REVISION HISTORY

Revisions to Version 1.0 (Original Protocol) **Current Version and Date: v2.0_18 Feb 2018 (Amendment 01)**		
Change	**Rationale**	**Affected Protocol Sections**
Revised lesion count wording during the Recurrence Follow-up Period to indicate that lesions 'within the treatment area' should be counted. Previously it was stated that lesions counted must be completely in the treatment area.	To address concern regarding possible underestimation of recurrence.	• Section 7.5.1
Deleted reference to analysis of treatment/location interaction to show concordance.	To provide clarification; the face and scalp will be analyzed as a whole; the face and scalp will also be analyzed separately to show consistency as to treatment location.	• Synopsis/Efficacy Analyses • Section 9.1.6.1
Provided language about pooling sites and additional analysis for site-to-site variability.	To address potential variability among sites.	• Synopsis/Efficacy Analyses • Section 9.1.6.1
Provided additional language about how recurrence rates will be analyzed.	Clarification of analysis for recurrence rate.	• Synopsis/Efficacy Analyses • Section 9.1.6.2
Added language for partial response rate analysis.	To address multiplicity issues for the secondary efficacy endpoint.	• Synopsis/Efficacy Analyses • Section 9.1.6.2
Revised subsection numbering for additional AK lesion count analysis.	Editorial.	• Section 9.1.6.3
Revised language regarding missing data handling/sensitivity and subgroup analyses.	Clarification for these efficacy analyses.	• Section 9.1.6.4 • Section 9.1.6.5
Deleted reduction in AK lesion count during Days 1-57 as a secondary objective/endpoint.	To limit the number of secondary objectives/endpoints being measured in the study.	• Synopsis - Secondary Objectives - Secondary Endpoints • Section 3.2 • Section 9.1.1.1.2
A urine pregnancy test, not a serum pregnancy test, will be conducted at Day 57/early termination visit, at the clinical site; pregnancy testing will be for women of childbearing potential.	Modification and clarification of pregnancy testing procedures.	• Table 1 • Section 7.3.5

Change	Rationale	Affected Protocol Sections
Standardized photography will be conducted at additional follow-up visits after Day 57 for subjects who have unresolved LSRs, hypo- or hyper-pigmentation, or scarring in the treatment area.	Clarification.	• Synopsis - Study Design - LSR assessments • Table 1/footnote b • Section 4.1 • Section 4.4 • Section 7.3.4.5 • Section 7.4
The complete physical examination at Screening will not include an assessment of the integumentary system, as that will be part of the expanded dermatological examination.	Clarification.	• Table 1/footnote g • Section 7.1.9
Information on study drug, label information, study kit dispensing, drug accountability, documentation, and instructions for requesting unblinding for medical emergencies or serious adverse events will be provided in a Pharmacy Manual, not a Clinical Operation Manual.	Clarification.	• Section 6.1.1 • Section 6.3 • Section 6.5.1 • Section 8.2.5
Medical history pertaining to actinic keratosis will include: • The initial diagnosis date of AK on the face or scalp, depending on the selection of the treatment area for the study • An AK treatment history of the face or scalp including all commercial and investigational products and surgical modalities dating back to the initial diagnosis.	Clarification.	• Section 6.4.1 • Section 7.1.4
Revised/reorganized the description of study endpoints.	Clarification.	• Synopsis/Statistical Methods/Endpoints • Section 3.2 • Section 9.1.1

TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	KX01-AK-003
Study Protocol Title:	A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp
Sponsor:	Athenex, Inc. 20 Commerce Drive Cranford NJ 07016, USA Tel: 908-340-6996
Investigational Product Name:	KX2-391 Ointment 1%
Indication:	Actinic keratosis on face or scalp
Phase:	3
Approval Date:	v1.0 29 Jun 2017 (original protocol) v2.0 18 Feb 2018 (Amendment 01)
IND Number:	122464
UTN Number:	U1111-1191-8233
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 Athenex, 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.

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 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp

Sites

Approximately 25 to 40 sites in the United States

Study Period and Phase of Development

First subject in to last subject out, approximately 20 months

Phase 3

Study Hypothesis

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

Objectives

Primary Objective

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

Secondary Objectives

- To evaluate the safety of topical KX2-391 Ointment 1% once daily for 5 consecutive days in terms of local skin reactions (LSRs) and other safety evaluations such as adverse events (AEs) and laboratory assessments
- To compare the rates of partial responders defined as ≥75% clearance of AK lesions in the treatment area on the face or scalp at Day 57 between the KX2-391 Ointment 1%-treated group and vehicle-treated group
- To determine the recurrence of AK in the treatment area up to 12 months post-Day 57 in subjects who had complete clearance at Day 57 after 5 consecutive days of treatment with KX2-391 Ointment 1%
- To evaluate the safety of topical KX2-391 Ointment 1% within the treatment area during the Recurrence Follow-up Period

Study Design

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

Enrollment will be controlled so that approximately two thirds of subjects enrolled will be treated on the face and approximately one third of subjects enrolled will be treated on the scalp.

The study consists of Screening, Treatment, Response Assessment Period, and a Recurrence Follow-up Period. After a Screening Period of up to 28 days, subjects will return to the site for confirmation of eligibility. Eligible subjects will be randomized on Day 1 to treatment in a 1:1 (KX2-391 Ointment 1% or vehicle) ratio in each treatment area subgroup.

The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site. Subjects will be given verbal and written instructions on self-administration of study drug/vehicle and a study kit containing 5 daily single-dose packets, 1 for each day of treatment. The first dose will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

Subjects will return to the clinical sites for assessments at the Response Assessment Visits on Days 5, 8, 15, 29, and 57.

All subjects who have unresolved LSRs, hypo- or hyper- pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up, which includes standardized photography of the treatment area, every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will continue in the Recurrence Follow-up Period to determine recurrence rate and safety for up to 12 months following the Day 57 Visit. Visits during the Recurrence Follow-up Period will occur every 3 months. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 300 subjects. At each site, a minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled.

Inclusion Criteria

1. Males and females ≥18 years old
2. A treatment area on the face or scalp that:
   - is a contiguous area measuring 25 cm^2
   - contains 4 to 8 clinically typical, visible, and discrete AK lesions
3. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - physical examination (PE) findings
   - vital signs
   - electrocardiogram (ECG), clinical chemistry, hematology, and urinalysis results
4. Females must be postmenopausal (>45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); 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 study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant, injection or patch, intrauterine device or complete abstinence from sexual intercourse.
5. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.

6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of study treatment.
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 randomization.
8. Willing to avoid excessive sunlight or ultraviolet (UV) light exposure, including the use of tanning beds, to the face or scalp
9. Able to comprehend and are willing to sign the informed consent form (ICF).

Exclusion Criteria

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area, eg, hypertrophic, hyperkeratotic, recalcitrant disease (had cryosurgery on two previous occasions) and/or cutaneous horn
2. Location of the treatment area is:
   - On any location other than the face or scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)
3. Been previously treated with KX2-391 Ointment
4. Anticipated need for in-patient hospitalization or in-patient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the treatment area or within 2 cm of the treatment area, within 8 weeks prior to the Screening visit
6. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the treatment area or within 2 cm of the selected treatment area
   - Topical salves (non-medicated/non-irritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Treatment with immunomodulators (eg, azathioprine), cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/interferon inducers
   - Treatment with systemic medications that suppress the immune system (eg, cyclosporine, prednisone, methotrexate, alefacept, infliximab)
8. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication
10. 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 unacceptable risk by study participation

11. 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
12. Females who are pregnant or nursing
13. 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

Study Treatments

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

Duration of Study

For the Screening, Treatment, and Response Assessment Periods, each subject will participate for up to 85 days: screening up to 28 days prior to Day 1, treatment for 5 consecutive days, and follow-up until Day 57. The Recurrence Follow-up Period will be for up to 12 months post-Day 57. Thus, the maximum overall duration of participation for each subject is approximately 15 months.

Concomitant Drug/Therapy

Use of any treatment for AK lesions other than study drug on the treatment area is prohibited during the study.

Assessments during the Treatment and Response Assessment Periods (Day 1 through Day 57)

Efficacy Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at Screening, Baseline (Day 1 predose), and at the Response Assessment Visits on Days 8, 15, 29, and 57.

Safety Assessments

Safety will be assessed periodically through Day 57 by recording AEs, serious adverse events (SAEs), LSRs, and events of special interest.

Safety assessments will also include vital signs, the performance of PEs, ECGs, laboratory evaluation of hematology, biochemistry, and urinalyses, and evaluation of pigmentation and scarring in the treatment area at prespecified timepoints (Table 1, Schedule of Procedures and Assessments).

At each study visit, subjects will be asked a general question "How have you been since the last visit?". Adverse events will be recorded at each study visit, before assessment of LSRs, pigmentation, and scarring in the treatment area. AEs will be reported separately from LSRs.

LSR Assessments

The LSR assessment is the Investigator's (or Subinvestigator'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=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). 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, itching, burning, stinging, tenderness, pain) will be reported as AEs. Standardized photography will be performed on Day 1 prior to dosing, and on Days 5, 8, 15, 29, and 57, and at additional follow-up visits for subjects who have unresolved LSRs, hypo- or hyper- pigmentation, or scarring in the treatment area.

Events of Special Interest

- Overdose of study medication
- Pregnancy
- Ocular exposures to study medication
- Skin cancers (including BCC, SCC, and melanoma); the location and treatment will be reported.

Assessments during the Recurrence Follow-up Period (up to 12 months post-Day 57)

Efficacy Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits.

Safety Assessments

During the Recurrence Follow-up Period, safety assessments will include the monitoring and recording of AEs and SAEs within the treatment area at the 3-, 6-, 9- and 12-month visits.

Events of Special Interest

- Skin cancers (including BCC, SCC, and melanoma) within the treatment area
- Pregnancy

Statistical Methods

Efficacy:

Primary Endpoint

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

Secondary Endpoints

Key Secondary Endpoint:

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

Additional Endpoint:

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

Safety:

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs)
- AEs within the treatment area after Day 57 and up to 12 months post-Day 57

Analysis Populations

Intent-To-Treat (ITT) Population: all randomized subjects. This is the primary efficacy population.

Per-Protocol (PP)/Evaluable Population: all randomized subjects who have received at least 4 of the 5 doses, conformed to the protocol as to entry criteria, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.

Safety Population: all randomized subjects who have received at least one dose of study treatment.

Recurrence Follow-up Population: all subjects who achieved complete clearance at Day 57, regardless of which treatment they received.

Efficacy Analyses

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

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

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

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

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

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

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

Recurrence rates will be estimated based on a Kaplan-Meier method at each nominal post-Day 57 visit. Subjects with missing AK assessments in the Recurrence Follow-up Period will be considered as censored.

Safety Analyses

For AEs, verbatim terms on the electronic case report form (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).

Treatment-emergent adverse events (TEAEs) are defined as either those AEs with an onset after the first dose or those pre-existing AEs that worsen after the first dose. The incidence of TEAEs will be summarized by treatment group. TEAEs will also be summarized by severity and relationship to study treatment. By-subject listings of all SAEs and events of special interest will be provided.

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by treatment group. Changes from baseline will also be summarized by treatment group. 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 Day 8 and baseline to Day 15 in each treatment group. LSR, hyper- or hypo-pigmentation and scarring assessment results obtained through Day 57 will be displayed and summarized by visit and treatment group. Safety data collected through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.
Interim Analyses No interim analysis is planned for this study.
Sample Size Rationale The sample size was estimated based on the primary efficacy endpoint for the comparison of KX2-391 Ointment 1% and vehicle control. By using a Pearson Chi-square method, a sample size of 100 scalp-treated subjects and 200 face-treated subjects, both of which are with a 1:1 treatment allocation ratio, will give a greater than 90% power to detect a 20% difference (30% for active treatment and 10% for vehicle control) with a two-tailed significant level 0.05.
FINAL: v2.0_18 Feb 2018

SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 1 Schedule of Procedures and Assessments in KX01-AK-003

Period	Screening	Treatment		Response Assessment					Recurrence Follow-up[a]
Clinic Visit	1	2	At home once-daily self-administration of treatment	3	4	5	6	7 / Early Term[b]	8, 9, 10, 11[a]
Day	-28 to -1	1 Baseline	2-5	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Visit time window (days)	None	None		None	±2	±2	±3	±5	±14
Informed consent	X								
Inclusion & exclusion criteria	X	X[d]							
Demographics	X								
Medical/surgical history	X								
AK history/AK treatment history	X								
Prior and concomitant medications/therapies	X	X[d]		X	X	X	X	X	X
Fitzpatrick skin-type scale	X								
Expanded dermatological exam[e]	X								
Treatment area identification	X	X[d,f]							
AK lesion count in treatment area	X	X[d]			X	X	X	X	X
Physical examination, including weight and height[g]	X							X	
Vital signs[h]	X	X[d]		X				X	
ECG[i]	X	X[d]		X		X			
Clinical chemistry, hematology, and UA	X[j]				X	X			
Serum pregnancy test for WOCBP	X				X				
Urine pregnancy test for WOCBP		X[k]						X	
AEs[l]	X	X[d]		X	X	X	X	X	X[m]
Focused dermatological exam of treatment area		X[d]		X	X	X	X	X	
LSRs		X[d]		X	X	X	X	X	
Pigmentation and scarring		X[d]		X	X	X	X	X	

Table 1 Schedule of Procedures and Assessments in KX01-AK-003

Period	Screening	Treatment		Response Assessment					Recurrence Follow-up[a]
Clinic Visit	1	2	At home once-daily self-administration of treatment	3	4	5	6	7 / Early Term[b]	8, 9, 10, 11[a]
Day	-28 to -1	1 Baseline	2-5	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Standardized photography		X[d]		X	X	X	X	X	
Randomization		X							
Instructions for self-administration; dispense study medication		X[d]							
Study medication application		X	X						
Study drug / dosing log return				X[n]					

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; Term = Termination; UA = urinalysis; WOCBP = women of child-bearing potential.

a. For Day 57 complete responders only
b. These are assessments to be completed by all subjects. For those who do not have complete response at Day 57 or who are discontinued early from the study, this will be their final visit. All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up, which includes standardized photography of the treatment area, every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.
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 assessments at the visit when the AK recurrence is identified.
d. These are baseline procedures/assessments and will be performed before randomization.
e. An expanded dermatological examination to cover the sun-exposed areas where photo-damage is likely will be conducted at Screening only.
f. The location and shape of the treatment area will be marked on an acetate transparency sheet for recording purposes and on the subject's skin for identification of the treatment area for daily self-administration of study ointment.
g. A complete PE will include weight and an assessment of HEENT, integumentary (Day 57 only), gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height will be measured at Screening only. This will be considered the baseline assessment.
h. Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.
i. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. Baseline ECG is performed predose.
j. This will be considered the baseline assessment.
k. For females of childbearing potential: urine pregnancy test on Day 1 before randomization.
l. At each study visit, subjects will be asked a general question "How have you been since the last visit?". AEs will be recorded before assessment of LSRs, pigmentation, and scarring in the treatment area. AEs will be reported separately from LSRs.
m. Only AEs in the treatment area will be collected.
n. On Day 5 (Visit 3), subjects are to come into the clinic after study treatment is self-administered. Subjects are to bring all 5 study drug packets (used and unused) in the study kit and the dosing log back to the site.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Terms
AE	adverse event
AK	actinic keratosis
BCC	basal cell carcinoma
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRA	clinical research associate
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
IRB	Institutional Review Board
ITT	Intent-To-Treat
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
PE	physical examination
PP	Per-Protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
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)

1 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Athenex, Inc. (the Sponsor) at approximately 25 to 40 investigational sites in the United States (US).

The name, telephone number, and email address of the Medical Monitor and other contact personnel at the Sponsor are listed in the Regulatory Binder provided to each site.

2 INTRODUCTION

2.1 Background

2.1.1 Indication

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

2.1.2 Mechanism of Action

KX2-391 (referred to as KX01 in study protocol numbers) 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 AK. KX2-391 is also being developed as an oral agent for oncology indications.

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. 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.

2.1.3 Nonclinical Studies

Details regarding KX2-391 nonclinical studies are provided in the KX2-391 Ointment Investigator's Brochure.

The bioavailability of KX2-391 after dermal administration to rats (1.59%) and rabbits (2.49% to 6.47%, depending on concentration) was low. Plasma concentrations of KX2-391 increased with repeat dermal administration, and in rats the plasma levels after 6 days dermal dosing reached or exceeded levels produced by oral administration of KX2-391 at the no observed adverse effect level (NOAEL) dose (1.25 mg/kg/dose) in a 28-day twice-daily oral toxicity study. Following 28 days of KX2-391 topical administration at increasing doses

(0.1%, 1%, and 2%) in rats and minipigs, an increase in KX2-391 plasma exposure was observed from Day 1 to Day 28, suggesting slight drug accumulation.

