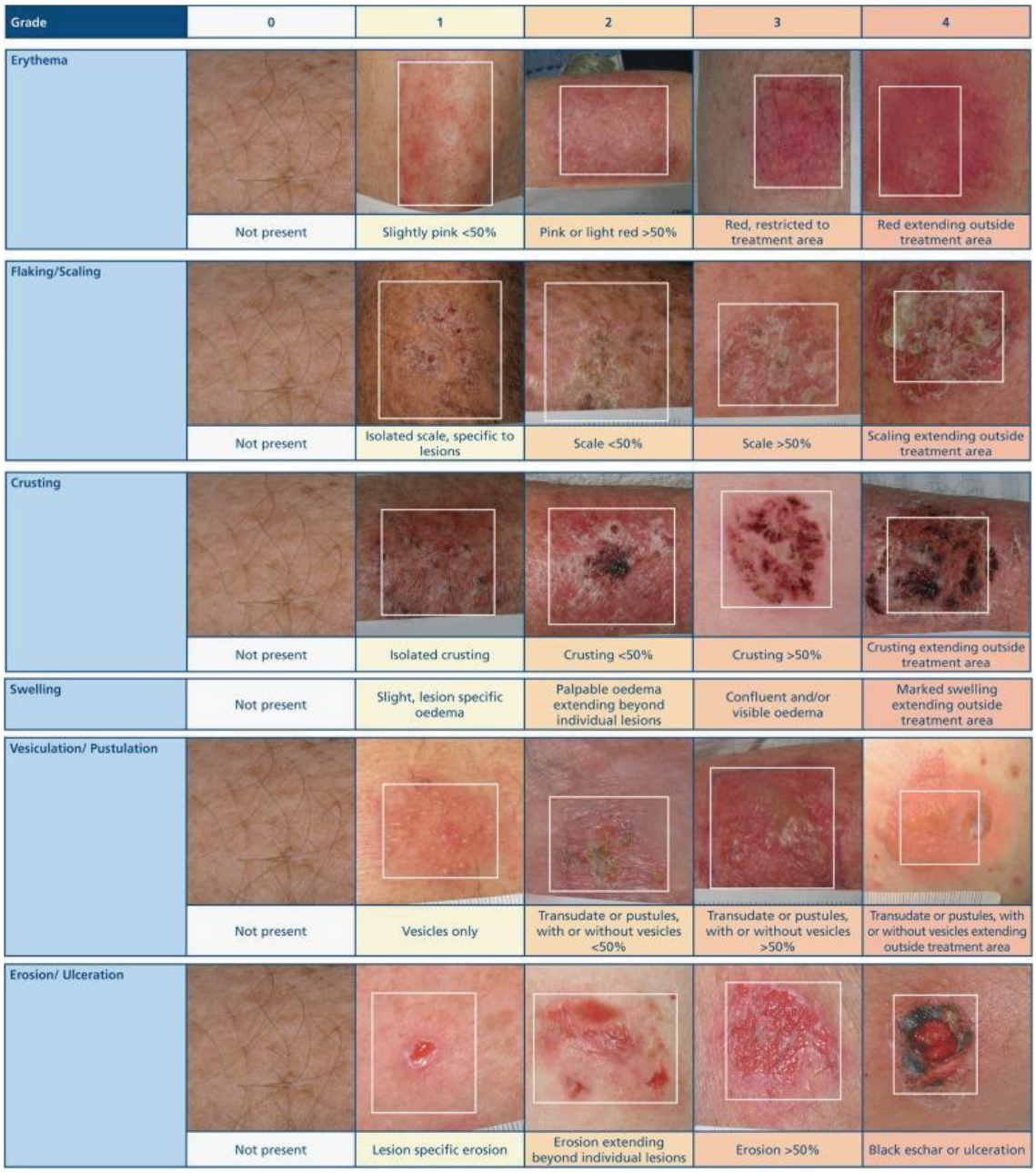
13. Food and Drug Administration Draft Guidance on Ingenol Mebutate; Recommended Jan 2016.

14. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through IV. Arch Dermatol 1998;124(6):869-71.

15. Rosen R, Marmur E, Anderson L, et al. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. Dermatol Ther (Heidelb) 2014;4:207-19.

11 APPENDICES

Appendix 1 Photographs of Local Skin Reactions



Source: Rosen R, Marmur E, Anderson L, et al. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. Dermatol Ther (Heidelb) 2014;4:207-19.

REVISION HISTORY

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Added a second cohort with a 3-day dosing regimen.	If the 5-day treatment regimen (Cohort 1) has sufficient activity and safety, a 3-day regimen (Cohort 2) will be evaluated.	• Throughout protocol • Table 1 • (new) Table 2 • List of In-Text Tables
Added a secondary objective.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Objectives • Section 8.2
Made sustained response an exploratory objective; removed it as a primary endpoint and revised exploratory endpoints and analyses to align with it as an exploratory objective; revised wording to describe analysis of recurrence rates.	Sustained response is more appropriate as exploratory because it is assessed post-Day 57; clarification	• Synopsis - Objectives - Statistical Methods / Study Endpoints - Activity Analyses • Section 8.3 • Section 9.7.1.1.1 • Section 9.7.1.1.3 • Section 9.7.1.6
Revised the number of subjects in the study.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Number of subjects • Section 9.1 • Section 9.1.1
Revised PK sampling timepoints.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Pharmacokinetic Assessments • Table 4
Removed reference to a Safety Management Plan; revised text regarding reporting of SAEs, deaths, and life-threatening events, and corresponding follow-up information.	Clarification.	• Section 9.5.3.1
Revised statistical-related text to reflect increased number of subjects based on the addition of Cohort 2; revised text regarding interim analysis.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis - Analysis Sets - Activity Analyses - Safety Analyses - Interim Analysis - Sample Size Rationale • Sections 9.7.1.2 - 9.7.1.6 • Section 9.7.1.8 (entirety) • Section 9.7.2 • Section 9.7.3
Added immunosuppressants and immunomodulators as exclusionary medications.	These medications may affect the intended effects of the study drug.	• Synopsis / Exclusion Criteria • Section 9.3.2

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Increased the duration of the study period overall and enrollment period.	To accommodate addition of a 3-day regimen (Cohort 2).	• Synopsis / Study Period and Phase of Development • Synopsis / Duration of Participation and Treatment
Increased the number of sites conducting the study. With addition of additional sites, specified that enrollment among sites would be monitored to avoid imbalance.	To accommodate increased number of subjects due to addition of Cohort 2; to facilitate enrollment. Clarification.	• Synopsis / Sites • Section 6 • Synopsis / Study Design • Section 9.1 • Section 9.4.3
Revised description of study treatment.	Clarification.	• Table 3
Specified "during the Treatment Period" with regard to withdrawal of subjects who become pregnant.	Clarification of timeframe.	• Section 9.5.3.2
Revised text regarding collection and following of adverse events. Removed reference to Screening Disposition CRF/eCRF.	Clarification of timeframe; only study drug-related AEs will be followed. There is no Screening Disposition CRF/eCRF in the study.	• Section 9.5.1.5.1
Removed Appendix 1 and renumbered remaining appendix; added appropriate literature citation for reference.	Investigators are familiar with the method for skin typing; questionnaire and scoring system in Appendix 1 is not validated.	• List of Appendices • Section 9.5.1.2.2 • Section 9.5.1.5.8 • Section 10 • (original) Appendix 1 (deleted)
Revised text regarding removal of subjects from the therapy or assessment; modified some of the reasons for discontinuation.	Clarification.	• Section 9.3.3
Modified text regarding restrictions on the use of concomitant medication/therapies/topical products during the study; referred the reader to an FDA draft guidance.	Per recommendation of the Investigators and subject matter experts; to provide further guidance to the investigators.	• Synopsis / Concomitant Drug/Therapy • Section 9.4.7.3
Revised description of the Final Visit; specified when the Final Visit is for those who do not have complete response at Day 57.	Clarification.	• Table 1 / Footnote c • Section 9.1.3 • Section 9.1.4

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Specified that use of sunblock in the treatment area will be recorded in the Concomitant Medication CRF. Removed text regarding subjects not changing their use of concomitant medications.	To be able to evaluate the activity of study drug in the presence and absence of sunblock. Subjects will be able to change concomitant medications per the Investigator's instructions.	• Section 9.4.7.2 • Section 9.5.1.5.8
Removed use of body charts for identifying the location and shape of the treatment area.	Not needed; this will be done with the acetate sheets.	• Section 9.1.1 • Section 9.1.2
Specified minimum timeframe during which subjects cannot touch or wet the treatment area after study treatment application; removed information regarding shower times; revised text about instructions to the subjects for care of the treatment area.	Clarification.	• Section 9.4.2.4
Revised description of sun exposure.	Clarification.	• Synopsis / Inclusion Criteria • List of Abbreviations and Definition of Terms • Section 9.3.1
Revised description of Medical History.	Clarification.	• Section 9.5.1.2.1
Revised description of the Final Visit; specified when the Final Visit is for those who do not have complete response at Day 57.	Clarification.	• Table 1 / Footnote c • Section 9.1.3 • Section 9.1.4
Removed exclusionary use of moisturizers or emollients on the face or scalp within 12 hours prior to Visit 1.	Not necessary to exclude before Visit 1.	• Synopsis / Exclusion Criteria • Section 9.3.2
Revised Medical Monitor signatory.	Administrative.	• Protocol Signature page
Specified that scarring, in addition to pigmentation, will be assessed at the visits cited.	Clarification.	• Section 9.5.1.5.8 / Pigmentation and Scarring
Revised description of procedures related to treatment area identification.	Clarification to align with streamlined procedures.	• Section 9.1.1
Revised text to ensure the signing of ICF prior to study procedures.	Clarification.	• Section 5.3

Revisions to KX01-AK-002 protocol v1.0_23 Jan 2016 (original protocol)
Current Version and Date: v2.0_26 Apr 2016 (Amendment 1)

Change	Rationale	Affected Protocol Sections
Revised the definition of the Evaluable Set.	Clarification.	• Synopsis / Number of Subjects
Revised definition of ICH.	Clarification to align with recent ICH organizational changes.	• Investigator Signature Page • Title Page • List of Abbreviations and Definition of Terms • Section 5.1
Corrected typographical/punctuation/grammar errors.	Administrative.	• Throughout protocol

PROTOCOL SIGNATURE PAGE

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

Investigational Product Name: KX2-391 Ointment 1%

UTN Number: U1111-1173-5677

SIGNATURES

Authors:

PPD
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MD
Medical Monitor
Kinex Pharmaceuticals, Inc.
PPD
Date

PPD
PPD
PhD
Clinical Pharmacologist
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Date

INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	KX2-391 Ointment 1%
UTN Number:	U1111-1173-5677

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name, degree(s)>		
Investigator	Signature	Date

<Name of study site>

Study Site

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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
Sponsor:	United States: Kinex Pharmaceuticals, Inc. 20 Commerce Drive Cranford, New Jersey 07016, US Tel: +1 908-272-0628
Investigational Product Name:	KX2-391 Ointment 1%
Indication:	Actinic keratosis on the face or scalp
Phase:	2a
Approval Date:	v1.0 23 Jan 2016 (original protocol) v2.0 26 Apr 2016 (Amendment 1)
UTN Number:	U1111-1173-5677
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Kinex Pharmaceuticals, Inc. (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. KX2-391
Name of Active Ingredient: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide
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
Investigators PPD, MD, Lead Principal Investigator
Sites Approximately 8 to 16 sites in the United States
Study Period and Phase of Development First subject in to last subject out, approximately 24 months Phase 2a
Objectives **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 **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 the pharmacokinetics (PK) 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 **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
Study Design This study will be 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, and 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. Thereafter, 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.

The same study sites for the most part of Cohort 1 will be used for Cohort 2. The Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

Number of Subjects

In each cohort, approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set, defined as subjects who complete all planned treatments and most evaluations, including the Day 57 Follow-up visit. Therefore, a total of 160 subjects in 2 cohorts may be enrolled, but the sample size of Cohort 2 may be adjusted, depending on the results of Cohort 1.

Inclusion Criteria

Eligible subjects must have/be:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 18 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 90 days prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device. Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.
8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that the Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities

- clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable

9. Willing to avoid direct sun or ultraviolet (UV) light exposure to the face or scalp
10. Able to comprehend and are willing to sign an informed consent form (ICF)

Exclusion Criteria

Eligible subjects must not have/be:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days
   - immunosuppressants or immunomodulators; 28 days
4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)
   - imiquimod (eg, Aldara; Zyclara)
   - diclofenac with or without hyaluronic acid (eg, Solaraze)
6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy
   - electrodesiccation
   - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
   - chemical peels (eg, tricholoracetic acid)
   - dermabrasion
   - surgical removal (eg, curettage, excision)
7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which

exposes the subject to an unacceptable risk by study participation

10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 14 days or 5 half-lives of the investigational product, whichever is longer, before Screening

Study Treatment

50 mg of KX2-391 Ointment 1% will be applied topically once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total).

Duration of Participation and Treatment

- Planned enrollment period for each cohort: approximately 3 months (90 days)
- Planned subject participation is approximately 64 weeks:
  - Screening Period: up to 28 days
  - Treatment Period: For Cohort 1, 5 consecutive treatment days (Days 1-5); for Cohort 2, 3 consecutive treatment days (Days 1-3)
  - Follow-up Period: Visits at Days 8, 15, 29, and 57
  - Recurrence Follow-up Period: only for complete responders at Day 57, visits every 3 months for 12 months after Day 57 (ie, at 3, 6, 9, and 12 months post-Day 57).

Length of stay: On Day 1 (Visit 2, Cohorts 1 and 2) and Day 5 (Visit 6, Cohort 1) or Day 3 (Visit 4, Cohort 2), subjects may stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected.

Concomitant Drug/Therapy

Use of any non-study drug treatment for AK lesions on the treatment area is prohibited until Day 57. Any lesion in the treatment area that is treated during the Recurrence Follow-up Period will be considered as a recurrence.

Assessments

Activity Assessments

The Investigator will perform a count of AK lesions for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

Safety Assessments

Safety will be assessed by recording all adverse events (AEs), serious adverse events (SAEs), laboratory evaluation of hematology, biochemistry, and urinalysis values, measurement of weight and vital signs, evaluation of ECGs, and the performance of physical examinations.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions (LSRs). AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events.

Other Assessments

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst). In addition to LSRs, hypo- and hyper- pigmentation and scarring on the treatment area will

be assessed as being present or absent. Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events. All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization. LSRs will be reported separately from AEs.

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Pharmacokinetic Assessments

PK samples will be collected at the following timepoints for Cohort 1:

- Day 1: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose
- Day 5: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose

PK samples will be collected at the following timepoints for Cohort 2:

- Day 1: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose
- Day 3: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Statistical Methods

Study Endpoints

Primary Endpoint

- Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57.