In 28-day repeat-dose toxicology studies, KX2-391 ointment was administered to rats and minipigs at dose strengths 0.1%, 1%, and 2%. Ointment volumes of 2 mL/kg body weight were applied to approximately 10% of the body surface area of the skin. The administration sites were occluded with gauze and the applications left for 8 h/day in rats. The application site was semi-occluded for 20-22 hours in minipigs. These doses contained 2, 20, or 40 mg/kg KX2-391, respectively, equivalent to 12, 120, or 240 mg/m^2 in rats and 70, 700, or 1400 mg/m^2 in minipigs. Systemic exposures on Day 28 to KX2-391 following daily application of 0.1% ointment were C_{max} 22.9 ng/mL (male)/33.7 ng/mL (female) and $AUC_{0\text{-}24h}$ 205 h*ng/mL (male)/216 h*ng/mL (female) in rats, and C_{max} 2.03 ng/mL (male)/7.25 ng/mL (female), $AUC_{0\text{-}24h}$ 37.4 h*ng/mL (male)/65.5 h*ng/mL (female) in minipigs. Exposure (AUC) in humans was not calculated due to the lack of quantifiable plasma concentrations following topical KX2-391 administration. However, the maximum C_{max} value at the NOAEL in rats and minipigs is approximately 24 and 5 times greater than the maximum plasma KX2-391 concentration of 1.42 ng/mL achieved in the clinic (Study KX01-AK-002).

Other dermal toxicity studies with KX2-391 showed that KX2-391 ointment may be sensitizing to the skin (Buehler assay and murine local lymph node assay), that KX2-391 ointment was negative for phototoxicity, and that KX2-391 ointment was an irritant to the eyes of rabbits after single application (effects cleared within 3 days post dose).

KX2-391 was negative in a bacterial mutagenicity study (Ames test). KX2-391 caused chromosomal aberrations in Chinese Hamster Ovary (CHO) cells at very high doses that are not likely to be clinically relevant.

Studies of the effects of KX2-391 oral on reproduction and fetal development have been performed. In embryo-fetal development studies in rats and rabbits, KX2-391 was administered orally in order to increase systemic exposure. Embryo and fetal toxicity, including implantation loss and fetal malformations, occurred at oral doses of ≥1.25 mg/kg (rats) and 3 mg/kg (rabbits). The no-effect doses for fetal and reproductive effects were 0.5 mg/kg (rats) and 1 mg/kg (rabbits). At these doses, maternal C_{max} and $AUC_{0\text{-}8\ h}$ systemic exposures to KX2-391 were 25.4 ng/mL and 82.4 h*ng/mL (rats, Day 17) and 144 ng/mL and 251 h*ng/mL (rabbits, Day 18), respectively. Systemic plasma exposure (AUC) in humans could not be determined due to the lack of quantifiable plasma concentrations across multiple timepoints. However, maternal C_{max} values at the NOAEL in rats and rabbits are approximately 18 and 100 times greater than the highest KX2-391 plasma concentration achieved clinically of 1.42 ng/mL (Study KX01-AK-002).

2.1.4 Clinical Experience with KX2-391

2.1.4.1 KX2-391 in Cancer (Oral)

KX2-391 has been administered orally as a treatment for cancer to approximately 120 patients with various types of malignancies in 4 clinical studies sponsored by Athenex, Inc. A summary of the safety information from these patients is provided in an appendix of the KX2-391 Ointment Investigator's Brochure.

Due to the differences in route of administration and short duration of treatment (5 days), topical KX2-391 has minimal systemic exposure and is not likely to have the same toxicity profile as oral KX2-391.

2.1.4.2 KX2-391 as a Topical Treatment for Actinic Keratosis

To date, 2 clinical studies have been conducted to evaluate the activity and safety of KX2-391 Ointment 1% in subjects with AK.

Study KX01-AK-01-US, a Phase 1, safety, tolerability, and pharmacokinetic study, demonstrated that KX2-391 Ointment 1% was well-tolerated and showed clinical activity in 30 adults with AK on dorsal forearm when given at 50 or 200 mg daily over 3 or 5 consecutive days in an area of 25 or 100 cm^2. Most subjects experienced mild to moderate and transient local skin reactions (LSRs). The majority of the LSRs observed were erythema and flaking/scaling that peaked around Day 5-10, before returning to or close to baseline. Symptoms of pruritus, stinging, and burning at the treatment area were generally mild and transient. There were no serious adverse events (SAEs) or deaths, and no subjects discontinued due to an adverse event (AE).

Study KX01-AK-002, an ongoing Phase 2a, open-label, sequential group study, evaluated the activity and safety of KX2-391 Ointment 1% when applied daily in a treatment area of 25 cm^2 for 3 consecutive days (n=84 subjects) or 5 consecutive days (n=84 subjects) in adults with AK on face or scalp. Preliminary data showed that most of the 168 subjects treated had mild to moderate LSRs (primarily erythema and flaking/scaling. Eleven (6.5%) subjects had 16 treatment-emergent adverse events (TEAEs) considered treatment-related by the Investigator. Eight of these subjects had mild application site reactions including pruritus, tenderness, or stinging. The remaining AEs considered by the Investigator to be treatment-related were mild headache, mild to moderate dizziness, mild arthralgia, or mild darkening of hair color near the treatment area. All treatment-related TEAEs resolved prior to or stabilized by Day 57. Four subjects reported 5 treatment-emergent SAEs. All SAEs were considered unrelated to study drug. No subject discontinued treatment due to AEs.

Thirty-six of 84 subjects (43%) in the 5-day regimen and 27 of 84 subjects (32%) in the 3-day regimen had 100% clearance of AK lesions in the treatment area on Day 57.

Plasma concentrations of KX2-391 were measured in Study KX01-AK-002 using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 0.1 ng/mL. Pharmacokinetic results showed that following 3 or

5 consecutive days of treatment with KX2-391 Ointment 1%, low systemic exposure (< 2 ng/mL) and limited drug accumulation were observed.

Details of both studies are available in the KX2-391 Ointment Investigator's Brochure.

2.2 Study Rationale

Actinic keratosis represents 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.[1,2] The risk of progression has been determined to be between 0.025% and 16% per year,[1,3] and the calculated lifetime risk of malignant transformation for a patient with AK lesions followed up for 10 years is between 6.1% and 10.2%.[4] The rationale behind treating every AK lesion is based on the difficulty in predicting which single AK lesion will progress to SCC.[5,6] The goal of treatment is to completely eliminate AK lesions, thereby minimizing their risk of progression to invasive SCC, and reducing the potential to metastasize and cause death, while obtaining the best cosmetic outcomes.

2.3 Potential Risks and Benefits

Preliminary results of studies KX01-AK-01-US and KX01-AK-002 indicate that KX2-391 Ointment 1% administered once daily for up to 5 days demonstrates clinically relevant activity in the treatment of AK lesions on both the face and scalp, as well as on the dorsal forearm. Data from KX01-AK-002 suggest that the 5-day regimen of KX2-391 Ointment 1% has greater activity (43%) than the 3-day regimen (32%).

Preliminary safety results from both studies showed that KX2-391 Ointment 1% is safe and well tolerated. Even though LSRs (primarily erythema and/or flaking/scaling) were reported by the majority of treated subjects, they were generally mild or moderate in severity and mostly transient. The treatment-related TEAEs that subjects experienced mainly consisted of mild application site reactions such as itching, burning, stinging, tenderness, and pain. No subjects discontinued treatment due to AEs and no treatment-related SAEs were reported. Based on these findings, the clinical benefit of treating actinic keratosis, a precancerous condition, with a short course of topical KX2-391 outweighs the risk of transient LSRs observed.

At systemic KX2-391 concentrations that were significantly higher than those observed following topical administration in humans, KX2-391 was associated with testicular toxicity in multiple-dose nonclinical toxicity studies in animals. As a precaution, male subjects must agree to practice medically acceptable contraception during study participation and for at least 90 days after stopping treatment.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoint

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

The primary endpoint will be complete (100%) clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area.

3.2 Secondary Objectives and Endpoints

The secondary objectives of the study are:

- To evaluate the safety of topical KX2-391 Ointment 1% once daily for 5 consecutive days in terms of LSRs and other safety evaluations such as AEs and laboratory assessments
- To compare the rates of partial responders defined as ≥75% clearance of AK lesions in the treatment area on the face or scalp at Day 57 between the KX2-391 Ointment 1%-treated group and vehicle-treated group
- To determine the recurrence of AK in the treatment area up to 12 months post-Day 57 in subjects who had complete clearance at Day 57 after 5 consecutive days of treatment with KX2-391 Ointment 1%
- To evaluate the safety of topical KX2-391 Ointment 1% within the treatment area during the Recurrence Follow-up Period.

The secondary endpoints are:

Efficacy:

Key Secondary Endpoint:

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

Additional Endpoint:

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

Safety:

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])
- AEs within the treatment area after Day 57 up to 12 months post-Day 57

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

Enrollment will be controlled so that approximately two thirds of subjects enrolled will be treated on the face and approximately one third of subjects enrolled will be treated on the scalp. A sufficient number of subjects will be screened to randomize approximately 300 subjects. At each site, a minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled.

The study consists of Screening, Treatment, a Response Assessment Period, and a Recurrence Follow-up Period. After a Screening Period of up to 28 days, subjects will return to the site for confirmation of eligibility. Eligible subjects will be randomized on Day 1 to treatment in a 1:1 (KX2-391 Ointment 1% or vehicle) ratio in each treatment area subgroup.

The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site. Subjects will be given verbal and written instructions on self-administration of study drug/vehicle and a study kit containing 5 daily single-dose packets, one for each day of treatment. The first dose will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

Subjects will return to the clinical sites for assessments at the Response Assessment Visits at Days 5, 8, 15, 29, and 57.

All subjects who have unresolved LSRs, hypo- or hyper- pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up, which includes standardized photography of the treatment area, every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will continue in the Recurrence Follow-up Period to determine recurrence rate and safety for up to 12 months following the Day 57 Visit. Visits during the Recurrence Follow-up Period will occur every 3 months. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

An overview of the study design is presented in Figure 1.

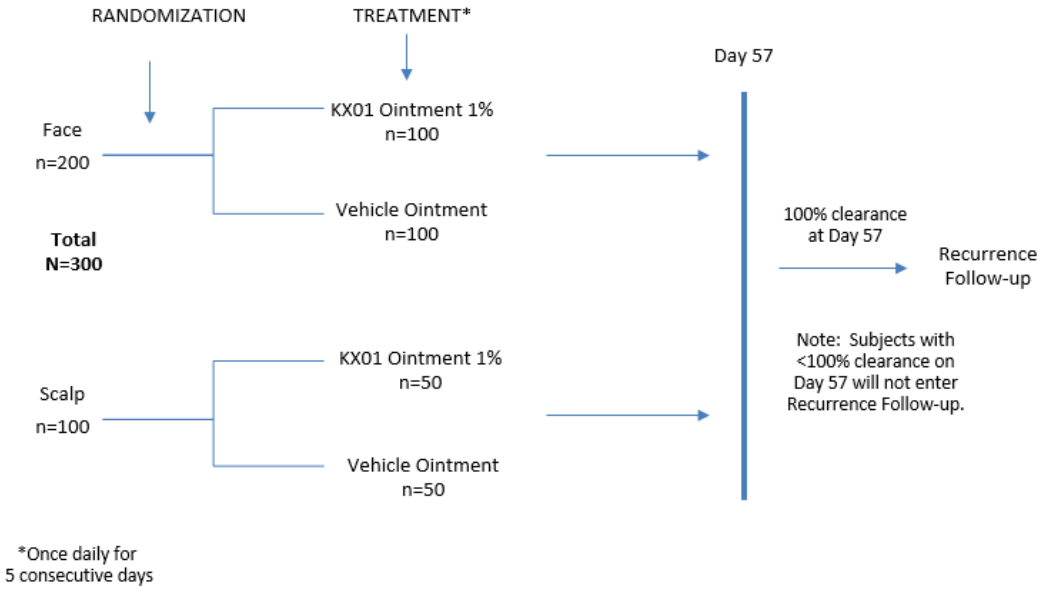

Figure 1 Study Design for KX01-AK-003

4.2 Screening Period

Screening (Visit 1) will occur between Day –28 and Day –1. Subject eligibility will be established during the Screening Period.

Details of screening procedures/assessments are provided in Section 7.1.

4.3 Treatment Period

The Treatment Period will be Days 1 to 5. Protocol eligibility will be confirmed at Baseline (Day 1 predose).

All screening and baseline assessments should be evaluated for acceptability prior to randomization of the subject. Eligible subjects will be randomized separately for face and scalp to treatment in a 1:1 ratio of KX2-391 Ointment 1% or vehicle (see Section 6.3).

Baseline and Treatment Period procedures and assessments, and timing thereof, are shown in Table 1; details are provided in Section 7.2 and Section 7.3, respectively.

4.4 Response Assessment Period

Subjects will return to the clinical sites for Response Assessment Visits postdose on Day 5 (Visit 3) and on Days 8, 15, 29, and 57 (Visits 4 through 7). Procedures and assessments and timing thereof during the Response Assessment Period are shown in Table 1 and the details are provided in Section 7.3.

All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up, which includes standardized photography of the treatment area, every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

4.5 Recurrence Follow-up Period

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will be eligible to continue in the Recurrence Follow-up Period to determine AK recurrence rates and evaluate concomitant medications and AEs in the treatment area for up to 12 months post-Day 57.

Procedures and assessments and timing thereof during the Recurrence Follow-up Period are shown in Table 1 and the details are provided in Section 7.5. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

4.6 Discussion of Study Design, Including Choice of Dosing and Control Groups

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel group, efficacy and safety study of KX2-391 Ointment 1% administered topically on the face or scalp of adult subjects with AK for 5 consecutive days.

The dosing regimen for this study is based on the Phase 2a study (KX01-AK-002). KX01-AK-002 is an open-label, sequential group, non-randomized, multi-center study that evaluated the dosing regimen of daily dosing for either 3 or 5 consecutive days of KX2-391 Ointment 1% on a treatment area of 25 cm^2 on the face or scalp that contained 4 to 8 AK lesions in 168 adults (84 subjects per cohort). Preliminary analyses showed that a higher percentage of subjects achieved complete clearance of AK on Day 57 for the 5-day treatment group (43%) than the 3-day treatment group (32%). For both the 5-day and 3-day treatment groups, KX2-391 Ointment 1% was found to be safe, well tolerated and minimally absorbed throughout treatment and follow up for both cohorts. Thus, these data support the evaluation of KX2-391 Ointment 1% once daily topical application for a 5-consecutive day dosing regimen for the treatment of adults with AK on the face or scalp in this Phase 3 double-blind, vehicle-controlled study. The 12-month Recurrence Follow-up Period allows for long-term evaluation of AK recurrence rates and safety.

5 STUDY POPULATION

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

A sufficient number of subjects will be screened to randomize approximately 300 subjects at approximately 25 to 40 sites. A minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled at each site.

5.1 Inclusion Criteria

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

1. Males and females ≥18 years old
2. A treatment area on the face or scalp that:
   - is a contiguous area measuring 25 cm^2
   - contains 4 to 8 clinically typical, visible, and discrete AK lesions
3. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - physical examination (PE) findings
   - vital signs
   - ECGs, clinical chemistry, hematology, and urinalysis results
4. Females must be postmenopausal (>45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); 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 study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant, injection or patch, intrauterine device or complete abstinence from sexual intercourse.
5. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of study treatment.
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 randomization.
8. Willing to avoid excessive sunlight or ultraviolet (UV) light exposure, including the use of tanning beds, to the face or scalp
9. Able to comprehend and are willing to sign the informed consent form (ICF).

5.2 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, eg, hypertrophic, hyperkeratotic, recalcitrant disease (had cryosurgery on two previous occasions) and/or cutaneous horn
2. Location of the treatment area is:
   - On any location other than the face or scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected basal cell carcinoma (BCC) or SCC
3. Been previously treated with KX2-391 Ointment
4. Anticipated need for in-patient hospitalization or in-patient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the treatment area or within 2 cm of the treatment area, within 8 weeks prior to the Screening visit
6. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the treatment area or within 2 cm of the selected treatment area
   - Topical salves (non-medicated/non-irritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Treatment with immunomodulators (eg, azathioprine), cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/interferon inducers
   - Treatment with systemic medications that suppress the immune system (eg, cyclosporine, prednisone, methotrexate, alefacept, infliximab)
8. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication

10. 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 unacceptable risk by study participation
11. 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
12. Females who are pregnant or nursing
13. 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

5.3 Subject Withdrawal / Discontinuation Criteria

The Investigator may withdraw a subject from 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 must document the reason for discontinuing a subject from treatment or from the study if known, or why the subject withdrew consent, if applicable. Subject disposition information will be collected on the electronic case report form (eCRF).

Subjects who do not complete 5 days of treatment and withdraw from study treatment (for reasons other than death or withdrawal of consent) will be encouraged to continue the post-treatment visits. At the time of withdrawal from the study, the subject should complete the early termination assessments (Day 57 assessments) (Table 1). A subject who does not return for the post-treatment visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the eCRF.