Secondary Endpoints

- Activity: Reduction in lesion counts during Days 1-57
- Safety: Evaluation of AEs and clinical laboratory data; the results of other safety assessments (vital signs, physical examinations, ECGs) will also be evaluated.
- Pharmacokinetic: Determination of C_{max} and where applicable, AUC_t, C_{min}, and accumulation ratio R

Exploratory Endpoints

- Recurrence rate will be defined as the proportion of subjects who achieved 100% complete 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 defined as the proportion of subjects who achieved 100% complete clearance at Day 57 (Visit 10) without any identified AK lesions on the treatment area at 12 months post-Day 57.

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 evaluation.
- Evaluable Set: the group of subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of treatment and complete most evaluations including the Day 57 Follow-up Visit.
- Safety Analysis/Full Analysis Set: the group of subjects who receive at least one dose of study treatment.
- PK Analysis Set: the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

Activity Analyses

AK lesion counts will be summarized by cohort at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 will be estimated by cohort in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be estimated by timepoint and cohort in the Evaluable Set.

A 95% CI for the sustained response rate at 12 months post-Day 57 will be estimated by cohort in the Evaluable Set.

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

Safety Analyses

All subjects who receive at least one dose of KX2-391 Ointment 1% will be included in the safety analyses. Treatment-emergent AEs (TEAEs) are defined as either those AEs with an onset after dosing or those pre-existing AEs that worsen after dosing. For AEs, verbatim terms on the case report form/electronic case report form (CRF/eCRF) will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; v 16.0 or higher). Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized by cohort. Adverse events will also be summarized by severity, relationship to study drug, and cohort. Subject incidence of SAEs will also be displayed by cohort. Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by cohort. Changes from baseline will also be summarized by cohort. In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up in each cohort.

Local skin reactions, pigmentation, and scarring as reported by the Investigator, will be displayed and summarized by visit and cohort for all subjects.

Similar to the activity analyses, any contrast between the 2 cohorts will mainly be noninferential in the safety analyses.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

Plasma concentrations for KX2-391 will be analyzed to determine applicable PK parameters.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses Not applicable
Interim Analysis 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. The decision to open Cohort 2 will be documented.
Statistical Methods Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.
Sample Size Rationale For either cohort, a sample size of 60 subjects is sufficient to detect a 100% complete 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% 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.
FINAL v2.0_26 Apr 2016

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 1)

Period	Screening	Treatment					Follow-up				Recurrence Follow-up [a]
Visit	1	2	3	4	5	6	7	8	9	10 [b]/ Early Term	11, 12, 13, 14 [a]
Day	-28 to -1	1	2	3	4	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Visit time window (days)	None	None	None	None	None	None	±2	±2	±2	±2	±14
Informed consent	X										
Inclusion & exclusion criteria	X	X[d]									
Demographics	X										
Medical/surgical history	X										
AK history/AK treatment history	X										
Fitzpatrick skin-type scale	X										
Vital signs[e]	X					X	X	X	X	X	
Prior and concomitant medications/therapies	X	X[d]	X	X	X	X	X	X	X	X	X
Physical examination, including weight[f]	X									X	
Treatment area identification	X	X[d]									
AK lesion count	X	X[d]					X	X	X	X	X
ECG[g]	X						X			X	
Clinical chemistry, hematology, and urinalysis[h]	X						X			X	
Pregnancy test	X	X[d,i]					X			X	
PK blood samples		X[j]				X[j]					
Study medication application		X	X	X	X	X					
AEs[k]	X	X	X	X	X	X	X	X	X	X	X[l]
LSRs		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Pigmentation and scarring		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Standardized photography	X	X[d]					X			X	X

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 1)

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; PK = pharmacokinetic; Term = Termination.

a For Day 57 complete responders only.

b For subjects who do not have complete response at Day 57, Day 57 is the Final Visit.

c For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

d Assessment performed before study medication application. Day 1 evaluation will serve as baseline for these assessments.

e Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.

f A complete PE will include weight and an assessment of HEENT, integumentary, gastrointestinal, cardiovascular, respiratory, muscular-skeleton, and neurological systems.

g Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

h Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments.

i For females of childbearing potential; urine pregnancy test on Day 1 before study medication application. All other pregnancy tests are performed with serum.

j PK assessments on Day 1 and Day 5 at 0 hour (just before study medication application) and at 0.5 (±5 min), 1 and 4 hours (±10 min) after study drug application.

k Before LSR assessment, subjects will be queried for spontaneously reported AEs.

l Only AEs in the selected treatment area will be recorded.

Table 2 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 2)

Period	Screening	Treatment					Follow-up				Recurrence Follow-up [a]
Visit	1	2	3	4	5 [b]	6 [b]	7	8	9	10[c]/ Early Term	11, 12, 13, 14 [a]
Day	-28 to -1	1	2	3	4	5	8	15	29	57[c]	3, 6, 9, 12 Months Post-Day 57[d]
Visit time window (days)	None	None	None	None			±2	±2	±2	±2	±14
Informed consent	X										
Inclusion & exclusion criteria	X	X[e]									
Demographics	X										
Medical/surgical history	X										
AK history/AK treatment history	X										
Fitzpatrick skin-type scale	X										
Vital signs[f]	X			X			X	X	X	X	
Prior and concomitant medications/therapies	X	X[e]	X	X			X	X	X	X	X
Physical examination, including weight[g]	X									X	
Treatment area identification	X	X[e]									
AK lesion count	X	X[e]					X	X	X	X	X
ECG[h]	X						X			X	
Clinical chemistry, hematology, and urinalysis[i]	X						X			X	
Pregnancy test	X	X[e,j]					X			X	
PK blood samples		X[k]		X[k]							
Study medication application		X	X	X							
AEs[l]	X	X	X	X			X	X	X	X	X[m]
LSRs		X[e]	X[e]	X[e]			X	X	X	X	
Pigmentation and scarring		X[e]	X[e]	X[e]			X	X	X	X	
Standardized photography	X	X[e]					X			X	X

Table 2 Schedule of Procedures/Assessments in Study KX01-AK-002 (Cohort 2)

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; PK = pharmacokinetic; Term = Termination.

a For Day 57 complete responders only.

b These visits are not required for Cohort 2 subjects.

c For subjects who do not have complete response at Day 57, Day 57 is the Final Visit.

d For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

e Assessment performed before study medication application. Day 1 evaluation will serve as baseline for these assessments.

f Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.

g A complete PE will include weight and an assessment of HEENT, integumentary, gastrointestinal, cardiovascular, respiratory, muscular-skeleton, and neurological systems.

h Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

i Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments.

j For females of childbearing potential; urine pregnancy test on Day 1 before study medication application. All other pregnancy tests are performed with serum.

k PK assessments on Day 1 and Day 3 at 0 hour (just before study medication application) and at 0.5 (±5 min), 1 and 4 hours (±10 min) after study drug application.

l Before LSR assessment, subjects will be queried for spontaneously reported AEs.

m Only AEs in the selected treatment area will be recorded.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Terms
AE	adverse event
AK	actinic keratosis
AUC	area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum (trough) plasma concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetics
PT	preferred term
R	accumulation ratio
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
US	United States
UV	ultraviolet (light)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, any protocol amendments, informed consent form (ICF), and appropriate related documents must be reviewed and approved before subjects are screened for entry by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice [GCP][1]), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [CFR] Part 56). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the Principal Investigator (PI) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)
- ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.
- Title 21 of the United States CFR (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it, and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject provides verbal consent to the subject's participation in the study and has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF and all authorizations required by local law (eg, Protected Health Information in North America) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Kinex Pharmaceuticals, Inc. at approximately 8 to 16 investigational sites in the United States (US).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of any contract research organizations (CROs) will be listed in the Regulatory Binder provided to the site.

7 INTRODUCTION

7.1 Indication

In this study, the activity, safety, and pharmacokinetics (PK) of KX2-391 Ointment 1% will be evaluated in adult subjects with a clinical diagnosis of stable, clinically typical actinic keratosis (AK) on the face or scalp.

7.1.1 Mechanism of Action

KX2-391 (also referred to as KX01) is a synthetic and highly selective inhibitor of Src tyrosine kinase signaling and tubulin polymerization. KX2-391 ointment is being developed as a topical treatment for actinic keratosis. KX2-391 is also being developed as an oral agent for oncology indications. In defining its pharmacological activity in tumor cells, both in vitro and in vivo, KX2-391 has been shown to have potent activity against a wide range of solid tumors as well as leukemia cell lines, including cell lines that are resistant to commonly used cancer drugs. Clinically, the safety, tolerability and pharmacokinetics of KX2-391 have been studied in approximately 120 patients in both solid and liquid tumors using either once or twice daily dosing. The best overall response in these early studies has been 'stable disease' in 25-30% of patients.

KX2-391 promotes the induction of p53, G2/M arrest of proliferating cell populations and subsequent apoptosis via the stimulation of Caspase-3 and PARP cleavage. Data from pre-clinical dermatology studies coupled with an understanding of the mechanism of action of KX2-391 suggests that this compound will have clinical activity in dermatology indications such as actinic keratosis. Potent inhibition of the growth of primary human keratinocytes and several melanoma cell lines in vitro (50% growth inhibition [GI_{50} values] $\leq$50 nM), suggests that KX2-391 has the potential to inhibit the proliferative expansion and promote apoptosis of abnormally proliferating cells in the epidermal and dermal layers upon topical application. KX2-391 has also been observed to inhibit T cell migration and endothelial tubule formation in vitro, suggesting additional potential therapeutic benefits for conditions where pathology is supported by lymphocyte infiltration, inflammation, and/or angiogenesis.

Information regarding KX2-391 nonclinical studies is provided in the Investigator's Brochure.

7.1.2 Clinical Experience with KX2-391

KX2-391 Ointment 1% has been administered to humans in ongoing study KX01-AK-01-US. Based on preliminary PK data from this study in AK lesions on the forearm, the systemic exposure to KX2-391 following topical administration is limited, and is considerably lower than observed in previous clinical studies of oral KX2-391. Patients should be monitored for the occurrence of application site reactions and systemic toxicity.

KX2-391 has been administered orally to approximately 120 patients with malignancy.

The Kinex studies of oral KX2-391 are as follows:

KX2-391 was evaluated in a Phase I clinical trial, Study No. KX01-01-07, entitled "A Combined Rising Single-Dose (RSD) and Rising Multiple-Dose (RMD) Phase I Study to Evaluate Safety, Tolerability, and Pharmacokinetics of KX2-391 in Patients with Advanced Malignancies That Are Refractory to Conventional Therapies".

KX2-391 has been evaluated in Study No. KX01-002-09, entitled "A Phase II, Open-Label, Single-Arm Study Evaluating the Safety, Efficacy and Pharmacokinetics of KX2-391 in

Patients with Bone-Metastatic, Castration-Resistant Prostate Cancer Who Have Not Received Prior Chemotherapy."

KX2-391 was evaluated in Study No, KX01-03-11, "A Phase 1b Rising Multiple-Dose Clinical Study to Evaluate Safety, Tolerability and Activity of Oral Monotherapy with KX2-391 in Elderly Subjects with Acute Myeloid Leukemia (AML) Who Are Refractory to or Have Declined Standard Induction Therapy".

7.2 Study Rationale

Actinic keratoses represent the initial intra-epidermal manifestation of abnormal keratinocyte proliferation having the potential to progress to squamous cell carcinoma (SCC). Squamous cell carcinoma is the second leading cause of skin cancer deaths in the US, with up to 65% of SCC arising from pre-existing actinic keratoses.[2,3] The risk of progression has been determined to be between 0.025% and 16% per year,[2,4] and the calculated lifetime risk of malignant transformation for a patient with AKs followed up for 10 years is between 6.1% and 10.2%.[5] The rationale behind treating every AK is based on the difficulty in predicting which single AK will progress to squamous cell carcinoma.[6,7] Suchniak et al[8] reported 36% of lesions previously diagnosed clinically as AKs being in fact SCC, with 14% being in situ SCC. Ehrig et al[9] showed that 4% of AKs clinically diagnosed by board-certified dermatologists were in fact SCC and 5% were considered occult early stage of cutaneous malignancy. Spontaneous regression has been reported in up to 25.9% of AKs over a 12-month period, although 15% later reappeared.[10,11,12] The goals of treatment are to completely eliminate AKs, minimizing their risk of progression to invasive SCC, reducing the potential to metastasize and cause death, while obtaining the best cosmetically acceptable outcomes. Current approved/marketed treatment has shown up to approximately 60% efficacy, with a recurrence rate of approximately 35%.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is:

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

8.2 Secondary Objectives

The secondary objectives of the study are:

- 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 the PK 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

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- 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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be 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, and Follow-up Periods.

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. Thereafter, 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.

Cohort 2:
Eligible subjects will receive 3 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 3. Subjects will return for Follow-up visits until Day 57. Thereafter, 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.

For both cohorts, subjects may stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected on Days 1 and 5 (Cohort 1) or Days 1 and 3 (Cohort 2).

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.

The same study sites for the most part of Cohort 1 will be used for Cohort 2. The Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

In each cohort, approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set, defined as subjects who complete all planned treatments and most evaluations, including the Day 57 Follow-up visit. Therefore, a total of 160 subjects in 2 cohorts may be enrolled, but the sample size of Cohort 2 may be adjusted, depending on the results of Cohort 1.

9.1.1 Screening Period

The Screening Period may last up to 28 days for each cohort.

Subject eligibility will be established during the Screening Period. Subjects will be screened within 28 days of the first dose of study drug. All screening assessments/evaluations, as presented in Table 1 and Table 2 will be performed after the subject provides informed consent and eligibility criteria are met.

Treatment Area Identification

At Screening (Visit 1), the Investigator will select a continuous treatment area affected with AK on the face or scalp for each subject that:

- measures 25 cm^2
- contains 4 to 8 AK lesions that are clinically typical

The location and approximate shape of the treatment area will be recorded on an acetate transparency sheet.

At Visit 1, the Investigator and an investigational center staff member will identify the treatment area by:

- Examining the face or scalp and locating each AK with a dot of removable marker.
- Using an 8 x 11 acetate transparency sheet with 1x1 cm squares.
- Mapping at least 2 anatomical landmarks on the acetate sheet. Example of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
- Indicating the location of AK lesions with permanent marker dots on the acetate transparency sheet.

- Outlining the treatment area on the transparency sheet with the permanent marker.
- Removing marker dots on the face/scalp with alcohol swabs or water (after taking the screening photo).

9.1.2 Treatment Period

The inclusion/exclusion criteria will be reviewed again prior to treatment on Day 1, to re-confirm subjects' eligibility to participate in the study.

Subjects in Cohort 1 will be treated for 5 consecutive days (Days 1-5 [Visits 2-6]) during the Treatment Period. Visits 2 through 6 should be scheduled to occur at approximately the same time each day.

Subjects in Cohort 2 will be treated for 3 consecutive days (Days 1-3 [Visits 2-4]) during the Treatment Period. Subjects will not return on Day 4 (Visit 5) or Day 5 (Visit 6). Visits 2 through 4 should be scheduled to occur at approximately the same time each day.