Subjects who discontinue early from the study will be discontinued for one of these primary reasons:

- AE(s)
- Lost to follow-up
- Withdrawal of consent (subjects will be asked but not required to provide a reason)
- Study terminated by Sponsor
- Noncompliance (specify)
- AK recurrence during the Recurrence Follow-up Period prior to the 12-month visit
- Investigator decision (specify)
- Death
- Other (specify)

Subjects who do not achieve 100% clearance of AK lesions in the treatment area at Day 57 will be considered to have completed their participation in the study.

6 STUDY TREATMENTS

6.1 Identity of Study Drugs

Treatments administered will be topical KX2-391 Ointment 1% and vehicle ointment.

6.1.1 Formulation, Packaging, and Labeling

KX2-391 Ointment 1% will be supplied in single-use packets, each of which contains 250 mg of the ointment, equivalent to 2.5 mg of KX2-391 free base. Vehicle ointment will be supplied in the same single-use packets, each of which contains 250 mg of the ointment without the active drug. Each packet is for use as a single-dose application. Complete formulation contents for both KX2-391 Ointment 1% and vehicle ointment are provided in the KX2-391 Ointment Investigator's Brochure.

Each eligible randomized subject will be assigned an enrollment number and a study kit with the same enrollment number. The study kit will contain 5 packets filled with either KX2-391 Ointment 1% or vehicle ointment. Each packet and study kit will be labeled in accordance with national regulations. Detailed information regarding the study drugs, including labeling information, will be in the Pharmacy Manual provided to the site.

The following treatments will be administered to subjects in this study (Table 2).

Table 2 Treatments in KX01-AK-003

Investigational Product	Strength	Size of Treatment Area	Number Applications and Frequency	Study Days Administered
KX2-391 Ointment 1%	1%	25 cm^2	1 application once daily for 5 consecutive days	Days 1-5
Vehicle Ointment	N/A	25 cm^2	1 application once daily for 5 consecutive days	Days 1-5

N/A = not applicable

6.1.2 Storage Conditions

Study drug will be stored in accordance with labeled storage conditions.

6.2 Dosage and Administration of Study Drugs

6.2.1 Administration of Study Drugs

At Baseline (Day 1 predose), subjects will receive verbal and written instructions on how to apply the topical medication and how to care for the treatment area (Appendix 1).

The study medication is for external topical use on the treatment area. The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site (see Section 7.2.3). Subjects will be provided with a study kit comprised of individual plastic bags with 5 single-dose packets containing either KX2-391 Ointment 1% or vehicle ointment and a dosing log.

The first dose will be administered by the subject under the supervision of study personnel on Day 1 at the site. Subjects will self-administer the remaining single-dose packets once daily at home for the next 4 consecutive days. Study medication should be applied each day at approximately the same time. It is preferable that study drug application is done early in the day. The treatment area should not be touched or wet for approximately 12 hours after application.

See Appendix 1 for subject instructions for study drug application. It is imperative that subjects wash hands **immediately** with water and soap after applying the ointment. The subject instructions also contain additional details including precautions associated with ointment application during the 5 days of treatment and throughout the study.

6.2.1.1 Instructions in the Event of Ocular Exposure

Subjects will be instructed to avoid getting ointment in their eyes. If ointment does get in the eyes, the subject is to flush their eyes with water immediately and extensively. The subject must immediately contact the Investigator who will provide further instructions and will refer

the subject to an ophthalmologist. The ophthalmologist's assessment will be included in the report of ocular exposure as an event of special interest (see Section 8.2.3).

6.2.2 Criteria for Interruption of Treatment/Dose Adjustments

Not applicable; dose adjustment is not allowed.

6.3 Randomization/Method of Assigning Subjects to Treatment Groups

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

Subjects will be assigned to treatments in a double-blinded manner based on a computer-generated randomization scheme. Based on the randomization scheme, 2 lists of enrollment numbers will be issued to each site; one list will be for subjects with the treatment area on the face and the other list will be for subjects with the treatment area on the scalp. Study kits bearing corresponding enrollment numbers will be provided to the site. One set of kits will be provided for subjects with the treatment area on the face and the second set of kits will be provided for subjects with the treatment area on the scalp.

Enrollment numbers and study kits are distributed sequentially. The first eligible subject with AK lesion on the face will be assigned the first enrollment number for treatment of the face and given a study kit bearing the same enrollment number on Day 1 of treatment. The next eligible subject with AK lesions on the face will receive the next enrollment number and corresponding study kit in a sequential order.

The same procedure will occur for subjects with the treatment area on the scalp. On Day 1, the first eligible subject with AK lesions on the scalp will be assigned the first enrollment number for treatment on the scalp and given a study kit bearing the same enrollment number. The next eligible subject with AK lesions on the scalp will receive the next enrollment number and corresponding study kit in a sequential order.

Refer to the Pharmacy Manual for details of procedures of study kit dispensing and documentation.

6.3.1 Blinding

The Sponsor, contract research organizations (CROs) involved in the clinical conduct of the study, the Investigators, study site personnel and study subjects will be blinded to the treatment that is assigned to each subject. The integrity of this clinical study must be maintained by observing the treatment blind. See Section 8.2.5 for breaking the blind.

6.4 Prior and Concomitant Medications / Therapy

6.4.1 Prior Medications / Therapy

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and procedures taken 28 days before Day 1 are considered prior therapy and will be recorded in the eCRF. An AK treatment history of the face or scalp will be recorded on the AK Treatment History eCRF (see Section 7.1.4).

6.4.2 Concomitant Medications/Therapy

Concomitant medication/therapies are any new or existing therapy received by the subject after signing the ICF through the final subject contact in the study. Concomitant medication/therapies will be recorded in the eCRF.

Use of sunblock from Day 15 onward or any topical products for treatment of LSRs in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication eCRF up to Day 57.

During the Recurrence Follow-up Period, sunblock and non-medicated topical products can be used in the treatment area. During the Recurrence Follow-up Period, only concomitant medications/therapies for the treatment of AEs in the treatment area and those that may affect the assessment of AK lesion recurrence in the treatment area will be entered in the eCRF.

6.4.3 Prohibited Medication/Therapy

Use of any treatment for AK lesions other than study drug on the treatment area is prohibited during the study. Subjects will be reminded that AK lesions located outside the treatment area may be treated by lesion-directed treatment only, eg, cryotherapy or biopsy.

Prohibited medications are as 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, photodynamic therapy, psoralen plus UVA or UVB therapy, artificial tanner, excessive or prolonged exposure to UV light source.[9]

Subjects are prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments, moisturizers, sunscreen, artificial tanners, or make-up to the treatment area up until the end of Day 57 (Visit 7), except when those medications are prescribed by the Investigator for the management of LSRs. Subjects should avoid direct sun or UV exposure to the treatment area throughout the study. However, 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.

During the Recurrence Follow-up Period, use of treatments that may interfere with the assessment of AK recurrence in the treatment area are prohibited. This includes use of AK treatment and medicated topical products in the treatment area and use of systemic therapies (eg, immunosuppressive agents and systemic AK treatment) that may interfere with the assessment of AK recurrence.

Any subjects who start systemic or topical therapies for the treatment of AK 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.

6.4.4 Other Prohibitions and Restrictions during Study

There are no restrictions during the study on smoking/tobacco use, diet, alcohol/caffeine, water or other beverages, or physical activity.

After self-application, subjects will avoid touching or wetting the treatment area for approximately 12 hours. When washing the treatment area, wash it gently with a mild, non-abrasive, non-medicated soap or shampoo.

The treatment area should not be occluded with bandages, band aids, tight-fitting scarfs or caps. The treatment area should not be exposed to excessive sunlight or UV light. See Appendix 1 for all prohibited activity.

6.5 Drug Accountability and Treatment Compliance

6.5.1 Drug Supplies and Accountability

Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (eg, shipment, dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional 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.

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 (or its designee).

The clinical research associate (CRA) will review drug accountability during monitoring site visits.

The Investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply. Post-Day 57, and as appropriate during the study, the Investigator (or a designated pharmacist) will return all used and unused drug packets, study kits, drug labels, and a copy of the completed drug disposition form to the clinical supply vendor.

Refer to the Pharmacy Manual for instructions and contact information.

6.5.2 Treatment Compliance

Subjects will return the used ointment packets (or unused ointment, if not administered) back to the clinical site on Day 5 (Visit 3) postdose, to check compliance.

The dosing logs for each subject will be kept during the study. The CRAs will review treatment compliance during monitoring site visits.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Screening Assessments

All screening assessments will be performed after the subject provides informed consent (Table 1). Screening (Visit 1) will occur between Day -28 and Day -1.

Subject screening numbers will be assigned at Visit 1.

The eCRF must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

7.1.1 Informed Consent

Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Documentation will be required (documented in the clinic notation) to confirm that the Investigator ensured that the informed consent process was done correctly, the subject understood what to expect, and agreed to participate.

Procedures to be followed when obtaining informed consent are detailed in Section 10.3.2.

7.1.2 Inclusion/Exclusion Criteria

Subject eligibility will be confirmed per the inclusion/exclusion criteria at Screening.

7.1.3 Demography

Subject demography information will be collected at Screening. Demography information includes age at time of consent, sex, race/ethnicity.

7.1.4 Medical/Surgical and Actinic Keratosis History

Medical and surgical history and current medical conditions will be recorded at Screening.

Medical history will include:

- Significant medical and surgical history; childhood diseases and common colds are not required unless it is ongoing at Screening
- The initial diagnosis date of AK on the face or scalp, depending on the selection of the treatment area for the study
- An AK treatment history of the face or scalp including all commercial and investigational products and surgical modalities dating back to the initial diagnosis.
- History of cancers including skin cancers, eg, BCC, SCC, melanoma.

7.1.5 Prior Medications

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies taken 28 days before Day 1 will be recorded at Screening.

7.1.6 Fitzpatrick Skin-Type Classification

The Fitzpatrick Skin-Type is a skin classification system[8] 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.

7.1.7 Expanded Dermatological Examination

An expanded dermatological examination to cover sun-exposed areas where photo-damage is likely will be conducted at Screening only.

7.1.8 Treatment Area Identification and AK Lesion Count Examination

At the Screening visit, a dermatologist (Investigator or Subinvestigator) will identify a contiguous treatment area affected with AK on the face or scalp for each subject that measures 25 cm^2 and contains 4 to 8 AK lesions that are clinically typical, visible, and discrete. A dermatologist (Investigator or Subinvestigator) will perform a count of AK lesions (lesion count) for all subjects.

7.1.9 Physical Examinations

A complete PE will be performed at Screening and will include weight and an assessment of the head, eyes, ears, nose, and throat (HEENT), gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height will be measured at Screening only. An expanded dermatological examination will be conducted at Screening only (Section 7.1.7). The complete PE will be part of the baseline assessments.

7.1.10 Vital Signs

Vital signs will be recorded at Screening. 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. Serial vital signs may be obtained to confirm accurate readings.

7.1.11 Electrocardiograms

Electrocardiogram training, equipment, and a procedural manual will be provided to the site by the central ECG vendor. The ECG vendor and the Sponsor will ensure that the study site ECG operator is properly trained prior to start of study.

A standard 12-lead ECG will be obtained at Screening. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. Screening ECGs must be reviewed prior to the subject being randomized.

ECGs will be transferred electronically to the central ECG vendor.

7.1.12 Laboratory Measurements

Samples for clinical laboratory testing (hematology, chemistry, urinalysis) will be collected at Screening. Clinical laboratory testing will be part of the baseline assessments. See Section 7.3.4.9 for further details about laboratory tests.

7.1.13 Pregnancy Testing

In females of childbearing potential, a serum pregnancy test will be obtained at Screening. Test results must be reviewed before randomization of subjects.

7.2 Baseline Assessments

All baseline assessments should be completed by Day 1 (Visit 2) prior to randomization, according to the Schedule of Procedures and Assessments (Table 1).

7.2.1 Inclusion/Exclusion Criteria

Subject eligibility will be re-confirmed per the inclusion/exclusion criteria at Baseline.

7.2.2 Prior Medications

All prior medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies will be confirmed at Baseline.

7.2.3 Treatment Area Identification

At Baseline (Day 1 predose), the Investigator will confirm the 25 cm^2 treatment area affected with 4 to 8 AK lesions on the face or scalp that was identified at Screening.

At Baseline (Day 1 predose), the location and shape of the treatment area and the specific AK lesions will be recorded on an acetate transparency sheet gridded with 1 cm^2 squares. The Investigator or Subinvestigator will identify the treatment area by:

1. Placing the transparency sheet over the treatment area
2. With a fine-tip indelible marker:
    - Mark at least 3 anatomical landmarks in the vicinity of the treatment area on the transparency sheet. Examples of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
    - Mark the outline of the treatment area on the transparency sheet.
    - Mark the location of each of the AK lesions inside the treatment area on the transparency sheet.
3. On the subject's skin, outline the treatment area with dots and dashes with the indelible marker.

The transparency sheet will be kept at the site and will be used to locate the treatment area and AK lesions during the follow-up visits.

7.2.4 Actinic Keratosis Lesion Count

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at Baseline (Day 1 predose). The same Investigator or Subinvestigator will conduct the lesion count at all visits for an individual subject.

For this assessment, an AK lesion should be counted only if it is completely inside the treatment area.

7.2.5 Focused Dermatological Exam of Treatment Area

At Baseline (Day 1 predose), the focused dermatological exam of treatment area will include evaluation for LSRs, hypo- or hyper-pigmentation, and scarring (see below). These assessments will be used as baseline assessments.

7.2.5.1 Local Skin Reactions

At Baseline (Day 1 predose), after the assessment of AEs, the Investigator or Subinvestigator will assess for LSRs on the treatment area. The same Investigator or Subinvestigator will conduct the LSR assessment at all visits for an individual subject.

LSR signs on the treatment area include the following: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a 4-point grading scale; 0=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense).

Application site reactions not classified as LSRs (eg, itching, burning, stinging, tenderness, pain) will be reported as AEs.

LSRs will be reported separately from AEs.

7.2.5.2 Pigmentation and Scarring

At the time of LSR assessment, hypo- and hyper-pigmentation and scarring on the treatment area will be assessed by the Investigator or Subinvestigator as being present or absent.

Pigmentation and scarring will be assessed at Baseline (Day 1 predose), after the assessment of adverse events. The same Investigator or Subinvestigator will assess pigmentation and scarring at all visits for an individual subject.

7.2.6 Standardized Photography

At Baseline (Day 1 predose), 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.

7.2.7 Vital Signs

Vital signs will be measured at Baseline (Day 1 predose). See Section 7.1.10 for details.

7.2.8 Electrocardiograms

A 12-lead ECG will be obtained at Baseline (Day 1 predose). See Section 7.1.11 for details.

7.2.9 Pregnancy Testing

In females of childbearing potential, a urine pregnancy test will be performed at the site at Baseline (Day 1 predose). Test results must be reviewed before randomization on Day 1.

7.2.10 Randomization

After screening and baseline assessments confirm a subject's eligibility to participate in the study, he/she will be assigned the next enrollment number appropriate for the area being treated (see Section 6.3).

7.2.11 Instructions for Self-administration of Study Treatment, Dispensing, and Return of Study Treatment

At Baseline (Day 1 predose), subjects will receive both verbal and written instructions (Appendix 1) for daily self-administration of study treatment. Any questions will be answered by the clinic staff.

Randomized subjects will be assigned an enrollment number and a study kit with the same enrollment number. The study kit will have 5 single-dose packets (1 for each day of treatment) containing either KX2-391 Ointment 1% or vehicle ointment (see Section 6.1.1). The study kit will include a dosing log where the subjects will record the date and time of study drug self-administration.

Subjects will be instructed to place the used packets (including torn pieces) into the plastic bags in which they came, seal the plastic bags, put them back into the study kit, and return the study kit containing used and unused packets and the dosing log to the clinical site after self-administration on Day 5 to check compliance (Section 6.5.2).

7.3 Treatment Period and Response Assessment Period

7.3.1 Treatment Administration – Days 1-5

After baseline assessments are completed on Day 1, the first dose of study treatment will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

7.3.2 Efficacy Assessments

7.3.2.1 Actinic Keratosis Lesion Count

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at the Response Assessment Visits on Days 8, 15, 29, and 57 (Table 1). The same Investigator or Subinvestigator will conduct the lesion count at all visits for an individual subject.

The Investigator or Subinvestigator may use the transparency and/or photograph from Baseline to locate the treatment area. AK lesion counts from previous visits should not be used to assist in the assessment of AK lesion count at the current visit. Only AK lesions completely within the treatment area will be counted.

7.3.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

7.3.4 Safety Assessments

Safety assessments will include the monitoring and recording all AEs, SAEs, LSRs, and events of special interest.

At each study visit, subjects will be asked a general question "How have you been since the last visit?". Adverse events will be recorded at each study visit, before assessment of LSRs, pigmentation, and scarring in the treatment area. Adverse events will be reported separately from LSRs.