At Visit 2 (Day 1), prior to study drug application, the Investigator and any appropriate investigational staff member(s) (Investigator-trained designee) will confirm the location of the treatment area using the Visit 1 acetate sheet. The Investigator should re-mark the treatment area borders as needed so the study evaluations may be effectively completed.

Once the treatment area has been re-identified at Visit 2, photographs will be taken (Section 9.5.1.5.8). 50 mg of KX2-391 Ointment 1% will be applied topically once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total). See Section 9.4.2.4 for a detailed description of study medication application.

Pharmacokinetic blood sampling, activity, safety assessments, and local skin reaction (LSR) assessments (see Section 9.5 for details) will be performed (Table 1 and Table 2). Pigmentation and scarring in the treatment area also will be assessed by the Investigator (or a trained designee).

Standardized photography will be performed at designated visits throughout the study (Table 1 and Table 2).

9.1.3 Follow-up Period

After the Treatment Period for both cohorts, there will be Follow-up Visits at Days 8, 15, 29, and 57 to assess safety, activity, LSRs, pigmentation, and scarring.

For subjects who do not have complete response at Day 57, Day 57 is their Final Visit.

9.1.4 Recurrence Follow-up Period

For both cohorts, only for subjects who show complete response at Day 57, there will be additional visits every 3 months up to 12 months post-Day 57 (ie, at 3, 6, 9, and 12 months post-Day 57) to assess recurrence of AK lesions. These subjects will continue to undergo scheduled activity and safety assessments (Table 1 and Table 2).

For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Those subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is a nonrandomized, open-label study. No control group has been included.

9.3 Selection of Study Population

Eligible subjects will be adults (≥18 years of age) with a clinical diagnosis of stable, clinically typical AK on the face or scalp.

9.3.1 Inclusion Criteria

Inclusion criteria will be reviewed at Screening (Visit 1).

Subjects must meet all of the following criteria to be included in this study:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 18 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 90 days prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device. Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.

7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.
8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that the Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities
   - clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable
9. Willing to avoid direct sun or ultraviolet (UV) light exposure to the face or scalp
10. Able to comprehend and are willing to sign an informed consent form

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days
   - immunosuppressants or immunomodulators; 28 days
4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)
   - imiquimod (eg, Aldara; Zyclara)
   - diclofenac with or without hyaluronic acid (eg, Solaraze)

6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy
   - electrodesiccation
   - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
   - chemical peels (eg, tricholoracetic acid)
   - dermabrasion
   - surgical removal (eg, curettage, excision)
7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the subject to an unacceptable risk by study participation
10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 14 days or 5 half-lives of the investigational product, whichever is longer, before Screening

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

The Investigator will document the reason for discontinuing a subject from treatment or from the study.

The Investigator may discontinue treatment or discontinue a subject from the study for any of the reasons listed below:

- Occurrence of AEs
- Occurrence of pregnancy
- Use of a prohibited concomitant medication or treatment (see Section 9.4.7.3)
- Conditions that, in the opinion of the Investigator, would make the subject's continued participation in the study inadvisable (actual condition must be documented)
- Noncompliance (Investigator must describe)
- Withdrawal of consent (subject asked, but not required to give a reason)
- Other (Investigator must describe)

If the study is terminated by the Sponsor, the Investigator will promptly explain to the subject involved that the study will be discontinued and provide appropriate medical treatment and other necessary measures for the subject.

9.4 Treatments

The investigational product in the study is KX2-391 Ointment 1%.

9.4.1 Treatment Administered

Information regarding study treatment is provided in Table 3.

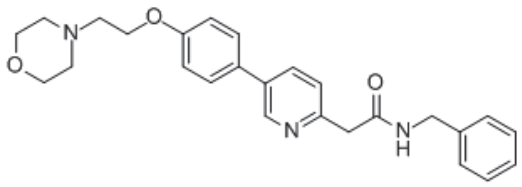
Table 3 Treatment Administered in KX01-AK-002

Investigational Product	Strength	Size of Treatment Area	Quantity study medication/ KX2-391	Number Applications and Frequency	Study Days Administered
KX2-391 Ointment 1%	1%	25 cm^2	50 mg of study drug = 0.5 mg of KX2-391	1 application daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2)	Days 1-5 (Cohort 1) Days 1-3 (Cohort 2)

9.4.2 Identity of Investigational Products

9.4.2.1 Chemical Name and Structural Formula of KX2-391

- Study drug code: KX2-391 Ointment 1%
- Drug Product: KX2-391 free base ointment formulated with glyceryl monostearate and propylene glycol
- Chemical name: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide
- Molecular formula: $C_{26}H_{29}N_3O_3$
- Molecular weight: 431.53 g/mole
- Structural formula:



9.4.2.2 Labeling for Study Drug

Investigational product will be packaged and labeled in a manner consistent with the study and will be designed by:

Kinex Pharmaceuticals, Inc.
1001 Main Street
Suite 600
Buffalo, NY 14203

Labels will be nonremovable in nature.

Labels for the investigational product will be in accordance with US regulations and will include (but will not be limited to) the following information:

- For clinical study use only
- Name and address of the Sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.3 Storage Conditions

Study drug will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.2.4 Administration of Investigational Products

The study medication is for external topical use on the treatment area. An investigational center staff member will perform the study medication applications. The staff member must wash her/his hands before and after each study medication application.

50 mg of KX2-391 Ointment 1% will be applied topically to a 25 cm^2 treatment area. This amount contains a total of 0.5 mg KX2-391 free base. KX2-391 Ointment 1% will be applied once daily for 5 consecutive days (Cohort 1) or 3 consecutive days (Cohort 2) (see Table 3).

The staff member will weigh the appropriate amount of study medication into a weighing boat (or equivalent) using a calibrated scale. The amount of study medication applied will be calculated by determining the difference of the weight of the weighing boat with study medication before and after application. The amount of study medication weighed will be as close to the intended dose as possible.

A study staff member will perform and document a scale accuracy check at least every day before weighing study medication.

The study medication will be applied to the subject's treatment area using a fingertip protected with a powder-free finger cot or examination glove. The study medication will be gently and evenly rubbed over the treatment area until no visible accumulation is evident. The time when the study medication application is completed (Application Completion Time) will be recorded.

The study medication should remain on the treatment area. Subjects must avoid touching or wetting the treatment area for at least 12 hours from time of last application and are not allowed to apply any topical products to the treatment area (see Section 9.4.7.3). Instructions will be sent home with the subject clarifying on how to care for the treatment area.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study with 2 sequential cohorts. Each site will enroll subjects for Cohort 1 (5-day regimen) first, and will not assign any subjects to Cohort 2 (3-day regimen) until being notified. The Sponsor will review accumulating data on Cohort 1 to decide if,

when, and where to start Cohort 2. In addition, the Sponsor study team will monitor the enrollment status closely and ensure that any individual site does not enroll too many subjects.

9.4.4 Selection of Doses in the Study

The dose of 50 mg of KX2-391 applied to a 25 cm^2 area on the face or scalp for 5 or 3 consecutive days is based on a previous study using the same dose regimen for the treatment of AK on the forearm (study KX01-AK-01-US). Preliminary data show that this regimen had an acceptable LSR and safety profile, with efficacy outcomes considered to warrant further investigation.

9.4.5 Selection and Timing of Dose for Each Subject

Section 9.4.2.4 provides detailed instructions for administering KX2-391 Ointment 1% in this study. Study medication should be applied at about the same time each day.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Prior Therapy

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies including radiotherapy taken 28 days before Day 1 through the final study visit must be recorded in the case report form/electronic case report form (CRF/eCRF). A complete AK treatment history will be recorded on the AK Treatment History CRF/eCRF (see Section 9.5.1.2.1).

9.4.7.2 Concomitant Medication/Therapy

Concomitant medication/therapies are any new or existing therapy received by the subject after signing the ICF until discharge from the study.

Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication CRF/eCRF.

Use of sunblock or any topical products in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication CRF/eCRF.

The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Subjects will refrain from receipt of any therapy in accordance with the inclusion/exclusion criteria

9.4.7.3 Prohibited Medication/Therapy

Use of any non-study drug treatment for AK lesions on the treatment area is prohibited until Day 57. AK lesions located outside the treatment area may be treated by lesion-directed treatment only, eg, cryotherapy or biopsy, as determined by the Investigator. A list of prohibited medications follows.

Prohibited drug products and treatments that might influence or mask the effects of treatment until Day 57 include: immunomodulators or immunosuppressive therapies, cytotoxic drugs, interferon/interferon inducers, topical or systemic steroids, 5-FU, ingenol mebutate, imiquimod, diclofenac, topical or systemic retinoids, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, acid-containing therapeutic products, benzoyl peroxide, chemodestruction, medicated/therapeutic topical salves or topical steroids, photodynamic therapy, psoralen plus UVA or UVB therapy, artificial tanner, excessive or prolonged exposure to UV light source.[13]

During the Recurrence Follow-up Period, lesion-directed treatment such as cryotherapy or biopsy, and topical treatment is allowed for treatment of AK lesions emerging in any part of the body. Any lesion in the treatment area that is treated during the Recurrence Follow-up Period will be considered as a recurrence.

Subjects are prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments to the treatment area up until the end of Visit 10 (Day 57), except when those medications are prescribed by the Investigator for the management of local skin reactions. All other routinely used topical products can be used on the treatment area from Day 57 onward, at the discretion of the Investigator.

All subjects should be reminded to avoid direct sun or UV exposure to the treatment area throughout the study. From Day 15 onward, if a subject is unable to avoid direct sun or UV exposure to the treatment area, the Investigator may allow the use of sunblock only.

Subjects have unrestricted use of nonmedicated topical products on areas outside of the treatment area during the study. After Day 57, all routinely used topical products can be used.

Any subjects who start systemic therapies for the treatment of AK will be withdrawn from the study.

Any subjects who start topical therapies for AK on the treatment area will be withdrawn from the study.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration.

9.4.8 Prohibitions and Restrictions during Study Period

Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments (see Section 9.5.1.5.3); otherwise there are no food, water, beverage, or physical activity restrictions during the study.

9.4.9 Treatment Compliance

Records of treatment administration for each subject will be kept during the study. The clinical research associates (CRAs) will review treatment administration throughout the course of the study.

9.4.10 Drug Supplies and Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to GCP guidelines, as well as national requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies and dispensing of study drug to the subject must be maintained. This includes, but is not limited to:

- documentation of receipt of clinical supplies
- study drugs dispensing/return reconciliation log, including amount and date of dispensing
- study drugs accountability log
- all shipping service receipts
- documentation of study drug returned to the Sponsor

All forms will be provided by the Sponsor (or its designee). Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. A copy of the drug accountability record must be provided to the Sponsor at the end of the study.

The supplies and inventory records must be made available, on request, for inspection by the Sponsor (or its designee) or a representative of a health authority. If applicable, all unused study drugs and empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor at the conclusion of the study unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. On completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, study drug that is to be returned to the

Sponsor, if necessary must be boxed and sealed and shipped back to the Sponsor following all local regulatory requirements.

The CRA(s) will review drug accountability during monitoring site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

All assessments and timing of the assessments should be performed according to the Schedule of Procedures and Assessments (Table 1 and Table 2).

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical/Surgical and Actinic Keratosis History

Medical and surgical history and current medical conditions will be recorded at Screening (Visit 1). All pertinent medical history must be noted in the CRF/eCRF. A complete AK medical history will also be recorded.

Medical history will include:

- Significant medical and surgical history; childhood diseases and common colds are not required unless it is ongoing at Screening
- A complete AK history from the time of initial diagnosis
- A complete AK treatment history including all commercial and investigational products, including medical therapies and surgical modalities, and other prescribed and nonprescription therapies dating back to the initial diagnosis.

9.5.1.2.2 Fitzpatrick Skin-Type Classification

The Fitzpatrick Skin-Type is a skin classification system13 which measures 2 components (genetic disposition and reaction to sun exposure). Skin-types range from very fair (Type I) to very dark (Type VI).

Subjects' skin will be typed using this classification system at Screening (Visit 1).

9.5.1.2.3 Prior Medications

Prior medications taken within 28 days before Day 1, including nonprescription remedies, vitamins, etc, will be recorded at Screening (Visit 1).

9.5.1.3 Activity Assessments

9.5.1.3.1 ACTINIC KERATOSIS LESION COUNT

The Investigator will perform a count of AK lesions (lesion count) for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

The AK lesion count is the Investigator's assessment of the number of AK lesions in the treatment area. A subject must have 4 to 8 AK lesions in the treatment area to be eligible to continue in the study at Visit 1.

For this assessment, an AK lesion is considered to be on the treatment area, and should be counted if it is completely inside the treatment area or is touching any of the borders of the treatment area. These lesions will be treated during the study medication application process.

The Investigator must NOT refer to any other evaluation to assist with the AK lesion count. This is not a comparison with the AK lesion count at any other timepoint.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (3 mL at each timepoint) for PK analysis of KX2-391 will be collected at the following timepoints (Table 4):

Table 4 Blood Sample Collection Times for Pharmacokinetic Analyses

Application Day	**Time (hours)**			
	0 predose	**0.5 postdose**	**1 postdose**	**4 postdose**
Window		±5 minutes	±10 minutes	±10 minutes
Both cohorts: Day 1 (Visit 2)	X[a]	X	X	X
Cohort 1: Day 5 (Visit 6)	X[a]	X	X	X
Cohort 2: Day 3 (Visit 4)	X[a]	X	X	X

a Prior to application of study treatment.

Approximately 24 mL will be collected for measurement of plasma concentrations of KX2-391.

The actual times of PK sampling will be recorded.

A description of collection, handling, and shipping procedures for PK samples will be provided to the sites.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will include recording all AEs and serious adverse events (SAEs).

Safety assessments also include laboratory evaluation of hematology, biochemistry, and urinalyses; periodic measurement of weight, vital signs, ECGs, and performance of PEs, as detailed in the sections below and shown in Table 1 and Table 2.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions. AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events. Treatments administered for LSRs will be recorded on the Concomitant Medications CRF.

9.5.1.5.1 ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is KX2-391 Ointment 1%.

Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing conditions that worsen after dosing

The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- any new disease or exacerbation of an existing disease
- any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug

- recurrence of an intermittent medical condition (eg, headache) not present at baseline

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the final contact in the Follow-up Period on Day 57. For subjects participating in the Recurrence Follow-up Period, only AEs at the treatment area will be collected.

Subjects with study drug-related AEs will be followed until resolution, resolved with sequelae, or under medical care. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

All AEs observed during the study will be reported on the CRF/eCRF.

Laboratory Adverse Events

A treatment-emergent abnormal laboratory test result should be considered as a treatment-emergent AE (TEAE) if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

An abnormal laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study drug
- results in withholding of study drug pending some investigational outcome
- results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- increases in severity compared with baseline

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF/eCRF.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs. An ECG abnormality in a subject with symptoms may meet the criteria for an AE as described in this protocol. In these instances, the AE corresponding to the symptomatic ECG abnormality will be recorded on the Adverse Events CRF/eCRF.

For symptomatic ECG abnormalities meeting criteria as SAEs, the study site must submit an SAE report, including the ECG report to the Sponsor, or designee, using the SAE reporting procedures (Section 9.5.3.1).

Assessing Severity of Adverse Events

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.

Adverse events will be graded for severity as follows:

Mild	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that is sufficiently discomforting to interfere with everyday activities
Severe	An event that prevents normal everyday activities

Investigators will assess severity for all AEs (for both increasing and decreasing severity). The criteria for assessing severity are different from those used for seriousness (see Section 9.5.1.5.2).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- temporal relationship of the onset of the event to the initiation of the study treatment
- the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- whether the event is known to be associated with the study treatment or with other similar treatments
- the presence of risk factors in the study subject known to increase the occurrence of the event
- the presence of nonstudy treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF/eCRF using the following criteria:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent or underlying disease or other drugs or conditions

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, conditions or concurrent or underlying disease provide plausible explanations

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

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

- results in death
- is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest, which include pregnancy, overdose, and significant treatment-emergent laboratory abnormality (See Section 9.5.1.5.1), are to be captured using the SAE procedures but are to be considered as SAEs only if they met one of the above criteria. All events of these types are to be reported on the CRF/eCRF whether or not they meet the criteria for SAEs.

The following hospitalization is not considered to be an SAE because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

9.5.1.5.3 LABORATORY MEASUREMENTS

Blood will be collected for clinical laboratory tests at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2). Collection of blood and urine (including samples for pregnancy testing, where applicable) will be conducted at the clinic site. Approximately 20 mL of blood will be collected for clinical laboratory testing, including pregnancy testing, when required. Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments. Fasting status must be documented for all laboratory samples.

Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator. When conducted, microscopic urinalysis results will be recorded on the CRF/eCRF.

The clinical laboratory tests to be measured during the study are provided in Table 5.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW)
Chemistry	
Electrolytes	chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), 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)[a]	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
Pregnancy Testing	serum pregnancy test, urine pregnancy test (where applicable)

a Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF/eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5.2), the site must electronically transmit the SAE report including the laboratory report to the Sponsor using the SAE form (see Section 9.5.3.1).

9.5.1.5.4 VITAL SIGNS

Vital sign (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) measurements will be taken after the subject has been seated for at least 5 minutes at Screening (Visit 1), Day 5 (Visit 6) for Cohort 1 or Day 3 (Visit 4) for Cohort 2, Day 8 (Visit 7), Day 15 (Visit 8), Day 29 (Visit 9), and Day 57 (Visit 10) (Table 1 and Table 2). Serial vital signs may be obtained to confirm accurate readings.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete PE will be performed at Screening (Visit 1) and Day 57 (Visit 10) (Table 1 and Table 2).

A complete PE will include weight and an assessment of head, eyes, ears, nose, and throat (HEENT), integumentary, gastrointestinal, cardiovascular, respiratory, muscular-skeleton, and neurological systems.

Documentation of the PE will be included in the source documentation at the site. Only changes from screening PE findings that meet the definition of an AE will be recorded on the Adverse Events CRF/eCRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

A 12-lead ECG will be completed at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2). ECGs may be performed at a convenient time during the visit. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. The ECG data recorded on the CRF/eCRF must include rate, rhythm, intervals, and QTc/QTcF.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs.

9.5.1.5.7 PREGNANCY TESTING

Serum pregnancy tests will be obtained in females of childbearing potential at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1 and Table 2).

A urine pregnancy test will be performed on females of childbearing potential before study medication application on Day 1 (Visit 2). Visit 1 and Visit 2 test results must be reviewed before dosing.

9.5.1.5.8 OTHER ASSESSMENTS

Concomitant Medications

Concomitant medications will be assessed at all clinic visits (Table 1 and Table 2). Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on

the Concomitant Medication CRF/eCRF. The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Use of sunblock or any topical products in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication CRF/eCRF.

Local Skin Reactions

At every post-Screening clinic visit through Day 57 (Visit 10), the Investigator or trained designee will assess any LSR on the treatment area for signs:

- Before study medication application (on dosing days)
- After the assessment of adverse events

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst) (Table 6).

Table 6 Local Skin Reaction Grading Criteria

	Grading Criteria				
Local Skin Response	**0**	**1**	**2**	**3**	**4**
Erythema	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking / Scaling	Not present	Isolated scale, specific to lesion	Scale <50%	Scale >50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation / Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles <50%	Transudate or pustules, with or without vesicles >50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion / Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

Examples of LSR signs are shown in photographs in Appendix 1.[15]

Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events.

All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization.

Treatment for any LSR or interruption/discontinuation of study treatment for an LSR will be recorded on the CRF/eCRF.

LSRs will be reported separately from adverse events.

Pigmentation and Scarring

Hypo- and hyper- pigmentation and scarring on the treatment area will be assessed by the Investigator (or a trained designee) as being present or absent.

Pigmentation and scarring will be assessed at every post-Screening clinic visit through Day 57 (Visit 10) (Table 1 and Table 2).

Standardized Photography

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Care must be taken to ensure the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph. Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

The photographs are to document the appearance of the subjects' treatment area and to assist with the identification and confirmation of the location of the treatment area throughout the study (Section 9.1.1).

Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

9.5.2 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in dermatology studies as well as in the routine clinical care of patients with actinic keratosis.

9.5.3 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.3.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event. SAE reporting requirements will be provided in the Investigator File.

All SAEs, regardless of causality assessment, must be collected through the last subject contact and followed to resolution or, if resolution is unlikely, to stabilization. SAEs reported to the site from the time of the last subject contact up to 30 days after the last contact, will be collected (ie, Day 57 plus 30 days). During the Recurrence Follow-up Period, all AEs, including SAEs in the treatment area will be collected until the last subject contact. These SAEs will be discussed in the clinical study report. Any SAE event judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Deaths and life-threatening events should be reported immediately by telephone. The initial report must be submitted within 1 business day by electronically transmitting the completed SAE form.

The detailed contact information for reporting of SAEs will be provided in the Investigator File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. All supporting documents should be sent de-identified and should contain the assigned subject number. Only supporting documents directly related to the event should be sent.

Any follow-up information received on SAEs should be forwarded as soon as possible. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

9.5.3.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy for which the estimated date of conception was either before the last visit or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs (see Section 9.5.3.1).

Pregnancies must be reported by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies is provided in the Investigator File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant during the Treatment Period must be withdrawn from the study.

9.5.3.3 Reporting of Other Events of Interest

9.5.3.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied.

Any study drug overdose should be noted on the Study Medication CRF/eCRF.

All AEs associated with overdose, or medication error should be captured on the Adverse Event CRF/eCRF and also reported using the procedures detailed in Section 9.5.3.1 even if the AEs do not meet serious criteria. If the AE associated with an overdose or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF/eCRF.

9.5.3.4 Expedited Reporting

The Sponsor (or its designee) must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

In determining what SAEs meet criteria for expedited reporting, the current version of the Investigator's Brochure will be used for reference safety information.

9.5.3.5 Breaking the Blind

Not applicable

9.5.3.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.4 Completion/Discontinuation of Subjects

A subject may elect to discontinue from the study at any time for any reason. See Section 9.3.3 for reasons why Investigators may discontinue subjects from the study. Investigators must document the actual reason(s) why they decided to discontinue subjects, or why subjects withdrew consent, as applicable. Study disposition information will be collected on the Disposition CRF/eCRF.

Subjects who withdraw from study treatment (with the exception of death or withdrawal of consent) will be encouraged to complete the Early Termination assessments at the time of withdrawal as indicated in Table 1 and Table 2. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF/eCRF.

9.5.5 Abuse or Diversion of Study Drug

Not applicable

9.5.6 Confirmation of Medical Care by another Physician

The Investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be documented in the subject source documentation, collected on the CRF/eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. A CRF/eCRF or a select CRF/eCRF page may

be used as a source document. CRF/eCRFs used as source documents will be listed in the Data Management Plan. As defined by ICH E6 guidelines (Section 1.11), the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject. In this study, the CRF may refer to either a paper (CRF) or electronic data collection form (eCRF), or both.

Data collected on the CRF/eCRF must be completed following the instructions described in the CRF/eCRF Completion Guidelines, which will be based on the Data Management Plan. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF/eCRF. The PI must sign the CRF/eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs/eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

Responsible site personnel will enter the information required by the protocol onto the CRF/eCRFs in accordance with the CRF/eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to review the CRF/eCRFs for completeness and accuracy against the source documents. They will identify any discrepancies and ensure that appropriate site personnel address the discrepancies.

The original CRFs/eCRFs will be maintained at the site in a central document repository. If used, a copy of the CRF will be forwarded to the Sponsor.

At the end of the study an electronic copy of the database along with appropriate system version will be archived.

Uniform procedures will be discussed at the Investigator meetings or at site initiation and/or will be documented in the CRF/eCRF Completion Guidelines.

9.6.2 Clinical Data Management

All data, both CRF/eCRF and external data, will be loaded into a clinical system as specified in the Data Management Plan.

Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

9.7 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked. Statistical analyses will be performed using Phoenix WinNonlin and SAS software or other validated statistical software as required.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.

For all analyses, study Day 1 will be defined as the date of the first dose of study drug.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

The primary endpoint is activity.

Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57.

9.7.1.1.2 SECONDARY ENDPOINTS

Activity

Reduction in lesion counts at each visit during Days 1-57 will be assessed as the secondary endpoint for activity.

Safety

Safety will be evaluated primarily by assessment of AEs and clinical laboratory data. The results of other safety assessments (vital signs, PEs, ECGs) will also be evaluated.

Pharmacokinetic

Secondary endpoints include the following PK parameters derived by noncompartmental analysis using the plasma concentration-time data of KX2-391: C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

9.7.1.1.3 EXPLORATORY ENDPOINTS

Exploratory endpoints include recurrence and sustained response rates.

Recurrence rate will be defined as the proportion of subjects who achieved 100% complete 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 defined as the proportion of subjects who achieved 100% complete clearance at Day 57 (Visit 10) without any identified AK lesions on the treatment area at 12 months post-Day 57.

9.7.1.2 Definitions of Analysis Sets

The Per-Protocol Set is 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 evaluation.

The Evaluable Set is the group of subjects who receive 5 days (Cohort 1) or 3 days (Cohort 2) of treatment and complete most evaluations including the Day 57 Follow-up Visit.

The Safety Analysis/Full Analysis Set is the group of subjects who receive at least one dose of study treatment.

The PK Analysis Set is the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

9.7.1.3 Subject Disposition

All subjects will be tabulated by cohort as to study discontinuation and the reasons for discontinuation as described in Section 9.3.3.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort. For continuous demographic variables, results will be summarized by cohort as well, and presented as N, mean, SD, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be used in each cohort. No statistical testing will be performed.

9.7.1.5 Prior and Concomitant Therapy

All Investigator terms for medications recorded in the CRF/eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary drug codes.

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

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. Prior and concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of prior and concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All medications will be presented by cohort in subject data listings.

9.7.1.6 Activity Analyses

AK lesion counts will be summarized by cohort at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 will be estimated by cohort in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be estimated by timepoint and cohort in the Evaluable Set.

A 95% CI for the sustained response rate at 12 months post-Day 57 will be estimated by cohort in the Evaluable Set.

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

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

PK analyses will be performed on the PK Analysis Set.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable

9.7.1.8 Safety Analyses

All subjects in the Safety Analysis Set will be included in the safety analyses.

Safety data will be summarized by cohort using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters, weight, vital signs, 12-lead ECG results, and physical examination findings.

Similar to the activity analyses, any contrast between the 2 cohorts will mainly be noninferential in the safety analyses.

9.7.1.8.1 EXTENT OF EXPOSURE

The actual number of doses for each subject will be summarized by cohort.

9.7.1.8.2 ADVERSE EVENTS

For AEs, verbatim terms on the CRFs/eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0 or higher). Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized by cohort. Adverse events will also be summarized by severity, relationship to study drug, and cohort. Subject incidence of SAEs will also be displayed by cohort.

Only those AEs that were treatment-emergent will be included in summary tables. Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing AEs that worsen after dosing

All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC, PT, and cohort. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC, PT, and cohort. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by cohort. Changes from baseline will also be summarized by cohort.

In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up in each cohort.

9.7.1.8.4 VITAL SIGNS

Vital sign values will be evaluated by cohort on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG data will be tabulated by cohort for each individual subject.

9.7.1.8.6 PHYSICAL EXAMINATIONS

Physical examination findings will be listed by cohort for each subject.

9.7.1.8.7 PREGNANCY TESTS

Results of pregnancy tests will be listed by cohort for all subjects, as applicable.

9.7.1.8.8 OTHER ANALYSES

Local Skin Reactions

Local skin reactions as reported by the Investigator will be displayed and summarized by visit and cohort for all subjects.

Pigmentation and Scarring

Pigmentation and scarring as reported by the Investigator will be displayed and summarized by visit and cohort for all subjects.

9.7.2 Determination of Sample Size

For either cohort, a sample size of 60 subjects is sufficient to detect a 100% complete 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% 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.

9.7.3 Interim Analysis

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. The decision to open Cohort 2 will be documented.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the prespecified plans need to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.

2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1(8589):795-7.

3. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115(11):2523-30.

4. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000;42(1 Pt 2):23-4.

5. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42(1 Pt 2):4-7.

6. Guidelines for the Management of Actinic Keratoses. 2004/2005 European Dermatology Forum. Available from: http://www.euroderm.org [Accessed 02 July 2012].

7. Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for actinic keratoses. Committee on Guidelines of Care. J Am Acad Dermatol 1995;32(1):95-8.

8. Suchniak JM, Baer S, Goldberg LH. High rate of malignant transformation in hyperkeratotic actinic keratoses. J Am Acad Dermatol 1997;37(3 Pt 1):392-4.

9. Ehrig T, Cockerell C, Piacquadio D, et al. Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg 2006;32(10):1261-5.

10. Berman B, Bienstock L, Kuritzky L, et al. Primary Care Education Consortium; Texas Academy of Family Physicians. Actinic keratoses: sequelae and treatments. Recommendations from a consensus panel. J Fam Pract 2006;55(5 Suppl):1-8.