Safety assessments will also include vital signs, the performance of PEs, ECGs, laboratory evaluation of hematology, biochemistry, and urinalyses, as detailed in the sections below.

7.3.4.1 Adverse Events

All AEs will be assessed periodically through Day 57 (Table 1).

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 drugs are KX2-391 Ointment 1% and vehicle ointment.

The criteria for identifying AEs in this study 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 non-protocol-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 of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (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 subject contact in the study. Subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment

area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who fail screening primarily due to AE(s) must have the AE(s) recorded in the AE eCRF and screen failure reported on the eCRF.

Subjects with onset of a study treatment-related AEs will be followed until resolution, under medical care, or deemed stabilized by the Investigator. 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 eCRF.

Laboratory Adverse Events

A treatment-emergent abnormal laboratory test result should be considered as a 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 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

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 eCRF.

Electrocardiogram Changes

Any changes from the baseline ECG will be evaluated for clinical significance. ECG changes that are determined to be clinically significant, regardless of relationship, will be reported as an AE.

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 8.1).

7.3.4.1.1 ASSESSING SEVERITY OF ADVERSE EVENTS

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

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in detail indicated on the eCRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 7.3.4.2 for the definition of an SAE).

7.3.4.1.2 ASSESSING RELATIONSHIP TO STUDY TREATMENT

Every effort must be made by the Investigator to categorize each AE according to its relationship to the 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 non-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 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

Not Related: The AE is clearly not related to investigational product and is clearly related to underlying disease, environmental or toxic factor(s), or other drug therapy.

7.3.4.2 Serious Adverse Events

All SAEs will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (Table 1).

A 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.

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

7.3.4.3 Events of Special Interest

All events of special interest will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (Table 1).

In addition to the AEs and SAEs described above, events of special interest are to be captured and reported in the appropriate eCRF and Events of Special Interest Forms (see Section 8.2). Events of special interest will be considered as SAEs if they meet the criteria for an SAE (Section 7.3.4.2).

Events of special interest during the Treatment and Response Assessment Periods (Days 1 to 57) are as follows:

- Overdose of study medication
- Pregnancy
- Ocular exposures to study medication
- Skin cancers (including BCC, SCC, and melanoma); location and treatment will be reported.

7.3.4.4 Concomitant Medications

Concomitant medications will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (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 eCRF up to Day 57. The Investigator will record any AE on the Adverse Event eCRF for which the concomitant medication/therapy was administered.

Use of sunblock from Day 15 onward or any topical products for the treatment of LSRs in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication eCRF up to Day 57.

7.3.4.5 Focused Dermatological Exam of Treatment Area and Standard Photography

The focused dermatological exam of the treatment area includes evaluation of LSRs, pigmentation, and scarring (see Section 7.3.4.5.1 and Section 7.3.4.5.2, respectively).

Standardized photography will be performed at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) and at additional follow-up visits after Day 57 for subjects who have unresolved LSRs, hypo- or hyper- pigmentation, or scarring in the treatment area (Table 1). See Section 7.2.6 for details.

7.3.4.5.1 Local Skin Reactions

After the assessment of AEs at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) (Table 1), the Investigator or Subinvestigator will assess for LSRs in the treatment area. See Section 7.2.5.1 for details. The same Investigator or Subinvestigator will conduct the LSR assessment at all visits for an individual subject.

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

Treatment for any LSR will be recorded on the Concomitant Medications eCRF. Interruption/discontinuation of study treatment for an LSR will be recorded on the eCRF.

7.3.4.5.2 PIGMENTATION AND SCARRING

Hypo- and hyper-pigmentation and scarring in the treatment area will be assessed at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) (Table 1). See Section 7.2.5.2 for details. The same Investigator or Subinvestigator will assess pigmentation and scarring at all visits for an individual subject.

7.3.4.6 Physical Examinations

A complete PE will be performed on Day 57 (Table 1) and will include weight and an assessment of the head, eyes, ears, nose, and throat (HEENT), integumentary, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height will be measured at Screening only.

Documentation of the PE will be included in the source documentation at the site(s). Changes from screening PE to findings at the last visit that meet the definition of an AE will be recorded on the Adverse Event eCRF.

7.3.4.7 Vital Signs

Vital signs will also be recorded at the Response Assessment Visits on Days 5 and 57 (Table 1). 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. Serial vital signs may be obtained to confirm accurate readings.

Clinically significant abnormal vital signs, as assessed by the Investigator, will be reported as adverse events.

7.3.4.8 Electrocardiograms

Electrocardiograms will be obtained at the Response Assessment Visits on Days 5 and 15 (Table 1). See Section 7.1.11 for details.

Any ECG abnormality that the Investigator considers as an AE should be recorded as such on the Adverse Event eCRF.

7.3.4.9 Laboratory Measurements

Blood will be collected for clinical laboratory tests at Response Assessment Visits on Days 8 and 15 (Table 1). Collection of blood and urine (including samples for pregnancy testing, where applicable) will be conducted at the clinic site. Approximately 8 mL of blood will be collected for clinical laboratory testing, including pregnancy testing, when required, for a total of 24 mL of blood per subject during the study. All samples will be sent to a central laboratory for testing.

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 eCRF.

The clinical laboratory tests to be measured during the study are provided in Table 3.

Table 3 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
Chemistry	
Electrolytes	chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), direct bilirubin, total bilirubin
Renal function tests	blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, uric acid
Urinalysis (dipstick)	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
Pregnancy Testing	serum pregnancy test or urine pregnancy test (see Table 1)

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 7.3.4.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 7.3.4.2), the site must report the SAE, including the laboratory report (as regionally required), to the Sponsor using the SAE form (see Section 8.1).

7.3.5 Pregnancy Testing

For women of childbearing potential, a serum pregnancy test will be obtained at the Response Assessment Visit on Day 8 and a urine pregnancy test will be performed on Day 57/early termination at the clinical site (Table 1). Serum samples will be sent to a central laboratory for testing.

7.4 Additional Follow-up Assessments

All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up, which includes standardized photography of the treatment area, every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

7.5 Recurrence Follow-up Period Assessments

7.5.1 Recurrence Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits (Table 1). The Investigator or Subinvestigator performing the lesion count should be the same Investigator or Subinvestigator who evaluated the subject previously during the study.

An AK lesion should be counted if it is within the treatment area. All AK lesions within the treatment area must be counted and recorded in the eCRF as an AK recurrence.

When AK lesions are identified in the treatment area, the transparency which was used to map the AK lesions at Baseline should be used to determine if the lesion(s) is new (ie, one which was not identified in the target treatment area at Baseline and emergent during the Recurrence Follow-up Period) or recurred (ie, one which is at the same AK lesion location identified at Baseline and resolved at Day 57).

For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

7.5.2 Safety Assessments

During the Recurrence Follow-up Period, safety assessments will include the monitoring and recording of AEs and SAEs within the treatment area at the 3-, 6-, 9- and 12-month visits (Table 1). See Section 7.3.4.1 for further information on the assessments of AEs.

Concomitant medications/therapies given for AEs within the treatment area and any concomitant medications/therapies given that may affect assessment of AK lesions recurrence in the treatment area will be assessed during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits (Table 1) and will be recorded on the Concomitant Medication eCRF. The Investigator will record any AE within the treatment area on the Adverse Event eCRF for which the concomitant medication/therapy was administered.

Events of special interest during the Recurrence Follow-up Period include skin cancers (including BCC, SCC, melanoma) within the treatment area and pregnancy. Information on skin cancers will be collected during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits and reported as an event of special interest and as an AE in the Adverse Event eCRF (see Section 8.2.4).

7.6 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of adults with AK.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, PEs, ECGs, and assessment of AEs, are standard evaluations to ensure subject safety. The tests used to evaluate AK lesions including AK lesion counting, LSR grading, application site AEs, and evaluation of pigmentation and scarring in the treatment area are standard.

8 EXPEDITED REPORTING

Serious adverse events and events of special interest (overdose of study medication, pregnancy, ocular exposure to study medication, and skin cancers [including BCC, SCC, and melanoma]) are to be reported to the Sponsor within 1 business day of the Investigator becoming aware of the event. Specific forms for reporting each type of event will be provided to the sites.

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 and events of special interest information in the manner described below.

In determining what SAEs meet criteria for expedited reporting, the current version of the KX2-391 Ointment Investigator's Brochure will be used as the reference safety information for KX2-391 Ointment 1%.

8.1 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.

Detailed contact information and SAE reporting requirements will be provided in the Investigator File.

During Screening, Treatment and Response Assessment Periods, all SAEs must be reported beginning from the time the subject signs the study ICF, up to 30 days following the last contact or Day 57, whichever is shorter. All SAEs will be reported regardless of causality.

During the Recurrence Follow-up Period, only SAEs within the treatment area will be reported. SAEs within the treatment area will be reported regardless of causality. Once recurrence of AK lesions occurs in the treatment area, and the subject is discontinued from the Recurrence Follow-up Period, SAEs will no longer be collected.

Any SAE event judged by the Investigator to be related (definitely, probably, or possibly related) to 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.

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 subject's assigned enrollment 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 redacted copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

8.2 Reporting of Events of Special Interest

8.2.1 Pregnancy

Any pregnancy, whether occurring in a subject or in the female partner of a male subject, must be reported. Pregnancies in female subjects for which the estimated date of conception was prior to Day 57 must be reported; pregnancies in female partners of male subjects for which the estimated date of conception was within 90 days of the last study treatment must be reported.

The Pregnancy Report Form must be used for reporting. 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.

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 SAEs and should be reported in the same timeframe and in the same format as all other SAEs (see Section 8.1).

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 female subject who becomes pregnant during the Treatment Period must be withdrawn from study treatment, but may continue all study assessments and be followed for study outcome. Male subjects whose female partners become pregnant during the Treatment Period may continue with study treatment and all assessments.

A pregnant female subject should be requested to provide outcome information on any pregnancy occurring during the Treatment Period or the Recurrence Follow-up Period whether or not the subject elects to continue with study assessments. Male subjects whose female partners become pregnant within 90 days of the last study treatment should be requested to provide outcome information on the pregnancy.

8.2.2 Study Drug Overdose

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied or for a duration longer than specified in the protocol.

The Overdose Report Form must be used for reporting. The overdose 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 event. The contact information for the reporting of overdose is provided in the Investigator File.

Any study drug overdose during the study must be noted on the eCRF.

All AEs associated with overdose should be captured on the Overdose Report Form and the Adverse Event eCRF. If the overdose is associated with an SAE, an SAE Report Form should be completed and sent along with the Overdose Form.

8.2.3 Ocular Exposure

Ocular exposure to study medication will be reported as an event of special interest.

The Ocular Exposure Report Form must be used for reporting. The ocular exposure 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 event. The results of an ophthalmologist's assessment must be provided as a follow-up on the Ocular Exposure Report Form. The contact information for the reporting of ocular exposure is provided in the Investigator File.

Ocular exposure to study medication must be captured on the appropriate eCRF. If the ocular exposure is associated with an AE, the AE must be captured on the Ocular Exposure Report Form and the Adverse Event eCRF. If the ocular exposure is associated with an SAE, an SAE Report Form should be completed and sent along with Ocular Exposure Report Form.

8.2.4 Skin Cancer

During the Treatment and Response Assessment Periods (Days 1 to 57), all skin cancers (including BCC, SCC, and melanoma) will be reported as events of special interest. The

location and treatment will be reported. During the Recurrence Follow-up Period, skin cancers (including BCC, SCC, and melanoma) within the treatment area will be reported as events of special interest. The treatment of the skin cancer will be reported.

The Skin Cancer Report Form must be used for reporting. The skin cancer 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 event. The contact information for the reporting of skin cancers is provided in the Investigator File.

The skin cancer must be captured on the Adverse Event eCRF. Any other AEs associated with the skin cancer must be captured on the Skin Cancer Report Form and the Adverse Event eCRF. If the skin cancer is associated with an SAE, an SAE Report Form should be completed and sent along with Skin Cancer Report Form.

8.2.5 Breaking the Blind

The Pharmacovigilance department will maintain a secure copy of the set of sealed envelopes, each containing the subject's treatment allocation for this study. The Investigator may request to unblind the treatment assignment of any subject when this is needed for proper medical management of a medical emergency or SAE. Agreement of the Sponsor's Medical Monitor or designee should be sought prior to unblinding. Instructions for requesting unblinding of a subject will be provided in the Pharmacy Manual.

The Pharmacovigilance department may unblind individual cases when required for safety reporting. The treatment assignment will be included on the MedWatch or CIOMS form for suspected unexpected serious adverse reaction (SUSAR) reports provided to health authorities.

9 STATISTICAL METHODS

9.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the database is locked and released for unblinding. Database lock, randomization code release, and subsequent data analyses will be performed in 2 steps.

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

For the second step, after the entire study has been completed, the data collected during the Recurrence Follow-up Period will be locked and the randomization code will be released to

the study sites as well. Then, the recurrence rate and AEs in the treatment area after Day 57 will be analyzed.

Statistical analyses will be performed using SAS software or other validated statistical software as required. The statistical analyses of the study data are described in this section. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP), which will be written and signed off prior to unblinding of Day 57 data.

If not specified, the baseline value of each assessment will be defined as the latest non-missing value assessed before the first dose of study treatment.

9.1.1 Study Endpoints

9.1.1.1 Efficacy

9.1.1.1.1 PRIMARY ENDPOINT

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

9.1.1.1.2 SECONDARY ENDPOINTS

Key Secondary Endpoint:

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

Additional Endpoint:

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

9.1.1.2 Safety

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs)
- AEs within the treatment area after Day 57 and up to 12 months post-Day 57

9.1.2 Definitions of Analysis Sets

Intent-To-Treat (ITT) Population: all randomized subjects. This is the primary efficacy population.

Per-Protocol (PP)/Evaluable Population: all randomized subjects who have received at least 4 of the 5 doses, conformed to the protocol as to entry criteria, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.

Safety Population: all randomized subjects who have received at least one dose of study treatment.

Recurrence Follow-up Population: all subjects who achieved complete clearance at Day 57, regardless of which treatment they received.

9.1.3 Subject Disposition

All subjects will be tabulated as to study discontinuation and the reasons for discontinuation as described in Section 5.3.

Discontinuations through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.

9.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. For continuous demographic variables, results will be presented as n, mean, standard deviation (SD), median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be summarized for each category.

9.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded using the WHO Drug Dictionary.

Prior medications will be defined as medications/therapies taken 28 days before Day 1. Concomitant medications/therapies will be defined as medications/therapies 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 summary of concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All prior and concomitant medications/therapies will be presented in subject data listings.

9.1.6 Efficacy Analyses

9.1.6.1 Primary Efficacy Endpoint Analysis

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

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

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

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

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

To explore heterogeneity of the odds ratios across analysis sites, the Breslow-Day test at a significance level of 10% will be applied. A finding of statistical significance in this test will be followed by exploratory analyses to identify outlier study sites.

The outlier sites will be discussed and an exploratory analysis excluding the outlier sites may be carried out to estimate the impact of site-by-treatment interactions. This process will be documented as an appendix to the final version of the SAP, prior to the first database lock.

9.1.6.2 Secondary Efficacy Endpoint Analyses

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

Recurrence rates will be estimated based on a Kaplan-Meier method at each nominal post-Day 57 visit. Subjects with missing AK assessments in the Recurrence Follow-up Period will be considered as censored.

9.1.6.3 Additional AK Lesion Count Analysis

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

9.1.6.4 Missing Data Handling and Sensitivity Analysis

For the primary and the key secondary efficacy endpoint analyses, all missing data caused by subject early discontinuation will be imputed with a last observation carried forward (LOCF) method.

In addition, the following approaches will be used as sensitivity analyses for the primary and key secondary efficacy endpoints:

1. Observed Cases (OC): Those subjects with missing AK lesion counts at Day 57 visit will be excluded from the analysis populations (ITT and PP/Evaluable) and then the primary and key secondary endpoint analyses described above will be repeated to show concordance.

2. Subjects without Day 57 AK lesion counts due to early termination or other reasons will be considered as non-responders for complete/partial clearance rate analysis

3. Multiple Imputation (MI): A multiple imputation method may be applied to impute missing values (only for the primary and key secondary efficacy variables).

9.1.6.5 Subgroup Analysis

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

9.1.7 Safety Analyses

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

Safety data will be summarized by treatment group using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs).

Safety data collected through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.

9.1.7.1 Extent of Exposure

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

9.1.7.2 Adverse Events

For AEs, verbatim terms on the eCRF 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).

All AEs, treatment-emergent or otherwise, will be presented in subject data listings. Only those AEs that are treatment-emergent will be included in summary tables.

Treatment-emergent AEs are defined as:

- either those AEs with an onset after the first dose or
- those pre-existing AEs that worsen after the first dose.

TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT and treatment group. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (by highest mild, moderate or severe rating) and by relationship to study treatment. Treatment-related TEAEs include those events considered by the Investigator to be related (definitely, probably, or possibly related) to study treatment.