11. Quaedvlieg PJ, Tirsi E, Thissen MR, et al. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol 2006;16(4):335-9.

12. Marks R, Foley P, Goodman G, et al. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115(6):649-55.

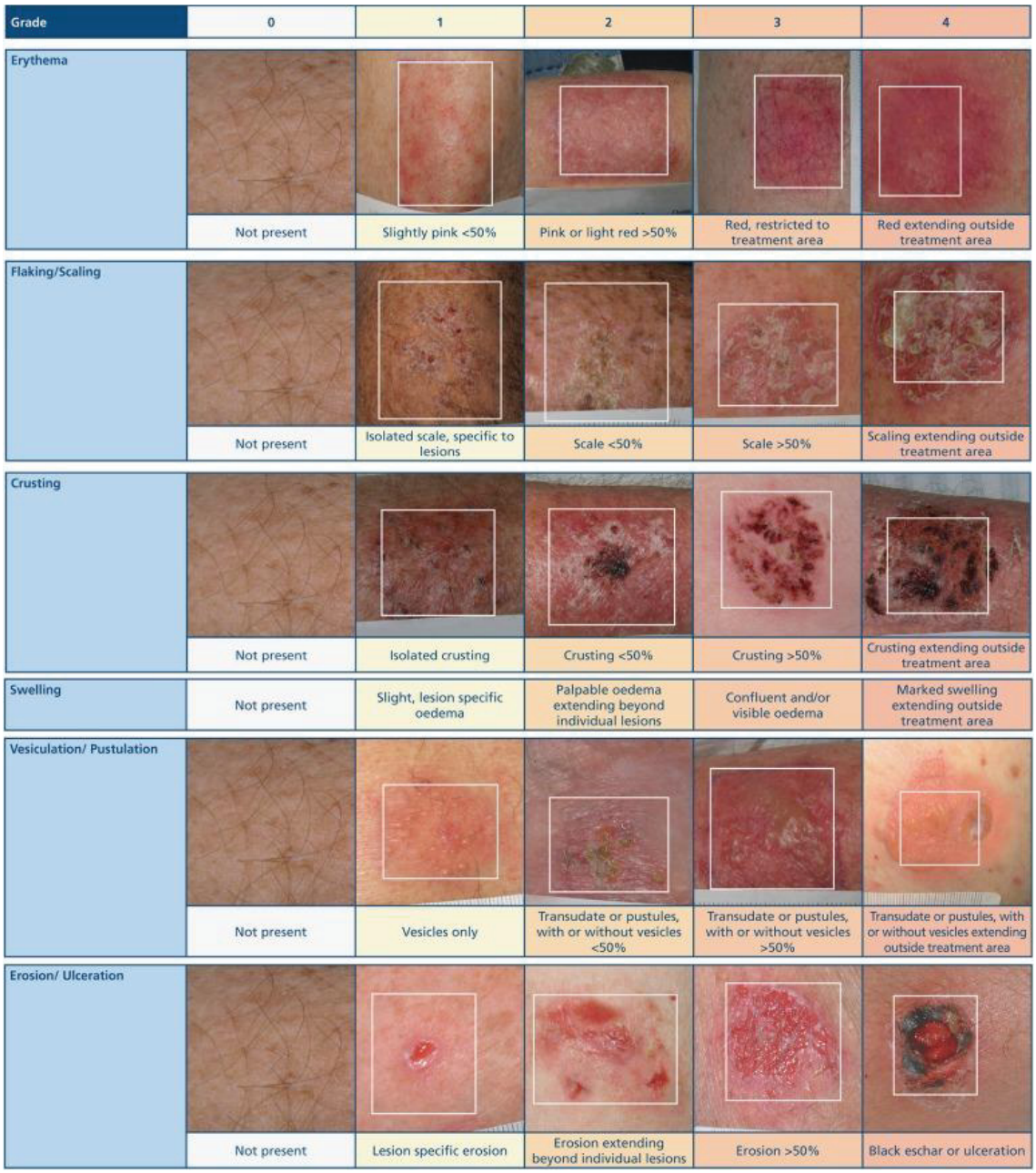
13. Food and Drug Administration Draft Guidance on Ingenol Mebutate; Recommended Jan 2016.

14. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through IV. Arch Dermatol 1998;124(6):869-71.

15. Rosen R, Marmur E, Anderson L, et al. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. Dermatol Ther (Heidelb) 2014;4:207-19.

11 APPENDICES

Appendix 1 Photographs of Local Skin Reactions



Source: Rosen R, Marmur E, Anderson L, et al. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. Dermatol Ther (Heidelb) 2014;4:207-19.

PROTOCOL SIGNATURE PAGE

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

Investigational Product Name: KX2-391 Ointment 1%

UTN Number: U1111-1173-5677

SIGNATURES

Authors:

PPD MD Date

Medical Monitor
Kinex Pharmaceuticals, Inc.

PPD PhD Date

Clinical Pharmacologist
Kinex Pharmaceuticals, Inc.

PPD PhD Date

Biostatistician
Kinex Pharmaceuticals, Inc.

INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	KX2-391 Ointment 1%
UTN Number:	U1111-1173-5677

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name, degree(s)>		
Investigator	Signature	Date

<Name of study site>

Study Site

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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
Sponsor:	United States: Kinex Pharmaceuticals, Inc. 20 Commerce Drive Cranford, New Jersey 07016, US Tel: +1 908-272-0628
Investigational Product Name:	KX2-391 Ointment 1%
Indication:	Actinic keratosis on the face or scalp
Phase:	2a
Approval Date:	v1.0 23 Jan 2016 (original protocol)
UTN Number:	U1111-1173-5677
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Kinex Pharmaceuticals, Inc. (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. KX2-391
Name of Active Ingredient: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide
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
Investigators PPD, MD, Lead Principal Investigator
Sites Approximately 4 to 6 sites in the United States
Study Period and Phase of Development First subject in to last subject out, approximately 18 months Phase 2a
Objectives **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 **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 the pharmacokinetics (PK) of KX2-391 Ointment 1% in subjects with AK on the face or scalp **Exploratory Objective:** • To determine recurrence rates to 12 months post-Day 57 for subjects who show response at Day 57
Study Design This study will be 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. The study consists of Screening, Treatment, and Follow-up Periods. 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. Thereafter, 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.
Number of Subjects Approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set,

defined as subjects who complete 5 days of treatment and the Day 57 Follow-up visit.

Inclusion Criteria

Eligible subjects must have/be:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 18 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 90 days prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device). Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.
8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities
   - clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable
9. Willing to avoid excessive sun exposure
10. Able to comprehend and are willing to sign an informed consent form (ICF)

Exclusion Criteria

Eligible subjects must not have/be:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma <u>not</u> on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days

4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
   - moisturizers or emollients on the face or scalp; 12 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)
   - imiquimod (eg, Aldara; Zyclara)
   - diclofenac with or without hyaluronic acid (eg, Solaraze)
6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy
   - electrodesiccation
   - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
   - chemical peels (eg, tricholoracetic acid)
   - dermabrasion
   - surgical removal (eg, curettage, excision)
7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the subject to an unacceptable risk by study participation
10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 14 days or 5 half-lives of the investigational product, whichever is longer, before Screening

Study Treatment

50 mg of KX2-391 Ointment 1% will be applied topically once daily to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total).

KX2-391 Ointment 1% will be applied once daily for 5 consecutive days.

Duration of Participation and Treatment

- Planned enrollment period: approximately 3 months (90 days)

- Planned subject participation is approximately 64 weeks:
  - Screening Period: up to 28 days
  - Treatment Period: 5 consecutive treatment days (Days 1-5)
  - Follow-up Period: Visits at Days 8, 15, 29, and 57
  - Recurrence Follow-up Period: only for complete responders at Day 57, visits every 3 months for 12 months after Day 57 (ie, at 3, 6, 9, and 12 months post-Day 57).

Length of stay: On Day 1 (Visit 2) and Day 5 (Visit 6), subjects will stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected.

Concomitant Drug/Therapy

Use of any non-study drug treatment for AK lesions on the face or scalp is prohibited during the study. During the Recurrence Follow-up Period, isolated lesion treatment such as cryotherapy or biopsy is allowed for treatment of AK lesions emerging in the selected treatment area. Any treated lesion will be considered as a recurrence.

Assessments

Activity Assessments

The Investigator will perform a count of AK lesions for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

Safety Assessments

Safety will be assessed by recording all adverse events (AEs), serious adverse events (SAEs), laboratory evaluation of hematology, biochemistry, and urinalysis values, measurement of weight and vital signs, evaluation of ECGs, and the performance of physical examinations.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions (LSRs). AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events.

Other Assessments

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst). In addition to LSRs, hypo- and hyper- pigmentation and scarring on the treatment area will be assessed as being present or absent. Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events. All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization. LSRs will be reported separately from AEs.

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Pharmacokinetic Assessments

PK samples will be collected at the following timepoints:

- Day 1: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose
- Day 5: predose, 0.5 (±5 minutes), 1 and 4 hours (±10 minutes) postdose

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Statistical Methods

Study Endpoints

Primary Endpoint

- Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57. Sustained response will be defined as the proportion of subjects achieving 100% (complete) clearance at Day 57 without any identified AK lesions on the treatment area at 12 months post-Day 57.

Secondary Endpoints

- Activity: Reduction in lesion counts during Days 1-57
- Safety: Evaluation of AEs and clinical laboratory data; the results of other safety assessments (vital signs, physical examinations, ECGs) will also be evaluated.
- Pharmacokinetic: Determination of C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R

Exploratory Endpoint

- Recurrence rate will be defined as the proportion of subjects who achieved 100% complete clearance at Day 57 (Visit 10) with any identified AK lesions on the face or scalp at 3, 6, 9, and 12 months post-Day 57.

Analysis Sets

- Per-Protocol Set: the group of protocol-eligible subjects who receive 5 days of study treatment and complete at least one scheduled post-treatment evaluation.
- Evaluable Set: the group of subjects who receive 5 days of treatment and complete most evaluations including the Day 57 Follow-up Visit.
- Safety Analysis/Full Analysis Set: the group of subjects who receive at least one dose of study treatment.
- PK Analysis Set: the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

Activity Analyses

AK lesion counts will be summarized at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 and 12 months post-Day 57 will be estimated in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be summarized by timepoint in the Evaluable Set.

Safety Analyses

All subjects who receive at least one dose of KX2-391 Ointment 1% will be included in the safety analyses. Treatment-emergent AEs (TEAEs) are defined as either those AEs with an onset after dosing or those pre-existing AEs that worsen after dosing. For AEs, verbatim terms on the case report form/electronic case report form (CRF/eCRF) will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; v 16.0 or higher). Subject incidence of AEs will be displayed by SOC. Adverse events will also be summarized by severity and relationship to study drug. Subject incidence of SAEs will also be displayed. Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint. Changes from baseline will also be summarized. In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up.

Local skin reactions, pigmentation, and scarring as reported by the Investigator, will be displayed and summarized by visit for all subjects.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

Plasma concentrations for KX2-391 will be analyzed to determine applicable PK parameters.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

Interim Analysis

Since this is an open-label study, after each group of approximately 20 subjects completes Day 57 assessments, activity data will be tabulated.

Statistical Methods

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.

Sample Size Rationale

A sample size of 60 subjects is sufficient to detect a 100% complete 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% CI with a half-width of less than 15% (ie, lower boundary of the CI above 20%).

FINAL v1.0_23 Jan 2016

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002

Period	Screening	Treatment					Follow-up				Recurrence Follow-up [a]
Visit	1	2	3	4	5	6	7	8	9	10 [b]/ Early Term	11, 12, 13, 14 [a]
Day	-28 to -1	1	2	3	4	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Visit time window (days)	None	None	None	None	None	None	±2	±2	±2	±2	±14
Informed consent	X										
Inclusion & exclusion criteria	X	X[d]									
Demographics	X										
Medical/surgical history	X										
AK history/AK treatment history	X										
Fitzpatrick skin-type scale	X										
Vital signs[e]	X					X	X	X	X	X	
Prior and concomitant medications/therapies	X	X[d]	X	X	X	X	X	X	X	X	X
Physical examination, including weight[f]	X									X	
Treatment area identification	X	X[d]									
AK lesion count	X	X[d]					X	X	X	X	X
ECG[g]	X						X			X	
Clinical chemistry, hematology, and urinalysis[h]	X						X			X	
Pregnancy test	X	X[d,i]					X			X	
PK blood samples		X[j]				X[j]					
Study medication application		X	X	X	X	X					
AEs[k]	X	X	X	X	X	X	X	X	X	X	X[l]
LSRs		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Pigmentation and scarring		X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	
Standardized photography	X	X[d]					X			X	X

Table 1 Schedule of Procedures/Assessments in Study KX01-AK-002

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; PK = pharmacokinetic; Term = Termination.

a For Day 57 complete responders only.

b For subjects who do not have complete response at Day 57, Day 57 is the Final Visit.

c For subjects who have complete response at Day 57, 12 months post-Day 57 is the Final Visit.

d Assessment performed before study medication application. Day 1 evaluation will serve as baseline for these assessments.

e Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.

f A complete PE will include weight and an assessment of HEENT, integumentary, gastrointestinal, cardiovascular, respiratory, muscular- skeleton, and neurological systems.

g Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

h Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments.

i For females of childbearing potential; urine pregnancy test on Day 1 before study medication application. All other pregnancy tests are performed with serum.

j PK assessments on Day 1 and Day 5 at 0 hour (just before study medication application) and at 0.5 (±5 min), 1, and 4 hours (±10 min) after study drug application.

k Before LSR assessment, subjects will be queried for spontaneously reported AEs.

l Only AEs in the selected treatment area will be recorded.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Terms
AE	adverse event
AK	actinic keratosis
AUC	area under the plasma concentration-time curve
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum (trough) plasma concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetics
PT	preferred term
R	accumulation ratio
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
US	United States

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, any protocol amendments, informed consent form (ICF), and appropriate related documents must be reviewed and approved before subjects are screened for entry by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice [GCP][1]), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [CFR] Part 56). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the Principal Investigator (PI) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)
- ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.
- Title 21 of the United States CFR (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it, and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject provides verbal consent to the subject's participation in the study and has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening visit and all authorizations required by local law (eg, Protected Health Information in North America) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Kinex Pharmaceuticals, Inc. at approximately 4 to 6 investigational sites in the United States (US).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of any contract research organizations (CROs) will be listed in the Regulatory Binder provided to the site.

7 INTRODUCTION

7.1 Indication

In this study, the activity, safety, and pharmacokinetics (PK) of KX2-391 Ointment 1% will be evaluated in adult subjects with a clinical diagnosis of stable, clinically typical actinic keratosis (AK) on the face or scalp.

7.1.1 Mechanism of Action

KX2-391 (also referred to as KX01) is a synthetic and highly selective inhibitor of Src tyrosine kinase signaling and tubulin polymerization. KX2-391 ointment is being developed as a topical treatment for actinic keratosis. KX2-391 is also being developed as an oral agent for oncology indications. In defining its pharmacological activity in tumor cells, both in vitro and in vivo, KX2-391 has been shown to have potent activity against a wide range of solid tumors as well as leukemia cell lines, including cell lines that are resistant to commonly used cancer drugs. Clinically, the safety, tolerability and pharmacokinetics of KX2-391 have been studied in approximately 120 patients in both solid and liquid tumors using either once or twice daily dosing. The best overall response in these early studies has been 'stable disease' in 25-30% of patients.