By-subject listings of all SAEs and events of special interest will be provided. If any deaths occur in the study, a by-subject listing of all AEs leading to death will be provided.

A subject data listing of all AEs leading to discontinuation from the study will be provided.

For subjects who have treatment-related AEs at Day 57, all safety endpoints observed during any additional follow-up assessments will be listed.

During the Recurrence Follow-up Period, TEAEs in the treatment area will be summarized separately.

9.1.7.3 Laboratory Values

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

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 Day 8 and baseline to Day 15 in each treatment group.

All laboratory data will be listed by subject.

9.1.7.4 Pregnancy Tests

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

9.1.7.5 Vital Signs

Vital sign values will be listed by subject.

9.1.7.6 Electrocardiograms

All ECG data will be listed for each subject. A by-subject listing of clinically significant ECG abnormality data will be provided.

9.1.7.7 Physical Examinations

Physical examination findings will be listed for each subject.

9.1.7.8 Local Skin Reactions and Pigmentation and Scarring

LSR, hyper- or hypo-pigmentation and scarring assessment results obtained through Day 57 will be displayed and summarized by visit and treatment group. In addition, a composite score, which is defined as the sum of 6 individual LSR scores from the same visit, will be analyzed in the same way.

All LSR, hyper- or hypo-pigmentation, and scarring assessment results during any additional follow-ups after Day 57 will be presented in the by-subject listings.

9.1.8 Determination of Sample Size

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

9.1.9 Interim Analysis

No interim analysis is planned for this study.

9.1.10 Other Statistical/Analytical Issues

Not applicable

9.1.11 Procedure for Revising the Planned Analysis

If the prespecified plans for analysis 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 PROCEDURES AND INSTRUCTIONS

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6[7], Section 4.5).

10.1 Access to Source Data / Documents

The Sponsor's CRA will maintain contact with the Investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and Institutional Review Board (IRB) review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Medical history or other questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRB

In addition to the routine monitoring procedures, qualified personnel designated by the Sponsor may conduct audits of clinical research activities in accordance with the Sponsor's standard operating procedures (SOPs) to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an

inspection during the study or after its completion, the Investigator must inform the Sponsor immediately.

10.2 Quality Control and 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 will 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.

10.2.1 Data Collection

Data required by the protocol will be documented in the participant source documentation and entered into a validated electronic data capture (EDC) system.

Responsible site personnel will enter the information required by the protocol onto the eCRFs in accordance with the eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to verify the data on eCRFs for completeness and accuracy against the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF.

Data that are provided by an external vendor will be transferred and validated according to the procedures specified in the Data Management Plan.

All data derived from the study will be the 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.

10.2.2 Clinical Data Management

There will be a Data Management Plan to detail all relevant data management activities, from eCRF design to database lock.

Quality control for all relevant data management activities and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

10.3 ETHICS

This study will be conducted in accordance with 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 GCP guidelines

- Title 21 of the US Code of Federal Regulations (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

10.3.1 Institutional Review Boards

The protocol, any protocol amendments, and ICF will be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 (GCP), Section 3, and any local regulations. Any protocol amendment and/or revision to the ICF will receive appropriate approval prior to implementation. Verification of unconditional approval of the protocol will be transmitted to the Sponsor prior to the shipment of drug supplies to the investigational site. The Investigators or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

A signed letter of study approval from the IRB chairman must be sent to the Principal Investigator 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 decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

Study progress is to be reported to IRB annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB, 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 of any reportable AEs per ICH guidelines and local IRB standards of practice. Upon completion of the study, the Investigator will provide the IRB with a brief report of the outcome of the study, if required.

At the end of the study, the Sponsor should notify the IRB within 90 days.

In the case of early termination/temporary halt of the study, the Investigator should notify the IRB within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

10.3.2 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator (or designee) 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.

The 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. At the Screening Visit, after the ICF and any other written information to be provided is read and explained, the subject will be asked to sign the ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An approved ICF must be prepared in accordance with ICH E6, and all applicable regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

10.4 Data Handling and Recordkeeping

10.4.1 Recording of Data

An eCRF must be completed for each subject by qualified and authorized personnel. Any correction to entries made on the eCRF must have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

10.4.2 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

10.4.3 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents, ICFs, and IRB correspondence. In addition, the Sponsor will send a list of treatment codes by study subject to the Investigator after the clinical database for this study has been locked. The sites should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

10.5 Publication Policy

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each Investigator and the Sponsor or CRO, as appropriate.

10.6 Other Administrative Policies

10.6.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's Medical Monitor and the IRB for the site(s) must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided the health or regulatory authority and IRBs are immediately notified and appropriate documentation of the urgent protocol change are submitted per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB should be kept informed of such changes as required by local regulations.

10.6.2 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the Investigator, the Investigator's staff, and the IRB, and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/Investigator and the Sponsor/CRO.

10.6.3 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB and provide them with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11 REFERENCE LIST

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12 APPENDICES

APPENDIX 1 INSTRUCTIONS FOR SUBJECTS' SELF-ADMINISTRATION OF STUDY TREATMENT

The study kit contains:

- 5 packets filled with study drug, inside individual plastic bags
- A dosing log

Storage:

Store the study kit at room temperature and in a secure place, out of direct sunlight, and away from food products, children, and pets.

Patient Instructions:

Application of study drug is preferably done early in the day and at approximately the same time every day for a total of 5 days. The first dose will be self-administered in the clinic.

Follow these steps to apply study drug:

- Take the dosing log in the study kit and record the date and time of dosing.
- Open the plastic bag and remove a single-dose packet.
- Tear the packet open along the perforations.
- Squeeze a small amount of ointment from the packet on your fingertip and apply it evenly over the entire treatment area (Note: Each packet contains more than the amount needed for 1 treatment application.).
- Place the used packet (including torn pieces) into the plastic bag in which it came, seal the plastic bag, and put it back into the study kit.
- Wash hands **immediately** with water and soap.
- Place the dosing log back into the study kit and store away the study kit, as instructed above, in a secure place.
- Repeat the above steps for each day of treatment at about the same time each day.
- On Day 5, apply treatment **before** returning to clinic. Bring the study kit (containing all used and unused packets) and the dosing log with you.

Precautions on Treatment Days (Days 1-5):

- Subjects who wear contact lenses should put on their contact lenses BEFORE applying study drug.
- Avoid touching or wetting the treatment area for approximately 12 hours. If you touch the treatment area, wash your hands immediately.
- Avoid activities that might cause excessive sweating, so that the ointment will not get in your eyes.
- If ointment does get into your eyes, flush your eyes with water immediately and extensively. You must immediately contact the study doctor who will give you further instructions. You will be referred to an eye doctor so your eyes can be examined.
- If any severe local skin reaction occurs or persists, let your study doctor know immediately.
- Do not apply study drug more than once each day.
- Do not allow other people or pets to come into contact with the treatment area. If the treatment area is touched, the area of contact on the other person or pet should be washed immediately.
- Do not cover the treatment area with bandages, band aids, tight-fitting scarfs, or caps.

Precautions Throughout the Study:

- When washing the treatment area, wash it gently with a mild, non-abrasive, non-medicated soap or shampoo.
- Do not expose the treatment area to excessive sun light or ultraviolet light, including tanning beds. When outdoors, wear protective loose clothing over the treatment area.
- Do not use moisturizers, sunscreen, artificial tanners, make-up or other over the counter-topical products to the study treatment area until Day 57. If you are unsure of what to use, ask your study doctor. After 15 days, if you are unable to avoid excessive sun light or ultraviolet light to the treatment area, the study doctor may allow you to use sunblock.
- Do not use medications not approved by your study doctor.
- After Day 57, sunblock and non-medicated topical products can be used in the treatment area.

PROTOCOL SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

Study Protocol Number:	KX01-AK-003
Study Protocol Title:	A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp
Investigational Product Name:	KX2-391 Ointment 1%
IND Number:	122464
UTN Number:	U1111-1191-8233

SIGNATURES

Authors:

PPD , MD
Medical Monitor
Athenex, Inc.

Date

PPD
PPD MS PPD
Study Biostatistician
Athenex, Inc.

PPD
Date

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SIGNATURES

Authors:

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MD Date

Medical Monitor

Athenex, Inc.

PPD , MS Date

Study Biostatistician

Athenex, Inc.

INVESTIGATOR SIGNATURE PAGE

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Investigational Product Name:	KX2-391 Ointment 1%
IND Number:	122464
UTN Number:	U1111-1191-8233

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 of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	KX01-AK-003
Study Protocol Title:	A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp
Sponsor:	Athenex, Inc. 20 Commerce Drive Cranford NJ 07016, USA Tel: 908-340-6996
Investigational Product Name:	KX2-391 Ointment 1%
Indication:	Actinic keratosis on face or scalp
Phase:	3
Approval Date:	v1.0 29 Jun 2017 (original protocol)
IND Number:	122464
UTN Number:	U1111-1191-8233
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 Athenex, 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.

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 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp

Sites

Approximately 25 to 40 sites in the United States

Study Period and Phase of Development

First subject in to last subject out, approximately 20 months

Phase 3

Study Hypothesis

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

Objectives

Primary Objective

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

Secondary Objectives

- To evaluate the safety of topical KX2-391 Ointment 1% once daily for 5 consecutive days in terms of local skin reactions (LSRs) and other safety evaluations such as adverse events (AEs) and laboratory assessments
- To compare the rates of partial responders defined as ≥75% clearance of AK lesions in the treatment area on the face or scalp at Day 57 between the KX2-391 Ointment 1%-treated group and vehicle-treated group
- To evaluate the reduction in AK lesions counts from Day 1 through Day 57
- To determine the recurrence of AK in the treatment area up to 12 months post-Day 57 in subjects who had complete clearance at Day 57 after 5 consecutive days of treatment with KX2-391 Ointment 1%
- To evaluate the safety of topical KX2-391 Ointment 1% within the treatment area during the Recurrence Follow-up Period

Study Design

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

Enrollment will be controlled so that approximately two thirds of subjects enrolled will be treated on

the face and approximately one third of subjects enrolled will be treated on the scalp.

The study consists of Screening, Treatment, Response Assessment Period, and a Recurrence Follow-up Period. After a Screening Period of up to 28 days, subjects will return to the site for confirmation of eligibility. Eligible subjects will be randomized on Day 1 to treatment in a 1:1 (KX2-391 Ointment 1% or vehicle) ratio in each treatment area subgroup.

The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site. Subjects will be given verbal and written instructions on self-administration of study drug/vehicle and a study kit containing 5 daily single-dose packets, 1 for each day of treatment. The first dose will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

Subjects will return to the clinical sites for assessments at the Response Assessment Visits on Days 5, 8, 15, 29, and 57.

All subjects who have unresolved LSRs, hypo- or hyper- pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will continue in the Recurrence Follow-up Period to determine recurrence rate and safety for up to 12 months following the Day 57 Visit. Visits during the Recurrence Follow-up Period will occur every 3 months. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 300 subjects. At each site, a minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled.

Inclusion Criteria

1. Males and females ≥18 years old
2. A treatment area on the face or scalp that:
   - is a contiguous area measuring 25 cm^2
   - contains 4 to 8 clinically typical, visible, and discrete AK lesions
3. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - physical examination (PE) findings
   - vital signs
   - electrocardiogram (ECG), clinical chemistry, hematology, and urinalysis results
4. Females must be postmenopausal (>45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); 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 study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant, injection or patch, intrauterine device or complete abstinence from sexual intercourse.
5. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.

6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of study treatment.
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 randomization.
8. Willing to avoid excessive sunlight or ultraviolet (UV) light exposure, including the use of tanning beds, to the face or scalp
9. Able to comprehend and are willing to sign the informed consent form (ICF).

Exclusion Criteria

1. Clinically atypical and/or rapidly changing AK lesions on the treatment area, eg, hypertrophic, hyperkeratotic, recalcitrant disease (had cryosurgery on two previous occasions) and/or cutaneous horn
2. Location of the treatment area is:
   - On any location other than the face or scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)
3. Been previously treated with KX2-391 Ointment
4. Anticipated need for in-patient hospitalization or in-patient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the treatment area or within 2 cm of the treatment area, within 8 weeks prior to the Screening visit
6. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the treatment area or within 2 cm of the selected treatment area
   - Topical salves (non-medicated/non-irritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Treatment with immunomodulators (eg, azathioprine), cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/interferon inducers
   - Treatment with systemic medications that suppress the immune system (eg, cyclosporine, prednisone, methotrexate, alefacept, infliximab)
8. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication
10. 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 unacceptable risk by study participation

11. 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
12. Females who are pregnant or nursing
13. 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

Study Treatments

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

Duration of Study

For the Screening, Treatment, and Response Assessment Periods, each subject will participate for up to 85 days: screening up to 28 days prior to Day 1, treatment for 5 consecutive days, and follow-up until Day 57. The Recurrence Follow-up Period will be for up to 12 months post-Day 57. Thus, the maximum overall duration of participation for each subject is approximately 15 months.

Concomitant Drug/Therapy

Use of any treatment for AK lesions other than study drug on the treatment area is prohibited during the study.

Assessments during the Treatment and Response Assessment Periods (Day 1 through Day 57)

Efficacy Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at Screening, Baseline (Day 1 predose), and at the Response Assessment Visits on Days 8, 15, 29, and 57.

Safety Assessments

Safety will be assessed periodically through Day 57 by recording AEs, serious adverse events (SAEs), LSRs, and events of special interest.

Safety assessments will also include vital signs, the performance of PEs, ECGs, laboratory evaluation of hematology, biochemistry, and urinalyses, and evaluation of pigmentation and scarring in the treatment area at prespecified timepoints (Table 1, Schedule of Procedures and Assessments).

At each study visit, subjects will be asked a general question "How have you been since the last visit?". Adverse events will be recorded at each study visit, before assessment of LSRs, pigmentation, and scarring in the treatment area. AEs will be reported separately from LSRs.

LSR Assessments

The LSR assessment is the Investigator's (or Subinvestigator'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=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). 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, itching, burning, stinging, tenderness, pain) will be reported as AEs. Standardized photography will be performed on Day 1 prior to dosing, and on Days 5, 8, 15, 29, and 57.

Events of Special Interest

- Overdose of study medication
- Pregnancy

- Ocular exposures to study medication
- Skin cancers (including BCC, SCC, and melanoma); the location and treatment will be reported.

Assessments during the Recurrence Follow-up Period (up to 12 months post-Day 57)

Efficacy Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits.

Safety Assessments

During the Recurrence Follow-up Period, safety assessments will include the monitoring and recording of AEs and SAEs within the treatment area at the 3-, 6-, 9- and 12-month visits.

Events of Special Interest

- Skin cancers (including BCC, SCC, and melanoma) within the treatment area
- Pregnancy

Statistical Methods

Primary Endpoint

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

Secondary Endpoints

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs)
- Partial clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with a ≥75% reduction in the number of AK lesions identified at Baseline (Day 1 predose) in the treatment area
- Reduction in AK lesion counts during Days 1 to 57
- Recurrence rate of AK lesions in subjects who achieved complete clearance at Day 57
- AEs within the treatment area after Day 57 and up to 12 months post-Day 57

Analysis Populations

Intent-To-Treat (ITT) Population: all randomized subjects. This is the primary efficacy population.

Per-Protocol (PP)/Evaluable Population: all randomized subjects who have received at least 4 of the 5 doses, conformed to the protocol as to entry criteria, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.

Safety Population: all randomized subjects who have received at least one dose of study treatment.

Recurrence Follow-up Population: all subjects who achieved complete clearance at Day 57, regardless of which treatment they received.

Efficacy Analyses

To achieve statistical significance in the study as a whole with concordance in both face and scalp, the Day 57 complete clearance rate will be analyzed using a Cochran-Mantel-Haenszel (CMH) model controlling for treatment and treatment location (face and scalp); possible treatment/location interaction will be addressed by analyzing the treatment locations independently to show

concordance. The Pearson Chi Square (used to power the study) will be used to demonstrate basic agreement with the CMH. Prior to unblinding the data, the number of subjects enrolled per site will be reviewed and an investigator site analysis of how low enrollment sites might be combined and the impact of high enrollment sites will be fully discussed.

Exploratory analyses may be conducted to identify outlier study sites. The outlier sites will be discussed and an exploratory analysis excluding the outlier sites may be carried out to estimate the impact of site-by-treatment interactions. This process will be documented.

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

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

The number of AK lesions and the change from baseline at each scheduled visit will be summarized using descriptive statistics (ie, mean, standard deviation [SD], median, minimum and maximum) by treatment group and then contrasted for each treatment group.

Recurrence rate will be determined at each scheduled visit after Day 57.

Safety Analyses

For AEs, verbatim terms on the electronic case report form (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).

Treatment-emergent adverse events (TEAEs) are defined as either those AEs with an onset after the first dose or those pre-existing AEs that worsen after the first dose. The incidence of TEAEs will be summarized by treatment group. TEAEs will also be summarized by severity and relationship to study treatment. By-subject listings of all SAEs and events of special interest will be provided.

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoint by treatment group. Changes from baseline will also be summarized by treatment group. 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 Day 8 and baseline to Day 15 in each treatment group.

LSR, hyper- or hypo-pigmentation and scarring assessment results obtained through Day 57 will be displayed and summarized by visit and treatment group.

Safety data collected through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale

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

FINAL: v1.0_29 Jun 2017

SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 1 Schedule of Procedures and Assessments in KX01-AK-003

Period	Screening	Treatment		Response Assessment					Recurrence Follow-up[a]
Clinic Visit	1	2	At home once-daily self-administration of treatment	3	4	5	6	7 / Early Term[b]	8, 9, 10, 11[a]
Day	-28 to -1	1 Baseline	2-5	5	8	15	29	57[b]	3, 6, 9, 12 Months Post-Day 57[c]
Visit time window (days)	None	None		None	±2	±2	±3	±5	±14
Informed consent	X								
Inclusion & exclusion criteria	X	X[d]							
Demographics	X								
Medical/surgical history	X								
AK history/AK treatment history	X								
Prior and concomitant medications/therapies	X	X[d]		X	X	X	X	X	X
Fitzpatrick skin-type scale	X								
Expanded dermatological exam[e]	X								
Treatment area identification	X	X[d,f]							
AK lesion count in treatment area	X	X[d]			X	X	X	X	X
Physical examination, including weight and height[g]	X							X	
Vital signs[h]	X	X[d]		X				X	
ECG[i]	X	X[d]		X		X			
Clinical chemistry, hematology, and UA	X[j]				X	X			
Serum pregnancy test for WOCBP	X				X			X	
Urine pregnancy test		X[k]							
AEs[l]	X	X[d]		X	X	X	X	X	X[m]
Focused dermatological exam of treatment area		X[d]		X	X	X	X	X	
LSRs		X[d]		X	X	X	X	X	
Pigmentation and scarring		X[d]		X	X	X	X	X	

Table 1 Schedule of Procedures and Assessments in KX01-AK-003

Period	Screening	Treatment		Response Assessment					Recurrence Follow-up[a]
Clinic Visit	**1**	**2**	**At home once-daily self-administration of treatment**	**3**	**4**	**5**	**6**	**7 / Early Term[b]**	**8, 9, 10, 11[a]**
Day	**-28 to -1**	**1 Baseline**	**2-5**	**5**	**8**	**15**	**29**	**57[b]**	**3, 6, 9, 12 Months Post-Day 57[c]**
Standardized photography		X[d]		X	X	X	X	X	
Randomization		X							
Instructions for self-administration; dispense study medication		X[d]							
Study medication application		X	X						
Study drug / dosing log return				X[n]					

AE = adverse event; AK = actinic keratosis; ECG = electrocardiogram; HEENT = head, eyes, ears, nose, and throat; LSR = local skin reaction; Term = Termination; UA = urinalysis; WOCBP = women of child-bearing potential.

a. For Day 57 complete responders only
b. These are assessments to be completed by all subjects. For those who do not have complete response at Day 57 or who are discontinued early from the study, this will be their final visit. All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.
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 assessments at the visit when the AK recurrence is identified.
d. These are baseline procedures/assessments and will be performed before randomization.
e. An expanded dermatological examination to cover the sun-exposed areas where photo-damage is likely will be conducted at Screening only.
f. The location and shape of the treatment area will be marked on an acetate transparency sheet for recording purposes and on the subject's skin for identification of the treatment area for daily self-administration of study ointment.
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. This will be considered the baseline assessment.
h. Vital signs measurements will be taken after the subject has been seated for at least 5 minutes.
i. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. Baseline ECG is performed predose.
j. This will be considered the baseline assessment.
k. For females of childbearing potential: urine pregnancy test on Day 1 before randomization.
l. At each study visit, subjects will be asked a general question "How have you been since the last visit?". AEs will be recorded before assessment of LSRs, pigmentation, and scarring in the treatment area. AEs will be reported separately from LSRs.
m. Only AEs in the treatment area will be collected.
n. On Day 5 (Visit 3), subjects are to come into the clinic after study treatment is self-administered. Subjects are to bring all 5 study drug packets (used and unused) in the study kit and the dosing log back to the site.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Terms
AE	adverse event
AK	actinic keratosis
BCC	basal cell carcinoma
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRA	clinical research associate
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
IRB	Institutional Review Board
ITT	Intent-To-Treat
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
PE	physical examination
PP	Per-Protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
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)

1 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Athenex, Inc. (the Sponsor) at approximately 25 to 40 investigational sites in the United States (US).

The name, telephone number, and email address of the Medical Monitor and other contact personnel at the Sponsor are listed in the Regulatory Binder provided to each site.

2 INTRODUCTION

2.1 Background

2.1.1 Indication

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

2.1.2 Mechanism of Action

KX2-391 (referred to as KX01 in study protocol numbers) 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 AK. KX2-391 is also being developed as an oral agent for oncology indications.

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. Potent inhibition of the growth of primary human keratinocytes and several melanoma cell lines in vitro (50% growth inhibition [GI_{50} values] ≤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.

2.1.3 Nonclinical Studies

Details regarding KX2-391 nonclinical studies are provided in the KX2-391 Ointment Investigator's Brochure.

The bioavailability of KX2-391 after dermal administration to rats (1.59%) and rabbits (2.49% to 6.47%, depending on concentration) was low. Plasma concentrations of KX2-391 increased with repeat dermal administration, and in rats the plasma levels after 6 days dermal dosing reached or exceeded levels produced by oral administration of KX2-391 at the no observed adverse effect level (NOAEL) dose (1.25 mg/kg/dose) in a 28-day twice-daily oral toxicity study. Following 28 days of KX2-391 topical administration at increasing doses (0.1%, 1%, and 2%) in rats and minipigs, an increase in KX2-391 plasma exposure was observed from Day 1 to Day 28, suggesting slight drug accumulation.

In 28-day repeat-dose toxicology studies, KX2-391 ointment was administered to rats and minipigs at dose strengths 0.1%, 1%, and 2%. Ointment volumes of 2 mL/kg body weight were applied to approximately 10% of the body surface area of the skin. The administration sites were occluded with gauze and the applications left for 8 h/day in rats. The application site was semi-occluded for 20-22 hours in minipigs. These doses contained 2, 20, or 40 mg/kg KX2-391, respectively, equivalent to 12, 120, or 240 mg/m^2 in rats and 70, 700, or 1400 mg/m^2 in minipigs. Systemic exposures on Day 28 to KX2-391 following daily application of 0.1% ointment were C_{max} 22.9 ng/mL (male)/33.7 ng/mL (female) and AUC_{0-24h} 205 h*ng/mL (male)/216 h*ng/mL (female) in rats, and C_{max} 2.03 ng/mL (male)/7.25 ng/mL (female), AUC_{0-24h} 37.4 h*ng/mL (male)/65.5 h*ng/mL (female) in minipigs. Exposure (AUC) in humans was not calculated due to the lack of quantifiable plasma concentrations following topical KX2-391 administration. However, the maximum C_{max} value at the NOAEL in rats and minipigs is approximately 24 and 5 times greater than the maximum plasma KX2-391 concentration of 1.42 ng/mL achieved in the clinic (Study KX01-AK-002).

Other dermal toxicity studies with KX2-391 showed that KX2-391 ointment may be sensitizing to the skin (Buehler assay and murine local lymph node assay), that KX2-391 ointment was negative for phototoxicity, and that KX2-391 ointment was an irritant to the eyes of rabbits after single application (effects cleared within 3 days post dose).

KX2-391 was negative in a bacterial mutagenicity study (Ames test). KX2-391 caused chromosomal aberrations in Chinese Hamster Ovary (CHO) cells at very high doses that are not likely to be clinically relevant.

Studies of the effects of KX2-391 oral on reproduction and fetal development have been performed. In embryo-fetal development studies in rats and rabbits, KX2-391 was administered orally in order to increase systemic exposure. Embryo and fetal toxicity, including implantation loss and fetal malformations, occurred at oral doses of ≥1.25 mg/kg (rats) and 3 mg/kg (rabbits). The no-effect doses for fetal and reproductive effects were 0.5 mg/kg (rats) and 1 mg/kg (rabbits). At these doses, maternal C_{max} and $AUC_{0-8\ h}$ systemic exposures to KX2-391 were 25.4 ng/mL and 82.4 h*ng/mL (rats, Day 17) and 144 ng/mL and 251 h*ng/mL (rabbits, Day 18), respectively. Systemic plasma exposure (AUC) in humans could not be determined due to the lack of quantifiable plasma concentrations across multiple timepoints. However, maternal C_{max} values at the NOAEL in rats and rabbits are approximately 18 and 100 times greater than the highest KX2-391 plasma concentration achieved clinically of 1.42 ng/mL (Study KX01-AK-002).

2.1.4 Clinical Experience with KX2-391

2.1.4.1 KX2-391 in Cancer (Oral)

KX2-391 has been administered orally as a treatment for cancer to approximately 120 patients with various types of malignancies in 4 clinical studies sponsored by Athenex, Inc. A summary of the safety information from these patients is provided in an appendix of the KX2-391 Ointment Investigator's Brochure.

Due to the differences in route of administration and short duration of treatment (5 days), topical KX2-391 has minimal systemic exposure and is not likely to have the same toxicity profile as oral KX2-391.

2.1.4.2 KX2-391 as a Topical Treatment for Actinic Keratosis

To date, 2 clinical studies have been conducted to evaluate the activity and safety of KX2-391 Ointment 1% in subjects with AK.

Study KX01-AK-01-US, a Phase 1, safety, tolerability, and pharmacokinetic study, demonstrated that KX2-391 Ointment 1% was well-tolerated and showed clinical activity in 30 adults with AK on dorsal forearm when given at 50 or 200 mg daily over 3 or 5 consecutive days in an area of 25 or 100 cm^2. Most subjects experienced mild to moderate and transient local skin reactions (LSRs). The majority of the LSRs observed were erythema and flaking/scaling that peaked around Day 5-10, before returning to or close to baseline. Symptoms of pruritus, stinging, and burning at the treatment area were generally mild and transient. There were no serious adverse events (SAEs) or deaths, and no subjects discontinued due to an adverse event (AE).

Study KX01-AK-002, an ongoing Phase 2a, open-label, sequential group study, evaluated the activity and safety of KX2-391 Ointment 1% when applied daily in a treatment area of 25 cm^2 for 3 consecutive days (n=84 subjects) or 5 consecutive days (n=84 subjects) in adults with AK on face or scalp. Preliminary data showed that most of the 168 subjects treated had mild to moderate LSRs (primarily erythema and flaking/scaling. Eleven (6.5%) subjects had 16 treatment-emergent adverse events (TEAEs) considered treatment-related by the Investigator. Eight of these subjects had mild application site reactions including pruritus, tenderness, or stinging. The remaining AEs considered by the Investigator to be treatment-related were mild headache, mild to moderate dizziness, mild arthralgia, or mild darkening of hair color near the treatment area. All treatment-related TEAEs resolved prior to or stabilized by Day 57. Four subjects reported 5 treatment-emergent SAEs. All SAEs were considered unrelated to study drug. No subject discontinued treatment due to AEs.

Thirty-six of 84 subjects (43%) in the 5-day regimen and 27 of 84 subjects (32%) in the 3-day regimen had 100% clearance of AK lesions in the treatment area on Day 57.

Plasma concentrations of KX2-391 were measured in Study KX01-AK-002 using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 0.1 ng/mL. Pharmacokinetic results showed that following 3 or 5 consecutive days of treatment with KX2-391 Ointment 1%, low systemic exposure (< 2 ng/mL) and limited drug accumulation were observed.

Details of both studies are available in the KX2-391 Ointment Investigator's Brochure.

2.2 Study Rationale

Actinic keratosis represents 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.[1,2] The risk of progression has been determined to be between 0.025% and 16% per year,[1,3] and the calculated lifetime risk of malignant transformation for a patient with AK lesions followed up for 10 years is between 6.1% and 10.2%.[4] The rationale behind treating every AK lesion is based on the difficulty in predicting which single AK lesion will progress to SCC.[5,6] The goal of treatment is to completely eliminate AK lesions, thereby minimizing their risk of progression to invasive SCC, and reducing the potential to metastasize and cause death, while obtaining the best cosmetic outcomes.

2.3 Potential Risks and Benefits

Preliminary results of studies KX01-AK-01-US and KX01-AK-002 indicate that KX2-391 Ointment 1% administered once daily for up to 5 days demonstrates clinically relevant activity in the treatment of AK lesions on both the face and scalp, as well as on the dorsal forearm. Data from KX01-AK-002 suggest that the 5-day regimen of KX2-391 Ointment 1% has greater activity (43%) than the 3-day regimen (32%).

Preliminary safety results from both studies showed that KX2-391 Ointment 1% is safe and well tolerated. Even though LSRs (primarily erythema and/or flaking/scaling) were reported by the majority of treated subjects, they were generally mild or moderate in severity and mostly transient. The treatment-related TEAEs that subjects experienced mainly consisted of mild application site reactions such as itching, burning, stinging, tenderness, and pain. No subjects discontinued treatment due to AEs and no treatment-related SAEs were reported. Based on these findings, the clinical benefit of treating actinic keratosis, a precancerous condition, with a short course of topical KX2-391 outweighs the risk of transient LSRs observed.

At systemic KX2-391 concentrations that were significantly higher than those observed following topical administration in humans, KX2-391 was associated with testicular toxicity in multiple-dose nonclinical toxicity studies in animals. As a precaution, male subjects must agree to practice medically acceptable contraception during study participation and for at least 90 days after stopping treatment.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoint

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

The primary endpoint will be complete (100%) clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area.

3.2 Secondary Objectives and Endpoints

The secondary objectives of the study are:

- To evaluate the safety of topical KX2-391 Ointment 1% once daily for 5 consecutive days in terms of LSRs and other safety evaluations such as AEs and laboratory assessments
- To compare the rates of partial responders defined as ≥75% clearance of AK lesions in the treatment area on the face or scalp at Day 57 between the KX2-391 Ointment 1%-treated group and vehicle-treated group
- To evaluate the reduction in AK lesions counts from Day 1 through Day 57
- To determine the recurrence of AK in the treatment area up to 12 months post-Day 57 in subjects who had complete clearance at Day 57 after 5 consecutive days of treatment with KX2-391 Ointment 1%
- To evaluate the safety of topical KX2-391 Ointment 1% within the treatment area during the Recurrence Follow-up Period.

The secondary endpoints are:

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])
- Partial clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with a ≥75% reduction in the number of AK lesions identified at Baseline (Day 1 predose) in the treatment area
- Reduction in AK lesion counts during Days 1 through 57
- Recurrence rate of AK lesions in subjects who achieved complete clearance at Day 57
- AEs within the treatment area after Day 57 up to 12 months post-Day 57

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

Enrollment will be controlled so that approximately two thirds of subjects enrolled will be treated on the face and approximately one third of subjects enrolled will be treated on the scalp. A sufficient number of subjects will be screened to randomize approximately 300 subjects. At each site, a minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled.

The study consists of Screening, Treatment, a Response Assessment Period, and a Recurrence Follow-up Period. After a Screening Period of up to 28 days, subjects will return to the site for confirmation of eligibility. Eligible subjects will be randomized on Day 1 to treatment in a 1:1 (KX2-391 Ointment 1% or vehicle) ratio in each treatment area subgroup.

The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site. Subjects will be given verbal and written instructions on self-administration of study drug/vehicle and a study kit containing 5 daily single-dose packets, one for each day of treatment. The first dose will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

Subjects will return to the clinical sites for assessments at the Response Assessment Visits at Days 5, 8, 15, 29, and 57.

All subjects who have unresolved LSRs, hypo- or hyper- pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will continue in the Recurrence Follow-up Period to determine recurrence rate and safety for up to 12 months following the Day 57 Visit. Visits during the Recurrence Follow-up Period will occur every 3 months. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

An overview of the study design is presented in Figure 1.