KX2-391 promotes the induction of p53, G2/M arrest of proliferating cell populations and subsequent apoptosis via the stimulation of Caspase-3 and PARP cleavage. Data from pre-clinical dermatology studies coupled with an understanding of the mechanism of action of KX2-391 suggests that this compound will have clinical activity in dermatology indications such as actinic keratosis. Potent inhibition of the growth of primary human keratinocytes and several melanoma cell lines in vitro (50% growth inhibition [GI_{50} values] $\leq$50 nM), suggests that KX2-391 has the potential to inhibit the proliferative expansion and promote apoptosis of abnormally proliferating cells in the epidermal and dermal layers upon topical application. KX2-391 has also been observed to inhibit T cell migration and endothelial tubule formation in vitro, suggesting additional potential therapeutic benefits for conditions where pathology is supported by lymphocyte infiltration, inflammation, and/or angiogenesis.

Information regarding KX2-391 nonclinical studies is provided in the Investigator's Brochure.

7.1.2 Clinical Experience with KX2-391

KX2-391 Ointment 1% has been administered to humans in ongoing study KX01-AK-01-US. Based on preliminary PK data from this study in AK lesions on the forearm, the systemic exposure to KX2-391 following topical administration is limited, and is considerably lower than observed in previous clinical studies of oral KX2-391. Patients should be monitored for the occurrence of application site reactions and systemic toxicity.

KX2-391 has been administered orally to approximately 120 patients with malignancy.

The Kinex studies of oral KX2-391 are as follows:

KX2-391 was evaluated in a Phase I clinical trial, Study No. KX01-01-07, entitled "A Combined Rising Single-Dose (RSD) and Rising Multiple-Dose (RMD) Phase I Study to Evaluate Safety, Tolerability, and Pharmacokinetics of KX2-391 in Patients with Advanced Malignancies That Are Refractory to Conventional Therapies".

KX2-391 has been evaluated in Study No. KX01-002-09, entitled "A Phase II, Open-Label, Single-Arm Study Evaluating the Safety, Efficacy and Pharmacokinetics of KX2-391 in

Patients with Bone-Metastatic, Castration-Resistant Prostate Cancer Who Have Not Received Prior Chemotherapy."

KX2-391 was evaluated in Study No, KX01-03-11, "A Phase 1b Rising Multiple-Dose Clinical Study to Evaluate Safety, Tolerability and Activity of Oral Monotherapy with KX2-391 in Elderly Subjects with Acute Myeloid Leukemia (AML) Who Are Refractory to or Have Declined Standard Induction Therapy".

7.2 Study Rationale

Actinic keratoses represent the initial intra-epidermal manifestation of abnormal keratinocyte proliferation having the potential to progress to squamous cell carcinoma (SCC). Squamous cell carcinoma is the second leading cause of skin cancer deaths in the US, with up to 65% of SCC arising from pre-existing actinic keratoses.[2,3] The risk of progression has been determined to be between 0.025% and 16% per year,[2,4] and the calculated lifetime risk of malignant transformation for a patient with AKs followed up for 10 years is between 6.1% and 10.2%.[5] The rationale behind treating every AK is based on the difficulty in predicting which single AK will progress to squamous cell carcinoma.[6,7] Suchniak et al[8] reported 36% of lesions previously diagnosed clinically as AKs being in fact SCC, with 14% being in situ SCC. Ehrig et al[9] showed that 4% of AKs clinically diagnosed by board-certified dermatologists were in fact SCC and 5% were considered occult early stage of cutaneous malignancy. Spontaneous regression has been reported in up to 25.9% of AKs over a 12-month period, although 15% later reappeared.[10,11,12] The goals of treatment are to completely eliminate AKs, minimizing their risk of progression to invasive SCC, reducing the potential to metastasize and cause death, while obtaining the best cosmetically acceptable outcomes. Current approved/marketed treatment has shown up to approximately 60% efficacy, with a recurrence rate of approximately 35%.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is:

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

8.2 Secondary Objectives

The secondary objectives of the study are:

- 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 the PK of KX2-391 Ointment 1% in subjects with AK on the face or scalp

8.3 Exploratory Objective

The exploratory objective of the study is:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be 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.

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

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. Thereafter, 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.

On Day 1 (Visit 2) and Day 5 (Visit 6), subjects will stay for approximately 5 hours at the investigational center until after the last PK blood sample is collected.

9.1.1 Screening Period

The Screening Period may last up to 28 days.

Subject eligibility will be established during the Screening Period. Subjects will be screened within 28 days of the first dose of study drug. All screening assessments/evaluations, as presented in Table 1 will be performed after the subject provides informed consent and eligibility criteria are met.

Approximately 80 subjects will be enrolled to provide approximately 60 subjects in the Evaluable Set, defined as subjects who complete 5 days of treatment and the Day 57 Follow-up visit.

Treatment Area Identification

At Screening (Visit 1), the Investigator will select a continuous treatment area affected with AK on the face or scalp for each subject that:

- measures 25 cm^2
- contains 4 to 8 AK lesions that are clinically typical

The location and approximate shape of the treatment area will be recorded on the appropriate body chart.

At Visit 1, the Investigator and an investigational center staff member will identify the treatment area by:

- Examining the face or scalp and locating each AK with a dot of removable surgical skin marker.
- Using an 8 x 11 acetate transparency sheet with 1x1 cm squares. The acetate will have 20 squares across and 26 squares vertically.
- Mapping at least 2 anatomical landmarks on the acetate sheet. Example of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
- Indicating location of AK lesions with permanent marker dots on transparency acetate sheet.
- Removing surgical skin marker dots with alcohol swabs.
- Outlining the treatment area on the face or scalp with a fine-tipped indelible marker.

9.1.2 Treatment Period

The inclusion/exclusion criteria will be reviewed again prior to treatment on Day 1, to re-confirm subjects' eligibility to participate in the study.

Subjects will be treated for 5 consecutive days (Days 1-5 [Visits 2-6]) during the Treatment Period. Visits 2 through 6 should be scheduled to occur at approximately the same time each day.

At Visit 2 (Day 1), prior to study drug application, the Investigator and any appropriate investigational staff member(s) (Investigator-trained designee) will confirm the location of the treatment area using the Visit 1 acetate sheet and the body charts. The Investigator should re-mark the treatment area borders as needed so the study evaluations may be effectively completed.

Once the treatment area has been re-identified at Visit 2, photographs will be taken (Section 9.5.1.5.8). 50 mg of KX2-391 Ointment 1% will be applied topically once daily to the 25 cm^2 treatment area (2 mg/cm^2; 0.5 mg KX2-391 total). KX2-391 Ointment 1% will be applied for 5 consecutive days (see Section 9.4.2.4 for a detailed description of study medication application).

Pharmacokinetic blood sampling, activity, safety assessments, and local skin reaction (LSR) assessments (see Section 9.5 for details) will be performed (Table 1). Pigmentation and scarring in the treatment area also will be assessed by the Investigator (or a trained designee).

Standardized photography will be performed at designated visits throughout the study (Table 1).

9.1.3 Follow-up Period

After the Treatment Period, there will be Follow-up Visits at Days 8, 15, 29, and 57 to assess safety, activity, LSRs, pigmentation, and scarring.

9.1.4 Recurrence Follow-up Period

Only for subjects who show complete response at Day 57, there will be additional visits every 3 months up to 12 months post-Day 57 (ie, at 3, 6, 9, and 12 months post-Day 57) to assess recurrence of AK lesions. These subjects will continue to undergo scheduled activity and safety assessments (Table 1).

9.2 Discussion of Study Design, Including Choice of Control Groups

This is a nonrandomized, open-label study. No control group has been included.

9.3 Selection of Study Population

Eligible subjects will be adults (≥18 years of age) with a clinical diagnosis of stable, clinically typical AK on the face or scalp.

9.3.1 Inclusion Criteria

Inclusion criteria will be reviewed at Screening (Visit 1).

Subjects must meet all of the following criteria to be included in this study:

1. Males and females ≥18 years old
2. Clinical diagnosis of stable, clinically typical actinic keratosis
3. A treatment area on the face or scalp that:
   - is a continuous area measuring 25 cm^2
   - contains 4 to 8 AK lesions
4. Females must be postmenopausal (>50 years of age with at least 18 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy or tubal ligation) or otherwise incapable of pregnancy for at least 1 year; or, if of childbearing potential, must be using highly effective contraception for at least 90 days prior to treatment with KX2-391 Ointment 1% and must agree to continue to use highly effective contraception for at least 90 days following their last dose of KX2-391 Ointment 1%. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant or patch, or intrauterine device). Abstinence and double barrier methods do not qualify as highly effective methods of contraception.
5. Males who have not had a vasectomy must agree to use barrier contraception from Screening through 90 days after their last dose of KX2-391 Ointment 1%.

6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of KX2-391 Ointment 1%.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to administration of study treatment.
8. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - no physical examination (PE) findings that Principal Investigator (PI) determines would interfere with interpretation of study results
   - screening electrocardiogram (ECG) without clinically significant abnormalities
   - clinical chemistry, hematology, and urinalysis results that are within the reference ranges; clinical laboratory values outside the reference ranges that are considered by the PI to be clinically insignificant are also acceptable
9. Willing to avoid excessive sun exposure
10. Able to comprehend and are willing to sign an informed consent form

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area
2. Malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not on the treatment area that were treated with curative intent and are without recurrence
3. Used any of the following systemic therapies within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
   - methotrexate or other anti-metabolites; 28 days
4. Used any of the following topical therapies on the treatment area within the specified period before Visit 1:
   - retinoids; 90 days
   - glucocorticosteroids; 14 days
   - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
   - moisturizers or emollients on the face or scalp; 12 hours
5. Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
   - ingenol mebutate (eg, Picato)
   - 5-fluorouracil (eg, 5-FU; Efudex)

- imiquimod (eg, Aldara; Zyclara)
- diclofenac with or without hyaluronic acid (eg, Solaraze)

6. Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
   - cryotherapy
   - electrodesiccation
   - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
   - chemical peels (eg, tricholoracetic acid)
   - dermabrasion
   - surgical removal (eg, curettage, excision)
7. Currently, or has experienced any of the following on the treatment area within the specified period before Visit 1:
   - cutaneous malignancy; 180 days
   - sunburn; 28 days
   - body art (eg, tattoo, piercing); currently
8. A history of sensitivity and/or allergy to any of the ingredients in the study medication
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the subject to an unacceptable risk by study participation
10. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation
11. Females who are pregnant or nursing
12. Participated in an investigational drug trial during which an investigational study medication was administered within 14 days or 5 half-lives of the investigational product, whichever is longer, before Screening

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

Subjects will be removed from the study if any of the following occurs:

- Death
- Occurrence of serious or clinically significant AEs
- Occurrence of pregnancy
- Use of a prohibited concomitant medication or treatment (see Section 9.4.7.3)
- Conditions that, in the opinion of the Investigator, would make the subject's continued participation in the study inadvisable
- Noncompliance
- Withdrawal of consent (subject asked, but not required to give a reason)
- Other (Investigator must describe)

If the study is terminated by the Sponsor, the Investigator will promptly explain to the subject involved that the study will be discontinued and provide appropriate medical treatment and other necessary measures for the subject.

9.4 Treatments

The investigational product in the study is KX2-391 Ointment 1%.

9.4.1 Treatment Administered

Information regarding study treatment is provided in Table 2.

Table 2 Treatment Administered in KX01-AK-002

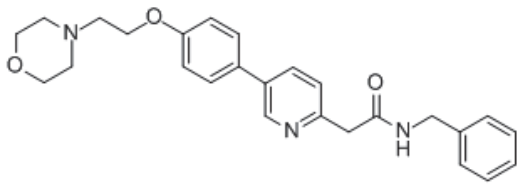
Investigational Product	Strength	Size of Treatment Area	Quantity study medication/ KX2-391	Number Applications and Frequency	Study Days Administered
KX2-391 Ointment 1%	1%	25 cm^2	50 mg/ 0.5 mg	1 application daily for 5 consecutive days	Days 1-5

9.4.2 Identity of Investigational Products

9.4.2.1 Chemical Name and Structural Formula of KX2-391

- Study drug code: KX2-391 Ointment 1%
- Drug Product: KX2-391 free base ointment formulated with glyceryl monostearate and propylene glycol
- Chemical name: *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl) acetamide

- Molecular formula: $C_{26}H_{29}N_3O_3$
- Molecular weight: 431.53 g/mole
- Structural formula:



9.4.2.2 Labeling for Study Drug

Investigational product will be packaged and labeled in a manner consistent with the study and will be designed by:

Kinex Pharmaceuticals, Inc.
1001 Main Street
Suite 600
Buffalo, NY 14203

Labels will be nonremovable in nature.

Labels for the investigational product will be in accordance with US regulations and will include (but will not be limited to) the following information:

- For clinical study use only
- Name and address of the Sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.3 Storage Conditions

Study drug will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.2.4 Administration of Investigational Products

The study medication is for external topical use on the treatment area. An investigational center staff member will perform the study medication applications. The staff member must wash her/his hands before and after each study medication application.

50 mg of KX2-391 Ointment 1% will be applied topically to a 25 cm^2 treatment area. This amount contains a total of 0.5 mg KX2-391 free base. KX2-391 Ointment 1% will be applied once daily for 5 consecutive days (see Table 2).

The staff member will weigh the appropriate amount of study medication into a weighing boat (or equivalent) using a calibrated scale. The amount of study medication applied will be calculated by determining the difference of the weight of the weighing boat with study medication before and after application. The amount of study medication weighed will be as close to the intended dose as possible.

A study staff member will perform and document a scale accuracy check at least every day before weighing study medication.

The study medication will be applied to the subject's treatment area using a fingertip protected with a powder-free finger cot or examination glove. The study medication will be gently and evenly rubbed over the treatment area until no visible accumulation is evident. The time when the study medication application is completed (Application Completion Time) will be recorded.

The study medication should remain on the treatment area. Subjects must avoid touching or wetting the treatment area and are not allowed to apply any topical products to the treatment area (see Section 9.4.7.3) up until the end of Visit 7 (Day 8). Showers may be taken in the morning on Days 1 through 5 in preparation for the study visit, approximately 24 hours after study drug application. Instructions will be sent home with the subject clarifying on how to care for the treatment area on Days 1 through 8.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is a study with one treatment group. All subjects will be assigned the same treatment.

9.4.4 Selection of Doses in the Study

The dose of 50 mg of KX2-391 applied to a 25 cm^2 area on the face or scalp for 5 consecutive days is based on a previous study using the same dose regimen for the treatment of AK on the forearm (study KX01-AK-01-US). Preliminary data show that this regimen had an acceptable LSR and safety profile, with efficacy outcomes considered to warrant further investigation.

9.4.5 Selection and Timing of Dose for Each Subject

Section 9.4.2.4 provides detailed instructions for administering KX2-391 Ointment 1% in this study. Study medication should be applied at about the same time each day.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Prior Therapy

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies including radiotherapy taken 28 days before Day 1 through the final study visit must be recorded in the case report form/electronic case report form (CRF/eCRF). A complete AK treatment history will be recorded on the AK Treatment History CRF/eCRF (see Section 9.5.1.2.1).

9.4.7.2 Concomitant Medication/Therapy

Concomitant medication/therapies are any new or existing therapy received by the subject after signing the ICF until discharge from the study.

Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication CRF/eCRF. The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Subjects will refrain from receipt of any therapy in accordance with the inclusion/exclusion criteria. Subjects should refrain from changing the use of any concomitant therapies during the study.

9.4.7.3 Prohibited Medication/Therapy

Use of any non-study drug treatment for AK lesions on the face or scalp is prohibited during the study. During the Recurrence Follow-up Period, isolated lesion treatment such as cryotherapy or biopsy is allowed for treatment of AK lesions emerging in the selected treatment area. Any treated lesion will be considered as a recurrence.

Subjects are prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments (Note: routine cleansers are allowed) to the treatment area up until the end of Visit 7 (Day 8), except when those medications are prescribed by the Investigator for the management of local skin reactions.

Subjects have unrestricted use of skin products on areas outside of the treatment area during the study. Lesions located outside the study treatment area may be treated topically as determined by the Investigator.

Subjects are excluded from participation in this study if they:

- Have used any of the following systemic therapies within the specified period before Visit 1:
  - retinoids; 90 days
  - glucocorticosteroids; 28 days (intra-articular and inhaled steroids are allowed)
  - methotrexate or other anti-metabolites; 28 days
- Have used any of the following topical therapies on the treatment area within the specified period before Visit 1:
  - retinoids; 90 days
  - glucocorticosteroids; 14 days
  - analgesic and/or anti-inflammatory medication on the face or scalp; 72 hours
  - moisturizers or emollients on the face or scalp; 12 hours
- Had any of the following on the treatment area within 90 days (or until the site has healed, whichever is longer) before Visit 1:
  - ingenol mebutate (eg, Picato)
  - 5-fluorouracil (eg, 5-FU; Efudex)
  - imiquimod (eg, Aldara; Zyclara)
  - diclofenac with or without hyaluronic acid (eg, Solaraze)
- Surgical or destructive modalities on the treatment area within 30 days (or until the site has healed following treatment, whichever is longer) before Visit 1:
  - cryotherapy
  - electrodesiccation
  - laser, light (eg, photodynamic therapy, intense pulsed light) or any other energy-based therapy
  - chemical peels (eg, tricholoracetic acid)
  - dermabrasion
  - surgical removal (eg, curettage, excision)

Subjects should not start such medications/treatments while enrolled in this protocol.

Any subjects who start systemic therapies for the treatment of AK will be withdrawn from the study.

Any subjects who start topical therapies for AK on the treatment area will be withdrawn from the study.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration.

9.4.8 Prohibitions and Restrictions during Study Period

Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments (see Section 9.5.1.5.3); otherwise there are no food, water, beverage, or physical activity restrictions during the study.

9.4.9 Treatment Compliance

Records of treatment administration for each subject will be kept during the study. The clinical research associates (CRAs) will review treatment administration throughout the course of the study.

9.4.10 Drug Supplies and Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to GCP guidelines, as well as national requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies and dispensing of study drug to the subject must be maintained. This includes, but is not limited to:

- documentation of receipt of clinical supplies
- study drugs dispensing/return reconciliation log, including amount and date of dispensing
- study drugs accountability log
- all shipping service receipts
- documentation of study drug returned to the Sponsor

All forms will be provided by the Sponsor (or its designee). Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. A copy of the drug accountability record must be provided to the Sponsor at the end of the study.

The supplies and inventory records must be made available, on request, for inspection by the Sponsor (or its designee) or a representative of a health authority. If applicable, all unused study drugs and empty containers, are to be returned to the Investigator by the subject and

ultimately to the Sponsor at the conclusion of the study unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. On completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, study drug that is to be returned to the Sponsor, if necessary must be boxed and sealed and shipped back to the Sponsor following all local regulatory requirements.

The CRA(s) will review drug accountability during monitoring site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

All assessments and timing of the assessments should be performed according to the Schedule of Procedures and Assessments (Table 1).

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical/Surgical and Actinic Keratosis History

Medical and surgical history and current medical conditions will be recorded at Screening (Visit 1). All pertinent medical history must be noted in the CRF/eCRF. A complete AK medical history will also be recorded.

Medical history will include:

- A complete medical and surgical history; childhood diseases and common colds are not required unless it is ongoing at Screening
- A complete AK history from the time of initial diagnosis
- A complete AK treatment history including all commercial and investigational products, including medical therapies and surgical modalities, and other prescribed and nonprescription therapies dating back to the initial diagnosis.

9.5.1.2.2 Fitzpatrick Skin-Type Classification

The Fitzpatrick Skin-Type is a skin classification system (Appendix 1) which measures 2 components (genetic disposition and reaction to sun exposure). Skin-types range from very fair (Type I) to very dark (Type VI).

Subjects' skin will be typed using this classification system at Screening (Visit 1).

9.5.1.2.3 PRIOR MEDICATIONS

Prior medications taken within 28 days before Day 1, including nonprescription remedies, vitamins, etc, will be recorded at Screening (Visit 1).

9.5.1.3 Activity Assessments

9.5.1.3.1 ACTINIC KERATOSIS LESION COUNT

The Investigator will perform a count of AK lesions (lesion count) for all subjects at Visits 1 and 2, Visits 7 through 10, and for Day 57 complete responders, also at Visits 11 through 14.

The AK lesion count is the Investigator's assessment of the number of AK lesions in the treatment area. A subject must have 4 to 8 AK lesions in the treatment area to be eligible to continue in the study at Visit 1.

For this assessment, an AK lesion is considered to be on the treatment area, and should be counted if it is completely inside the treatment area or is touching any of the borders of the treatment area. These lesions will be treated during the study medication application process.

The Investigator must NOT refer to any other evaluation to assist with the AK lesion count. This is not a comparison with the AK lesion count at any other timepoint.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (3 mL at each timepoint) for PK analysis of KX2-391 will be collected at the following timepoints (Table 3):

Table 3 Blood Sample Collection Times for Pharmacokinetic Analyses

Application Day	**Time (hours)**			
	0 predose	**0.5 postdose**	**1 postdose**	**4 postdose**
Window		±5 minutes	±10 minutes	±10 minutes
Day 1 (Visit 2)	X	X	X	X
Day 5 (Visit 6)	X[a]	X	X	X

a Prior to application of study treatment.

Approximately 24 mL will be collected for measurement of plasma concentrations of KX2-391.

The actual times of PK sampling will be recorded.

A description of collection, handling, and shipping procedures for PK samples will be provided to the sites.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Plasma concentrations of study drug will be measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will include recording all AEs and serious adverse events (SAEs).

Safety assessments also include laboratory evaluation of hematology, biochemistry, and urinalyses; periodic measurement of weight, vital signs, ECGs, and performance of PEs, as detailed in the sections below and shown in Table 1.

Subjects will be queried for spontaneously reported AEs at each study visit, before assessment of local skin reactions. AEs will be reported separately from LSRs.

Subject-reported LSRs will not be reported as adverse events. Treatments administered for LSRs will be recorded on the Concomitant Medications CRF.

9.5.1.5.1 ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is KX2-391 Ointment 1%.

Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing conditions that worsen after dosing

The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- any new disease or exacerbation of an existing disease

- any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- recurrence of an intermittent medical condition (eg, headache) not present at baseline

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the final contact in the Follow-up Period. For subjects participating in the Recurrence Follow-up Period, only AEs at the treatment area will be collected. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF/eCRF.

Subjects with onset of an AE or deterioration of a pre-existing condition will be followed until resolution, resolved with sequelae, or under medical care. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

All AEs observed during the study will be reported on the CRF/eCRF.

Laboratory Adverse Events

A treatment-emergent abnormal laboratory test result should be considered as a treatment-emergent AE (TEAE) if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

An abnormal laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study drug
- results in withholding of study drug pending some investigational outcome
- results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- increases in severity compared with baseline

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF/eCRF.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs. An ECG abnormality in a subject with symptoms may meet the criteria for an AE as described in this protocol. In these instances, the AE corresponding to the symptomatic ECG abnormality will be recorded on the Adverse Events CRF/eCRF.

For symptomatic ECG abnormalities meeting criteria as SAEs, the study site must submit an SAE report, including the ECG report to the Sponsor, or designee, using the SAE reporting procedures (Section 9.5.3.1).

Assessing Severity of Adverse Events

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.

Adverse events will be graded for severity as follows:

Mild	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that is sufficiently discomforting to interfere with everyday activities
Severe	An event that prevents normal everyday activities

Investigators will assess severity for all AEs (for both increasing and decreasing severity). The criteria for assessing severity are different from those used for seriousness (see Section 9.5.1.5.2).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- temporal relationship of the onset of the event to the initiation of the study treatment
- the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- whether the event is known to be associated with the study treatment or with other similar treatments
- the presence of risk factors in the study subject known to increase the occurrence of the event
- the presence of nonstudy treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF/eCRF using the following criteria:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent or underlying disease or other drugs or conditions

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, conditions or concurrent or underlying disease provide plausible explanations

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

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

- results in death
- is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest, which include pregnancy, overdose, and significant treatment-emergent laboratory abnormality (See Section 9.5.1.5.1), are to be captured using the SAE procedures but are to be considered as SAEs only if they met one of the above criteria. All events of these types are to be reported on the CRF/eCRF whether or not they meet the criteria for SAEs.

The following hospitalization is not considered to be an SAE because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

9.5.1.5.3 LABORATORY MEASUREMENTS

Blood will be collected for clinical laboratory tests at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1). Collection of blood and urine (including samples for pregnancy testing, where applicable) will be conducted at the clinic site. Approximately 20 mL of blood will be collected for clinical laboratory testing, including pregnancy testing, when required. Except for those diagnosed as having diabetes, subjects must be fasted for laboratory assessments. Fasting status must be documented for all laboratory samples.

Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator. When conducted, microscopic urinalysis results will be recorded on the CRF/eCRF.

The clinical laboratory tests to be measured during the study are provided in Table 4.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW)
Chemistry	
Electrolytes	chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), 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)[a]	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
Pregnancy Testing	serum pregnancy test, urine pregnancy test (where applicable)

a Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF/eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5.2), the site must electronically transmit the SAE report including the laboratory report to the Sponsor using the SAE form (see Section 9.5.3.1).

9.5.1.5.4 VITAL SIGNS

Vital sign (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) measurements will be taken after the subject has been seated for at least 5 minutes at Screening (Visit 1), Day 5 (Visit 6), Day 8 (Visit 7), Day 15 (Visit 8), Day 29 (Visit 9), and Day 57 (Visit 10) (Table 1). Serial vital signs may be obtained to confirm accurate readings.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete PE will be performed at Screening (Visit 1) and Day 57 (Visit 10) (Table 1).

A complete PE will include weight and an assessment of head, eyes, ears, nose, and throat (HEENT), integumentary, gastrointestinal, cardiovascular, respiratory, muscular-skeleton, and neurological systems.

Documentation of the PE will be included in the source documentation at the site. Only changes from screening PE findings that meet the definition of an AE will be recorded on the Adverse Events CRF/eCRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

A 12-lead ECG will be completed at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1). ECGs may be performed at a convenient time during the visit. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. The ECG data recorded on the CRF/eCRF must include rate, rhythm, intervals, and QTc/QTcF.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs.

9.5.1.5.7 PREGNANCY TESTING

Serum pregnancy tests will be obtained in females of childbearing potential at Screening (Visit 1), Day 8 (Visit 7), and Day 57 (Visit 10) (Table 1).

A urine pregnancy test will be performed on females of childbearing potential before study medication application on Day 1 (Visit 2). Visit 1 and Visit 2 test results must be reviewed before dosing.

9.5.1.5.8 OTHER ASSESSMENTS

Concomitant Medications

Concomitant medications will be assessed at all clinic visits (Table 1). Any medication (including nonprescription medications) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication CRF/eCRF. The Investigator will record any AE on the Adverse Events CRF/eCRF for which the concomitant medication/therapy was administered.

Local Skin Reactions

At every post-Screening clinic visit through Day 57 (Visit 10), the Investigator or trained designee will assess any LSR on the treatment area for signs:

- Before study medication application (on dosing days)
- After the assessment of adverse events

The LSR assessment is the Investigator's (or trained designee's) assessment of the following signs on the treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a grading scale ranging from 0 (not present) to 4 (worst) (Table 5).

Table 5 Local Skin Reaction Grading Criteria

	Grading Criteria				
Local Skin Response	**0**	**1**	**2**	**3**	**4**
Erythema	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking / Scaling	Not present	Isolated scale, specific to lesion	Scale <50%	Scale >50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation / Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles <50%	Transudate or pustules, with or without vesicles >50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion / Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

Examples of LSR signs are shown in photographs in Appendix 2.

Application site reactions not classified as LSRs (eg, pruritus, pain, infection) will be reported as adverse events.

All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization.

Treatment for any LSR or interruption/discontinuation of study treatment for an LSR will be recorded on the CRF/eCRF.

LSRs will be reported separately from adverse events.

Pigmentation and Scarring

Hypo- and hyper- pigmentation and scarring on the treatment area will be assessed by the Investigator (or a trained designee) as being present or absent.

Pigmentation will be assessed at every post-Screening clinic visit through Day 57 (Visit 10) (Table 1).

Standardized Photography

Standardized photography will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 8 (Visit 7), Day 57 (Visit 10), and during the Recurrence Follow-up (at 3, 6, 9, and 12 months post-Day 57). Before study medication application on Day 1, the Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication.

Care must be taken to ensure the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph. Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

The photographs are to document the appearance of the subjects' treatment area and to assist with the identification and confirmation of the location of the treatment area throughout the study (Section 9.1.1).

Equipment, supplies and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

9.5.2 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in dermatology studies as well as in the routine clinical care of patients with actinic keratosis.

9.5.3 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.3.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event. Instructions will be provided in the Safety Management Plan.

All SAEs, regardless of causality assessment, must be collected through the last subject contact and followed to resolution or, if resolution is unlikely, to stabilization. SAEs reported to the site from the time of the last subject contact up to 30 days after the last contact, will be collected (ie, Day 57 plus 30 days). These SAEs will be discussed in the clinical study report. Any SAE event judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by electronically transmitting the completed SAE form.

The detailed contact information for reporting of SAEs is provided in the Safety Management Plan, located in the Investigator File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. All supporting documents should be sent de-identified and should contain the assigned subject number. Send only supporting documents directly related to the event.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

9.5.3.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy for which the estimated date of conception was either before the last visit or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs (see Section 9.5.3.1).