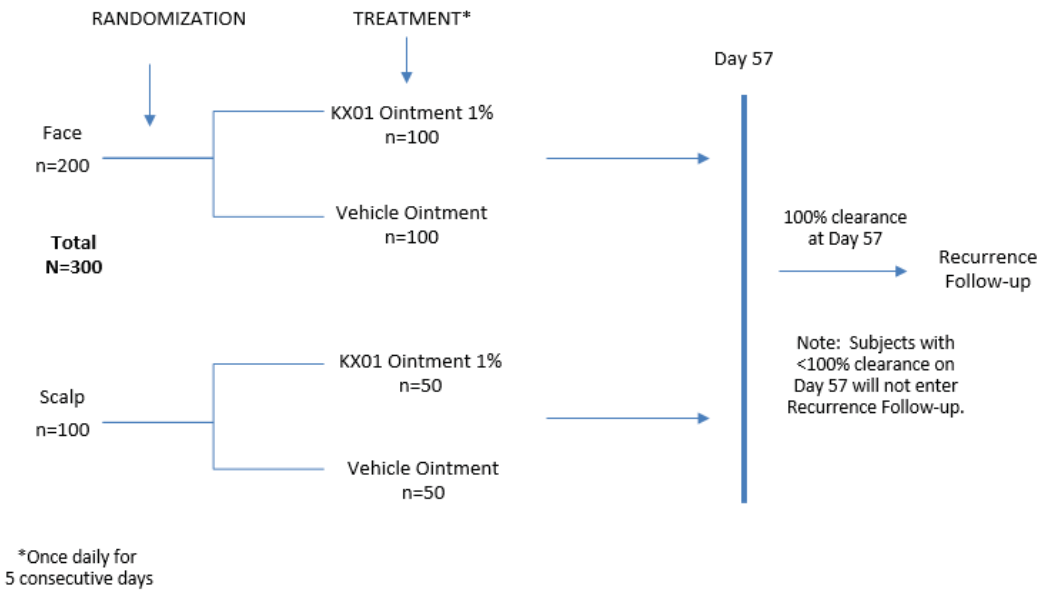

Figure 1 Study Design for KX01-AK-003

4.2 Screening Period

Screening (Visit 1) will occur between Day –28 and Day –1. Subject eligibility will be established during the Screening Period.

Details of screening procedures/assessments are provided in Section 7.1.

4.3 Treatment Period

The Treatment Period will be Days 1 to 5. Protocol eligibility will be confirmed at Baseline (Day 1 predose).

All screening and baseline assessments should be evaluated for acceptability prior to randomization of the subject. Eligible subjects will be randomized separately for face and scalp to treatment in a 1:1 ratio of KX2-391 Ointment 1% or vehicle (see Section 6.3).

Baseline and Treatment Period procedures and assessments, and timing thereof, are shown in Table 1; details are provided in Section 7.2 and Section 7.3, respectively.

4.4 Response Assessment Period

Subjects will return to the clinical sites for Response Assessment Visits postdose on Day 5 (Visit 3) and on Days 8, 15, 29, and 57 (Visits 4 through 7). Procedures and assessments and

timing thereof during the Response Assessment Period are shown in Table 1 and the details are provided in Section 7.3.

All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

4.5 Recurrence Follow-up Period

Subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 will be eligible to continue in the Recurrence Follow-up Period to determine AK recurrence rates and evaluate concomitant medications and AEs in the treatment area for up to 12 months post-Day 57.

Procedures and assessments and timing thereof during the Recurrence Follow-up Period are shown in Table 1 and the details are provided in Section 7.5. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

4.6 Discussion of Study Design, Including Choice of Dosing and Control Groups

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel group, efficacy and safety study of KX2-391 Ointment 1% administered topically on the face or scalp of adult subjects with AK for 5 consecutive days.

The dosing regimen for this study is based on the Phase 2a study (KX01-AK-002). KX01-AK-002 is an open-label, sequential group, non-randomized, multi-center study that evaluated the dosing regimen of daily dosing for either 3 or 5 consecutive days of KX2-391 Ointment 1% on a treatment area of 25 cm^2 on the face or scalp that contained 4 to 8 AK lesions in 168 adults (84 subjects per cohort). Preliminary analyses showed that a higher percentage of subjects achieved complete clearance of AK on Day 57 for the 5-day treatment group (43%) than the 3-day treatment group (32%). For both the 5-day and 3-day treatment groups, KX2-391 Ointment 1% was found to be safe, well tolerated and minimally absorbed throughout treatment and follow up for both cohorts. Thus, these data support the evaluation of KX2-391 Ointment 1% once daily topical application for a 5-consecutive day dosing regimen for the treatment of adults with AK on the face or scalp in this Phase 3 double-blind, vehicle-controlled study. The 12-month Recurrence Follow-up Period allows for long-term evaluation of AK recurrence rates and safety.

5 STUDY POPULATION

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

A sufficient number of subjects will be screened to randomize approximately 300 subjects at approximately 25 to 40 sites. A minimum of 10 subjects and a maximum of 20 subjects are projected to be enrolled at each site.

5.1 Inclusion Criteria

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

1. Males and females ≥18 years old
2. A treatment area on the face or scalp that:
   - is a contiguous area measuring 25 cm^2
   - contains 4 to 8 clinically typical, visible, and discrete AK lesions
3. Subjects who in the judgment of the Investigator, are in good general health based on:
   - medical history
   - physical examination (PE) findings
   - vital signs
   - ECGs, clinical chemistry, hematology, and urinalysis results
4. Females must be postmenopausal (>45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); 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 study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant, injection or patch, intrauterine device or complete abstinence from sexual intercourse.
5. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.
6. All subjects must agree not to donate sperm or eggs or attempt conception from Screening through 90 days following their last dose of study treatment.
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 randomization.
8. Willing to avoid excessive sunlight or ultraviolet (UV) light exposure, including the use of tanning beds, to the face or scalp
9. Able to comprehend and are willing to sign the informed consent form (ICF).

5.2 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, eg, hypertrophic, hyperkeratotic, recalcitrant disease (had cryosurgery on two previous occasions) and/or cutaneous horn
2. Location of the treatment area is:
   - On any location other than the face or scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected basal cell carcinoma (BCC) or SCC
3. Been previously treated with KX2-391 Ointment
4. Anticipated need for in-patient hospitalization or in-patient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the treatment area or within 2 cm of the treatment area, within 8 weeks prior to the Screening visit
6. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the treatment area or within 2 cm of the selected treatment area
   - Topical salves (non-medicated/non-irritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Treatment with immunomodulators (eg, azathioprine), cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/interferon inducers
   - Treatment with systemic medications that suppress the immune system (eg, cyclosporine, prednisone, methotrexate, alefacept, infliximab)
8. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication
10. 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 unacceptable risk by study participation

11. 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
12. Females who are pregnant or nursing
13. 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

5.3 Subject Withdrawal / Discontinuation Criteria

The Investigator may withdraw a subject from 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 must document the reason for discontinuing a subject from treatment or from the study if known, or why the subject withdrew consent, if applicable. Subject disposition information will be collected on the electronic case report form (eCRF).

Subjects who do not complete 5 days of treatment and withdraw from study treatment (for reasons other than death or withdrawal of consent) will be encouraged to continue the post-treatment visits. At the time of withdrawal from the study, the subject should complete the early termination assessments (Day 57 assessments) (Table 1). A subject who does not return for the post-treatment visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the eCRF.

Subjects who discontinue early from the study will be discontinued for one of these primary reasons:

- AE(s)
- Lost to follow-up
- Withdrawal of consent (subjects will be asked but not required to provide a reason)
- Study terminated by Sponsor
- Noncompliance (specify)
- AK recurrence during the Recurrence Follow-up Period prior to the 12-month visit
- Investigator decision (specify)
- Death
- Other (specify)

Subjects who do not achieve 100% clearance of AK lesions in the treatment area at Day 57 will be considered to have completed their participation in the study.

6 STUDY TREATMENTS

6.1 Identity of Study Drugs

Treatments administered will be topical KX2-391 Ointment 1% and vehicle ointment.

6.1.1 Formulation, Packaging, and Labeling

KX2-391 Ointment 1% will be supplied in single-use packets, each of which contains 250 mg of the ointment, equivalent to 2.5 mg of KX2-391 free base. Vehicle ointment will be supplied in the same single-use packets, each of which contains 250 mg of the ointment without the active drug. Each packet is for use as a single-dose application. Complete formulation contents for both KX2-391 Ointment 1% and vehicle ointment are provided in the KX2-391 Ointment Investigator's Brochure.

Each eligible randomized subject will be assigned an enrollment number and a study kit with the same enrollment number. The study kit will contain 5 packets filled with either KX2-391 Ointment 1% or vehicle ointment. Each packet and study kit will be labeled in accordance with national regulations. Detailed information regarding the study drugs, including labeling information, will be in the Clinical Operations Manual provided to the site.

The following treatments will be administered to subjects in this study (Table 2).

Table 2 Treatments in KX01-AK-003

Investigational Product	Strength	Size of Treatment Area	Number Applications and Frequency	Study Days Administered
KX2-391 Ointment 1%	1%	25 cm^2	1 application once daily for 5 consecutive days	Days 1-5
Vehicle Ointment	N/A	25 cm^2	1 application once daily for 5 consecutive days	Days 1-5

N/A = not applicable

6.1.2 Storage Conditions

Study drug will be stored in accordance with labeled storage conditions.

6.2 Dosage and Administration of Study Drugs

6.2.1 Administration of Study Drugs

At Baseline (Day 1 predose), subjects will receive verbal and written instructions on how to apply the topical medication and how to care for the treatment area (Appendix 1).

The study medication is for external topical use on the treatment area. The treatment area will be marked with indelible marker at Baseline (Day 1 predose) at the investigational site (see Section 7.2.3). Subjects will be provided with a study kit comprised of individual plastic bags with 5 single-dose packets containing either KX2-391 Ointment 1% or vehicle ointment and a dosing log.

The first dose will be administered by the subject under the supervision of study personnel on Day 1 at the site. Subjects will self-administer the remaining single-dose packets once daily at home for the next 4 consecutive days. Study medication should be applied each day at approximately the same time. It is preferable that study drug application is done early in the day. The treatment area should not be touched or wet for approximately 12 hours after application.

See Appendix 1 for subject instructions for study drug application. It is imperative that subjects wash hands **immediately** with water and soap after applying the ointment. The subject instructions also contain additional details including precautions associated with ointment application during the 5 days of treatment and throughout the study.

6.2.1.1 Instructions in the Event of Ocular Exposure

Subjects will be instructed to avoid getting ointment in their eyes. If ointment does get in the eyes, the subject is to flush their eyes with water immediately and extensively. The subject must immediately contact the Investigator who will provide further instructions and will refer the subject to an ophthalmologist. The ophthalmologist's assessment will be included in the report of ocular exposure as an event of special interest (see Section 8.2.3).

6.2.2 Criteria for Interruption of Treatment/Dose Adjustments

Not applicable; dose adjustment is not allowed.

6.3 Randomization/Method of Assigning Subjects to Treatment Groups

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

Subjects will be assigned to treatments in a double-blinded manner based on a computer-generated randomization scheme. Based on the randomization scheme, 2 lists of enrollment numbers will be issued to each site; one list will be for subjects with the treatment area on the face and the other list will be for subjects with the treatment area on the scalp. Study kits bearing corresponding enrollment numbers will be provided to the site. One set of kits will be provided for subjects with the treatment area on the face and the second set of kits will be provided for subjects with the treatment area on the scalp.

Enrollment numbers and study kits are distributed sequentially. The first eligible subject with AK lesion on the face will be assigned the first enrollment number for treatment of the face and given a study kit bearing the same enrollment number on Day 1 of treatment. The next eligible subject with AK lesions on the face will receive the next enrollment number and corresponding study kit in a sequential order.

The same procedure will occur for subjects with the treatment area on the scalp. On Day 1, the first eligible subject with AK lesions on the scalp will be assigned the first enrollment number for treatment on the scalp and given a study kit bearing the same enrollment number. The next eligible subject with AK lesions on the scalp will receive the next enrollment number and corresponding study kit in a sequential order.

Refer to the Clinical Operations Manual for details of procedures of study kit dispensing and documentation.

6.3.1 Blinding

The Sponsor, contract research organizations (CROs) involved in the clinical conduct of the study, the Investigators, study site personnel and study subjects will be blinded to the treatment that is assigned to each subject. The integrity of this clinical study must be maintained by observing the treatment blind. See Section 8.2.5 for breaking the blind.

6.4 Prior and Concomitant Medications / Therapy

6.4.1 Prior Medications / Therapy

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and procedures taken 28 days before Day 1 are considered prior therapy and will be recorded in the eCRF. A complete AK treatment history will be recorded on the AK Treatment History eCRF (see Section 7.1.4).

6.4.2 Concomitant Medications/Therapy

Concomitant medication/therapies are any new or existing therapy received by the subject after signing the ICF through the final subject contact in the study. Concomitant medication/therapies will be recorded in the eCRF.

Use of sunblock from Day 15 onward or any topical products for treatment of LSRs in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication eCRF up to Day 57.

During the Recurrence Follow-up Period, sunblock and non-medicated topical products can be used in the treatment area. During the Recurrence Follow-up Period, only concomitant medications/therapies for the treatment of AEs in the treatment area and those that may affect the assessment of AK lesion recurrence in the treatment area will be entered in the eCRF.

6.4.3 Prohibited Medication/Therapy

Use of any treatment for AK lesions other than study drug on the treatment area is prohibited during the study. Subjects will be reminded that AK lesions located outside the treatment area may be treated by lesion-directed treatment only, eg, cryotherapy or biopsy.

Prohibited medications are as 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, photodynamic therapy, psoralen plus UVA or UVB therapy, artificial tanner, excessive or prolonged exposure to UV light source.[9]

Subjects are prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments, moisturizers, sunscreen, artificial tanners, or make-up to the treatment area up until the end of Day 57 (Visit 7), except when those medications are prescribed by the Investigator for the management of LSRs. Subjects should avoid direct sun or UV exposure to the treatment area throughout the study. However, 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.

During the Recurrence Follow-up Period, use of treatments that may interfere with the assessment of AK recurrence in the treatment area are prohibited. This includes use of AK treatment and medicated topical products in the treatment area and use of systemic therapies (eg, immunosuppressive agents and systemic AK treatment) that may interfere with the assessment of AK recurrence.

Any subjects who start systemic or topical therapies for the treatment of AK 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.

6.4.4 Other Prohibitions and Restrictions during Study

There are no restrictions during the study on smoking/tobacco use, diet, alcohol/caffeine, water or other beverages, or physical activity.

After self-application, subjects will avoid touching or wetting the treatment area for approximately 12 hours. When washing the treatment area, wash it gently with a mild, non-abrasive, non-medicated soap or shampoo.

The treatment area should not be occluded with bandages, band aids, tight-fitting scarfs or caps. The treatment area should not be exposed to excessive sunlight or UV light. See Appendix 1 for all prohibited activity.

6.5 Drug Accountability and Treatment Compliance

6.5.1 Drug Supplies and Accountability

Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (eg, shipment, dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional 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.

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 (or its designee).

The clinical research associate (CRA) will review drug accountability during monitoring site visits.

The Investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply. Post-Day 57, and as appropriate during the study, the Investigator (or a designated pharmacist) will return all used and unused drug packets, study kits, drug labels, and a copy of the completed drug disposition form to the clinical supply vendor.

Refer to the Clinical Operations Manual for instructions and contact information.

6.5.2 Treatment Compliance

Subjects will return the used ointment packets (or unused ointment, if not administered) back to the clinical site on Day 5 (Visit 3) postdose, to check compliance.

The dosing logs for each subject will be kept during the study. The CRAs will review treatment compliance during monitoring site visits.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Screening Assessments

All screening assessments will be performed after the subject provides informed consent (Table 1). Screening (Visit 1) will occur between Day -28 and Day -1.

Subject screening numbers will be assigned at Visit 1.

The eCRF must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

7.1.1 Informed Consent

Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Documentation will be required (documented in the clinic notation) to confirm that the Investigator ensured that the informed consent process was done correctly, the subject understood what to expect, and agreed to participate.

Procedures to be followed when obtaining informed consent are detailed in Section 10.3.2.

7.1.2 Inclusion/Exclusion Criteria

Subject eligibility will be confirmed per the inclusion/exclusion criteria at Screening.

7.1.3 Demography

Subject demography information will be collected at Screening. Demography information includes age at time of consent, sex, race/ethnicity.

7.1.4 Medical/Surgical and Actinic Keratosis History

Medical and surgical history and current medical conditions will be recorded at Screening.

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 and surgical modalities dating back to the initial diagnosis.
- History of cancers including skin cancers, eg, BCC, SCC, melanoma.

7.1.5 Prior Medications

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies taken 28 days before Day 1 will be recorded at Screening.

7.1.6 Fitzpatrick Skin-Type Classification

The Fitzpatrick Skin-Type is a skin classification system[8] 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.

7.1.7 Expanded Dermatological Examination

An expanded dermatological examination to cover sun-exposed areas where photo-damage is likely will be conducted at Screening only.

7.1.8 Treatment Area Identification and AK Lesion Count Examination

At the Screening visit, a dermatologist (Investigator or Subinvestigator) will identify a contiguous treatment area affected with AK on the face or scalp for each subject that measures 25 cm^2 and contains 4 to 8 AK lesions that are clinically typical, visible, and discrete. A dermatologist (Investigator or Subinvestigator) will perform a count of AK lesions (lesion count) for all subjects.

7.1.9 Physical Examinations

A complete PE will be performed at Screening and 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 at Screening only. An expanded dermatological examination will be conducted at Screening only (Section 7.1.7). The complete PE will be part of the baseline assessments.

7.1.10 Vital Signs

Vital signs will be recorded at Screening. 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. Serial vital signs may be obtained to confirm accurate readings.

7.1.11 Electrocardiograms

Electrocardiogram training, equipment, and a procedural manual will be provided to the site by the central ECG vendor. The ECG vendor and the Sponsor will ensure that the study site ECG operator is properly trained prior to start of study.