Pregnancies must be reported by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies is provided in the Investigator File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.3.3 Reporting of Other Events of Interest

9.5.3.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied.

Any study drug overdose should be noted on the Study Medication CRF/eCRF.

All AEs associated with overdose, or medication error should be captured on the Adverse Event CRF/eCRF and also reported using the procedures detailed in Section 9.5.3.1 even if the AEs do not meet serious criteria. If the AE associated with an overdose or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF/eCRF.

9.5.3.4 Expedited Reporting

The Sponsor (or its designee) must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

In determining what SAEs meet criteria for expedited reporting, the current version of the Investigator's Brochure will be used for reference safety information.

9.5.3.5 Breaking the Blind

Not applicable

9.5.3.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.4 Completion/Discontinuation of Subjects

A subject may elect to discontinue from the study at any time for any reason. See Section 9.3.3 for reasons why Investigators may discontinue subjects from the study. Investigators must document the actual reason(s) why they decided to discontinue subjects, or why subjects withdrew consent, as applicable. Study disposition information will be collected on the Disposition CRF/eCRF.

Subjects who withdraw from study treatment (with the exception of death or withdrawal of consent) will be encouraged to complete the Early Termination assessments at the time of withdrawal as indicated in Table 1. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF/eCRF.

9.5.5 Abuse or Diversion of Study Drug

Not applicable

9.5.6 Confirmation of Medical Care by another Physician

The Investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be documented in the subject source documentation, collected on the CRF/eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. A CRF/eCRF or a select CRF/eCRF page may be used as a source document. CRF/eCRFs used as source documents will be listed in the Data Management Plan. As defined by ICH E6 guidelines (Section 1.11), the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject. In this study, the CRF may refer to either a paper (CRF) or electronic data collection form (eCRF), or both.

Data collected on the CRF/eCRF must be completed following the instructions described in the CRF/eCRF Completion Guidelines, which will be based on the Data Management Plan. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF/eCRF. The PI must sign the CRF/eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs/eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

Responsible site personnel will enter the information required by the protocol onto the CRF/eCRFs in accordance with the CRF/eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to review the CRF/eCRFs for completeness and accuracy against the source documents. They will identify any discrepancies and ensure that appropriate site personnel address the discrepancies.

The original CRFs/eCRFs will be maintained at the site in a central document repository. If used, a copy of the CRF will be forwarded to the Sponsor.

At the end of the study an electronic copy of the database along with appropriate system version will be archived.

Uniform procedures will be discussed at the Investigator meetings or at site initiation and/or will be documented in the CRF/eCRF Completion Guidelines.

9.6.2 Clinical Data Management

All data, both CRF/eCRF and external data, will be loaded into a clinical system as specified in the Data Management Plan.

Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

9.7 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked. Statistical analyses will be performed using Phoenix WinNonlin and SAS software or other validated statistical software as required.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRF/eCRF, as well as any derived data will be included in data listings.

For all analyses, study Day 1 will be defined as the date of the first dose of study drug.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

The primary endpoint is activity.

Activity will be evaluated by reduction in lesion count. Complete response rate will be defined as the proportion of subjects achieving 100% complete clearance of all treated AK lesions on the face or scalp at Day 57. Sustained response will be defined as the proportion of subjects achieving 100% (complete) clearance at Day 57 without any identified AK lesions on the treatment area at 12 months post-Day 57.

9.7.1.1.2 SECONDARY ENDPOINTS

Activity

Reduction in lesion counts at each visit during Days 1-57 will be assessed as the secondary endpoint for activity.

Safety

Safety will be evaluated primarily by assessment of AEs and clinical laboratory data. The results of other safety assessments (vital signs, PEs, ECGs) will also be evaluated.

Pharmacokinetic

Secondary endpoints include the following PK parameters derived by noncompartmental analysis using the plasma concentration-time data of KX2-391: C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoint in the study is recurrence rate.

Recurrence rate will be defined as the proportion of subjects who achieved 100% complete clearance at Day 57 (Visit 10) with any identified AK lesions on the face or scalp at 3, 6, 9, and 12 months post-Day 57.

9.7.1.2 Definitions of Analysis Sets

The Per-Protocol Set is the group of protocol-eligible subjects who receive 5 days of study treatment and complete at least one scheduled post-treatment evaluation.

The Evaluable Set is the group of subjects who receive 5 days of treatment and complete most evaluations including the Day 57 Follow-up Visit.

The Safety Analysis/Full Analysis Set is the group of subjects who receive at least one dose of study treatment.

The PK Analysis Set is the group of subjects who receive study treatment and complete at least one scheduled post-treatment PK evaluation.

9.7.1.3 Subject Disposition

All subjects will be tabulated as to study discontinuation and the reasons for discontinuation as described in Section 9.3.3.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. For continuous demographic variables, results will be summarized and presented as N, mean, SD, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be used. No statistical testing will be performed.

9.7.1.5 Prior and Concomitant Therapy

All Investigator terms for medications recorded in the CRF/eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary drug codes.

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

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. Prior and concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of prior and concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All medications will be presented in subject data listings.

9.7.1.6 Activity Analyses

AK lesion counts will be summarized at Day 1 (pretreatment) and at each subsequent timepoint for subjects in the Full Analysis Set and the Per-Protocol Set.

A 95% confidence interval (CI) for the complete clearance (response rate) at Day 57 and 12 months post-Day 57 will be estimated in the Evaluable Set.

Recurrence rates for all subjects who achieved complete clearance at Day 57 will be summarized by timepoint in the Evaluable Set.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

PK analyses will be performed on the PK Analysis Set.

Plasma concentrations of KX2-391 will be analyzed to determine C_{max}, and where applicable, AUC_t, C_{min}, and accumulation ratio R.

Individual timepoints will be tabulated and displayed graphically and listed for all subjects. Summary PK parameters will be analyzed as applicable.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable

9.7.1.8 Safety Analyses

All subjects in the Safety Analysis Set will be included in the safety analyses.

Safety data will be summarized using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters, weight, vital signs, 12-lead ECG results, and physical examination findings

9.7.1.8.1 EXTENT OF EXPOSURE

The actual number of doses for each subject will be summarized.

9.7.1.8.2 ADVERSE EVENTS

For AEs, verbatim terms on the CRFs/eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0 or higher). Subject incidence of AEs will be displayed by SOC. Adverse events will also be summarized by severity and relationship to study drug. Subject incidence of SAEs will also be displayed.

Only those AEs that were treatment-emergent will be included in summary tables. Treatment-emergent AEs are defined as:

- either those AEs with an onset after dosing or
- those pre-existing AEs that worsen after dosing

All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint. Changes from baseline will also be summarized.

In addition, shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up.

9.7.1.8.4 VITAL SIGNS

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG data will be tabulated for each individual subject.

9.7.1.8.6 PHYSICAL EXAMINATIONS

Physical examination findings will be listed for each subject.

9.7.1.8.7 PREGNANCY TESTS

Results of pregnancy tests will be listed for all subjects, as applicable.

9.7.1.8.8 OTHER ANALYSES

Local Skin Reactions

Local skin reactions as reported by the Investigator will be displayed and summarized by visit for all subjects.

Pigmentation and Scarring

Pigmentation and scarring as reported by the Investigator will be displayed and summarized by visit for all subjects.

9.7.2 Determination of Sample Size

A sample size of 60 subjects is sufficient to detect a 100% complete 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% CI with a half-width of less than 15% (ie, lower boundary of the CI above 20%).

9.7.3 Interim Analysis

Since this is an open-label study, after each group of 20 subjects completes Day 57 assessments, activity data will be tabulated.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the prespecified plans need to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996.

2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1(8589):795-7.

3. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115(11):2523-30.

4. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000;42(1 Pt 2):23-4.

5. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42(1 Pt 2):4-7.

6. Guidelines for the Management of Actinic Keratoses. 2004/2005 European Dermatology Forum. Available from: http://www.euroderm.org [Accessed 02 July 2012].

7. Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for actinic keratoses. Committee on Guidelines of Care. J Am Acad Dermatol 1995;32(1):95-8.

8. Suchniak JM, Baer S, Goldberg LH. High rate of malignant transformation in hyperkeratotic actinic keratoses. J Am Acad Dermatol 1997;37(3 Pt 1):392-4.

9. Ehrig T, Cockerell C, Piacquadio D, et al. Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg 2006;32(10):1261-5.

10. Berman B, Bienstock L, Kuritzky L, et al. Primary Care Education Consortium; Texas Academy of Family Physicians. Actinic keratoses: sequelae and treatments. Recommendations from a consensus panel. J Fam Pract 2006;55(5 Suppl):1-8.

11. Quaedvlieg PJ, Tirsi E, Thissen MR, et al. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol 2006;16(4):335-9.

12. Marks R, Foley P, Goodman G, et al. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115(6):649-55.

11 APPENDICES

Appendix 1 Fitzpatrick Skin-Type Classification

Australian Government
Australian Radiation Protection and Nuclear Safety Agency

Fitzpatrick Skin Type

The most commonly used scheme to classify a person's skin type by their response to sun exposure in terms of the degree of burning and tanning was developed by Thomas B. Fitzpatrick*, MD, PhD. Examples are given below.

* Fitzpatrick, T.B. (1988) The validity and practicality of sun reactive skin types I through VI. Arch Dermatol 124; 869-871.

Eye colour
0. Light colours
1. Blue, gray or green
2. Dark
3. Brown
4. Black

Do you turn brown?
0. Never
1. Seldom
2. Sometimes
3. Often
4. Always

Natural hair colour
0. Sandy red
1. Blond
2. Chestnut or dark blond
3. Brown
4. Black

How brown do you get?
0. Never
1. Light tan
2. Medium tan
3. Dark tan
4. Deep dark

Your skin colour (unexposed areas)
0. Reddish
1. Pale
2. Beige or olive
3. Brown
4. Dark brown

Is your face sensitive to the sun?
0. Very sensitive
1. Sensitive
2. Sometimes
3. Resistant
4. Never have a problem

Freckles (unexposed areas)
0. Many
1. Several
2. Few
3. Rare
4. None

How often do you tan?
0. Never
1. Seldom
2. Sometimes
3. Often
4. Always

If you stay in the sun too long?
0. Painful blisters, peeling
1. Mild blisters, peeling
2. Burn, mild peeling
3. Rare
4. No burning

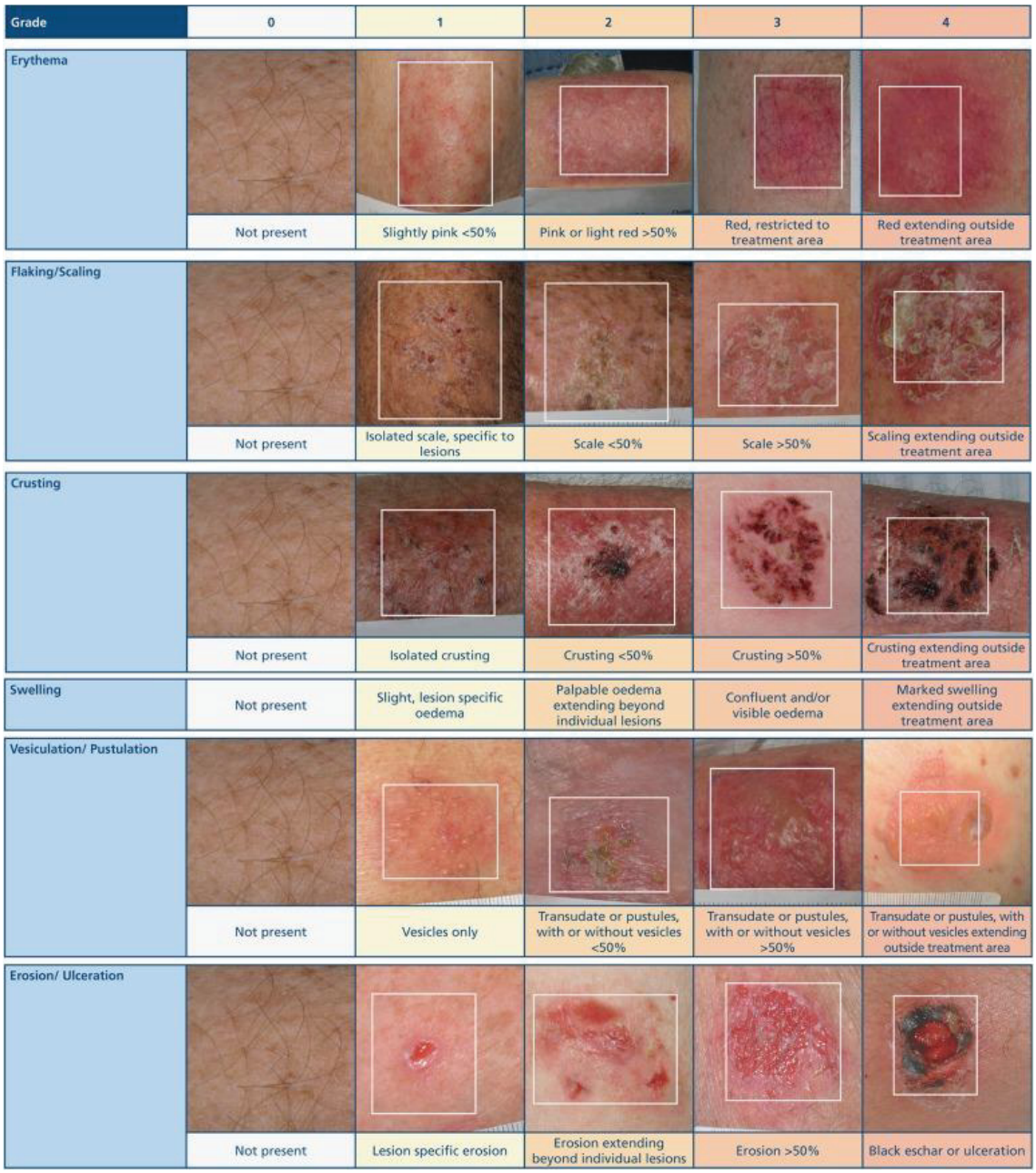
When was your last tan?
0. +3 months ago
1. 2–3 months ago
2. 1–2 months ago
3. Weeks ago
4. Days

Score		
0–6	Skin Type I	Always burns, never tans (pale white skin)
7–13	Skin Type II	Always burns easily, tans minimally (white skin)
14–20	Skin Type III	Burns moderately, tans uniformly (light brown skin)
21–27	Skin Type IV	Burns minimally, always tans well (moderate brown skin)
28–34	Skin Type V	Rarely burns, tans profusely (dark brown skin)
35+	Skin Type VI	Never burns (deeply pigmented dark brown to black skin)

Images sourced from iStockphoto

* The information published here is not intended to take the place of medical advice. Please seek advice from a qualified health care professional.

Appendix 2 Photographs of Local Skin Reactions



Source: (CDER) Clinical Review NDA 202833 PICATO™ (ingenol mebutate gel, PEP005 Gel) November 30, 2011.