A standard 12-lead ECG will be obtained at Screening. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. Screening ECGs must be reviewed prior to the subject being randomized.

ECGs will be transferred electronically to the central ECG vendor.

7.1.12 Laboratory Measurements

Samples for clinical laboratory testing (hematology, chemistry, urinalysis) will be collected at Screening. Clinical laboratory testing will be part of the baseline assessments. See Section 7.3.4.9 for further details about laboratory tests.

7.1.13 Pregnancy Testing

In females of childbearing potential, a serum pregnancy test will be obtained at Screening. Test results must be reviewed before randomization of subjects.

7.2 Baseline Assessments

All baseline assessments should be completed by Day 1 (Visit 2) prior to randomization, according to the Schedule of Procedures and Assessments (Table 1).

7.2.1 Inclusion/Exclusion Criteria

Subject eligibility will be re-confirmed per the inclusion/exclusion criteria at Baseline.

7.2.2 Prior Medications

All prior medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies will be confirmed at Baseline.

7.2.3 Treatment Area Identification

At Baseline (Day 1 predose), the Investigator will confirm the 25 cm^2 treatment area affected with 4 to 8 AK lesions on the face or scalp that was identified at Screening.

At Baseline (Day 1 predose), the location and shape of the treatment area and the specific AK lesions will be recorded on an acetate transparency sheet gridded with 1 cm^2 squares. The Investigator or Subinvestigator will identify the treatment area by:

1. Placing the transparency sheet over the treatment area
2. With a fine-tip indelible marker:
    - Mark at least 3 anatomical landmarks in the vicinity of the treatment area on the transparency sheet. Examples of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
    - Mark the outline of the treatment area on the transparency sheet.

- Mark the location of each of the AK lesions inside the treatment area on the transparency sheet.

3. On the subject's skin, outline the treatment area with dots and dashes with the indelible marker.

The transparency sheet will be kept at the site and will be used to locate the treatment area and AK lesions during the follow-up visits.

7.2.4 Actinic Keratosis Lesion Count

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at Baseline (Day 1 predose). The same Investigator or Subinvestigator will conduct the lesion count at all visits for an individual subject.

For this assessment, an AK lesion should be counted only if it is completely inside the treatment area.

7.2.5 Focused Dermatological Exam of Treatment Area

At Baseline (Day 1 predose), the focused dermatological exam of treatment area will include evaluation for LSRs, hypo- or hyper-pigmentation, and scarring (see below). These assessments will be used as baseline assessments.

7.2.5.1 Local Skin Reactions

At Baseline (Day 1 predose), after the assessment of AEs, the Investigator or Subinvestigator will assess for LSRs on the treatment area. The same Investigator or Subinvestigator will conduct the LSR assessment at all visits for an individual subject.

LSR signs on the treatment area include the following: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. These signs will be assessed using a 4-point grading scale; 0=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense).

Application site reactions not classified as LSRs (eg, itching, burning, stinging, tenderness, pain) will be reported as AEs.

LSRs will be reported separately from AEs.

7.2.5.2 Pigmentation and Scarring

At the time of LSR assessment, hypo- and hyper-pigmentation and scarring on the treatment area will be assessed by the Investigator or Subinvestigator as being present or absent.

Pigmentation and scarring will be assessed at Baseline (Day 1 predose), after the assessment of adverse events. The same Investigator or Subinvestigator will assess pigmentation and scarring at all visits for an individual subject.

7.2.6 Standardized Photography

At Baseline (Day 1 predose), 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.

7.2.7 Vital Signs

Vital signs will be measured at Baseline (Day 1 predose). See Section 7.1.10 for details.

7.2.8 Electrocardiograms

A 12-lead ECG will be obtained at Baseline (Day 1 predose). See Section 7.1.11 for details.

7.2.9 Pregnancy Testing

In females of childbearing potential, a urine pregnancy test will be performed at the site at Baseline (Day 1 predose). Test results must be reviewed before randomization on Day 1.

7.2.10 Randomization

After screening and baseline assessments confirm a subject's eligibility to participate in the study, he/she will be assigned the next enrollment number appropriate for the area being treated (see Section 6.3).

7.2.11 Instructions for Self-administration of Study Treatment, Dispensing, and Return of Study Treatment

At Baseline (Day 1 predose), subjects will receive both verbal and written instructions (Appendix 1) for daily self-administration of study treatment. Any questions will be answered by the clinic staff.

Randomized subjects will be assigned an enrollment number and a study kit with the same enrollment number. The study kit will have 5 single-dose packets (1 for each day of treatment) containing either KX2-391 Ointment 1% or vehicle ointment (see Section 6.1.1). The study kit will include a dosing log where the subjects will record the date and time of study drug self-administration.

Subjects will be instructed to place the used packets (including torn pieces) into the plastic bags in which they came, seal the plastic bags, put them back into the study kit, and return the study kit containing used and unused packets and the dosing log to the clinical site after self-administration on Day 5 to check compliance (Section 6.5.2).

7.3 Treatment Period and Response Assessment Period

7.3.1 Treatment Administration – Days 1-5

After baseline assessments are completed on Day 1, the first dose of study treatment will be applied by the subject under the supervision of study site personnel. Subjects will then take home the study kit containing the remaining single-dose packets of study drug for daily self-administration on the next 4 consecutive days.

7.3.2 Efficacy Assessments

7.3.2.1 Actinic Keratosis Lesion Count

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at the Response Assessment Visits on Days 8, 15, 29, and 57 (Table 1). The same Investigator or Subinvestigator will conduct the lesion count at all visits for an individual subject.

The Investigator or Subinvestigator may use the transparency and/or photograph from Baseline to locate the treatment area. AK lesion counts from previous visits should not be used to assist in the assessment of AK lesion count at the current visit. Only AK lesions completely within the treatment area will be counted.

7.3.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

7.3.4 Safety Assessments

Safety assessments will include the monitoring and recording all AEs, SAEs, LSRs, and events of special interest.

At each study visit, subjects will be asked a general question “How have you been since the last visit?”. Adverse events will be recorded at each study visit, before assessment of LSRs, pigmentation, and scarring in the treatment area. Adverse events will be reported separately from LSRs.

Safety assessments will also include vital signs, the performance of PEs, ECGs, laboratory evaluation of hematology, biochemistry, and urinalyses, as detailed in the sections below.

7.3.4.1 Adverse Events

All AEs will be assessed periodically through Day 57 (Table 1).

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 drugs are KX2-391 Ointment 1% and vehicle ointment.

The criteria for identifying AEs in this study 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 non-protocol-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 of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (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 subject contact in the study. Subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

Subjects who fail screening primarily due to AE(s) must have the AE(s) recorded in the AE eCRF and screen failure reported on the eCRF.

Subjects with onset of a study treatment-related AEs will be followed until resolution, under medical care, or deemed stabilized by the Investigator. 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 eCRF.

Laboratory Adverse Events

A treatment-emergent abnormal laboratory test result should be considered as a 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 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

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 eCRF.

Electrocardiogram Changes

Any changes from the baseline ECG will be evaluated for clinical significance. ECG changes that are determined to be clinically significant, regardless of relationship, will be reported as an AE.

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 8.1).

7.3.4.1.1 Assessing Severity of Adverse Events

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

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 7.3.4.2 for the definition of an SAE).

7.3.4.1.2 Assessing Relationship to Study Treatment

Every effort must be made by the Investigator to categorize each AE according to its relationship to the 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 non-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 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

Not Related: The AE is clearly not related to investigational product and is clearly related to underlying disease, environmental or toxic factor(s), or other drug therapy.

7.3.4.2 Serious Adverse Events

All SAEs will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (Table 1).

A 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.

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

7.3.4.3 Events of Special Interest

All events of special interest will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (Table 1).

In addition to the AEs and SAEs described above, events of special interest are to be captured and reported in the appropriate eCRF and Events of Special Interest Forms (see Section 8.2). Events of special interest will be considered as SAEs if they meet the criteria for an SAE (Section 7.3.4.2).

Events of special interest during the Treatment and Response Assessment Periods (Days 1 to 57) are as follows:

- Overdose of study medication
- Pregnancy
- Ocular exposures to study medication
- Skin cancers (including BCC, SCC, and melanoma); location and treatment will be reported.

7.3.4.4 Concomitant Medications

Concomitant medications will be assessed during the Treatment and Response Assessment Periods, on Days 1, 5, 8, 15, 29, and 57 (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 eCRF up to Day 57. The Investigator will record any AE on the Adverse Event eCRF for which the concomitant medication/therapy was administered.

Use of sunblock from Day 15 onward or any topical products for the treatment of LSRs in the treatment area allowed by the Investigator will be recorded in the Concomitant Medication eCRF up to Day 57.

7.3.4.5 Focused Dermatological Exam of Treatment Area and Standard Photography

The focused dermatological exam of the treatment area includes evaluation of LSRs, pigmentation, and scarring (see Section 7.3.4.5.1, and Section 7.3.4.5.2, respectively).

Standardized photography will be performed at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) (Table 1). See Section 7.2.6 for details.

7.3.4.5.1 LOCAL SKIN REACTIONS

After the assessment of AEs at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) (Table 1), the Investigator or Subinvestigator will assess for LSRs in the treatment area. See Section 7.2.5.1 for details. The same Investigator or Subinvestigator will conduct the LSR assessment at all visits for an individual subject.

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

Treatment for any LSR will be recorded on the Concomitant Medications eCRF. Interruption/discontinuation of study treatment for an LSR will be recorded on the eCRF.

7.3.4.5.2 PIGMENTATION AND SCARRING

Hypo- and hyper-pigmentation and scarring in the treatment area will be assessed at the Response Assessment Visits (Days 5, 8, 15, 29, and 57) (Table 1). See Section 7.2.5.2 for details. The same Investigator or Subinvestigator will assess pigmentation and scarring at all visits for an individual subject.

7.3.4.6 Physical Examinations

A complete PE will be performed on Day 57 (Table 1) and 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 at Screening only.

Documentation of the PE will be included in the source documentation at the site(s). Changes from screening PE to findings at the last visit that meet the definition of an AE will be recorded on the Adverse Event eCRF.

7.3.4.7 Vital Signs

Vital signs will also be recorded at the Response Assessment Visits on Days 5 and 57 (Table 1). 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. Serial vital signs may be obtained to confirm accurate readings.

Clinically significant abnormal vital signs, as assessed by the Investigator, will be reported as adverse events.

7.3.4.8 Electrocardiograms

Electrocardiograms will be obtained at the Response Assessment Visits on Days 5 and 15 (Table 1). See Section 7.1.11 for details.

Any ECG abnormality that the Investigator considers as an AE should be recorded as such on the Adverse Event eCRF.

7.3.4.9 Laboratory Measurements

Blood will be collected for clinical laboratory tests at Response Assessment Visits on Days 8 and 15 (Table 1). Collection of blood and urine (including samples for pregnancy testing, where applicable) will be conducted at the clinic site. Approximately 8 mL of blood will be collected for clinical laboratory testing, including pregnancy testing, when required, for a total of 24 mL of blood per subject during the study. All samples will be sent to a central laboratory for testing.

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 eCRF.

The clinical laboratory tests to be measured during the study are provided in Table 3.

Table 3 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
Chemistry	
Electrolytes	chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), direct bilirubin, total bilirubin
Renal function tests	blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, uric acid
Urinalysis (dipstick)	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
Pregnancy Testing	serum pregnancy test or urine pregnancy test (see Table 1)

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 7.3.4.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 7.3.4.2), the site must report the SAE, including the laboratory report (as regionally required), to the Sponsor using the SAE form (see Section 8.1).

7.3.5 Pregnancy Testing

Serum pregnancy tests will be obtained at the Response Assessment Visits on Days 8 and 57 (Table 1). All samples will be sent to a central laboratory for testing.

7.4 Additional Follow-up Assessments

All subjects who have unresolved LSRs, hypo- or hyper-pigmentation, scarring in the treatment area, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until resolution, returned to baseline, or deemed stabilized by the Investigators.

7.5 Recurrence Follow-up Period Assessments

7.5.1 Recurrence Assessments

A dermatologist (Investigator or Subinvestigator) will perform a count of clinically visible AK lesions (lesion count) for subjects who achieve 100% clearance of AK lesions in the treatment area at Day 57 during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits (Table 1). The Investigator or Subinvestigator performing the lesion count should be the same Investigator or Subinvestigator who evaluated the subject previously during the study.

An AK lesion should be counted only if it is completely inside the treatment area. All AK lesions in the treatment area must be counted and recorded in the eCRF as an AK recurrence.

When AK lesions are identified in the treatment area, the transparency which was used to map the AK lesions at Baseline should be used to determine if the lesion(s) is new (ie, one which was not identified in the target treatment area at Baseline and emergent during the Recurrence Follow-up Period) or recurred (ie, one which is at the same AK lesion location identified at Baseline and resolved at Day 57).

For subjects who have complete response at Day 57 and no recurrence, 12 months post-Day 57 is the Final Visit. Subjects who have AK recurrence in the treatment area will have their Final Visit at the visit when the AK recurrence is identified. Subjects who develop AK lesions in the treatment area during the Recurrence Follow-up Period will be discontinued at the time of recurrence.

7.5.2 Safety Assessments

During the Recurrence Follow-up Period, safety assessments will include the monitoring and recording of AEs and SAEs within the treatment area at the 3-, 6-, 9- and 12-month visits (Table 1). See Section 7.3.4.1 for further information on the assessments of AEs.

Concomitant medications/therapies given for AEs within the treatment area and any concomitant medications/therapies given that may affect assessment of AK lesions recurrence in the treatment area will be assessed during the Recurrence Follow-up Period at the 3-, 6-, 9- and 12-month visits (Table 1) and will be recorded on the Concomitant Medication eCRF. The Investigator will record any AE within the treatment area on the Adverse Event eCRF for which the concomitant medication/therapy was administered.

Events of special interest during the Recurrence Follow-up Period include skin cancers (including BCC, SCC, melanoma) within the treatment area and pregnancy. Information on skin cancers will be collected during the Recurrence Follow-up Period at the 3-, 6-, 9- and

12-month visits and reported as an event of special interest and as an AE in the Adverse Event eCRF (see Section 8.2.4).

7.6 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of adults with AK.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, PEs, ECGs, and assessment of AEs, are standard evaluations to ensure subject safety. The tests used to evaluate AK lesions including AK lesion counting, LSR grading, application site AEs, and evaluation of pigmentation and scarring in the treatment area are standard.

8 EXPEDITED REPORTING

Serious adverse events and events of special interest (overdose of study medication, pregnancy, ocular exposure to study medication, and skin cancers [including BCC, SCC, and melanoma]) are to be reported to the Sponsor within 1 business day of the Investigator becoming aware of the event. Specific forms for reporting each type of event will be provided to the sites.

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 and events of special interest information in the manner described below.

In determining what SAEs meet criteria for expedited reporting, the current version of the KX2-391 Ointment Investigator's Brochure will be used as the reference safety information for KX2-391 Ointment 1%.

8.1 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.

Detailed contact information and SAE reporting requirements will be provided in the Investigator File.

During Screening, Treatment and Response Assessment Periods, all SAEs must be reported beginning from the time the subject signs the study ICF, up to 30 days following the last contact or Day 57, whichever is shorter. All SAEs will be reported regardless of causality.

During the Recurrence Follow-up Period, only SAEs within the treatment area will be reported. SAEs within the treatment area will be reported regardless of causality. Once

recurrence of AK lesions occurs in the treatment area, and the subject is discontinued from the Recurrence Follow-up Period, SAEs will no longer be collected.

Any SAE event judged by the Investigator to be related (definitely, probably, or possibly related) to 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.

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 subject's assigned enrollment 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 redacted copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

8.2 Reporting of Events of Special Interest

8.2.1 Pregnancy

Any pregnancy, whether occurring in a subject or in the female partner of a male subject, must be reported. Pregnancies in female subjects for which the estimated date of conception was prior to Day 57 must be reported; pregnancies in female partners of male subjects for which the estimated date of conception was within 90 days of the last study treatment must be reported.

The Pregnancy Report Form must be used for reporting. 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.

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 SAEs and should be reported in the same timeframe and in the same format as all other SAEs (see Section 8.1).

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 female subject who becomes pregnant during the Treatment Period must be withdrawn from study treatment, but may continue all study assessments and be followed for study outcome. Male subjects whose female partners become pregnant during the Treatment Period may continue with study treatment and all assessments.

A pregnant female subject should be requested to provide outcome information on any pregnancy occurring during the Treatment Period or the Recurrence Follow-up Period whether or not the subject elects to continue with study assessments. Male subjects whose female partners become pregnant within 90 days of the last study treatment should be requested to provide outcome information on the pregnancy.

8.2.2 Study Drug Overdose

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied or for a duration longer than specified in the protocol.

The Overdose Report Form must be used for reporting. The overdose 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 event. The contact information for the reporting of overdose is provided in the Investigator File.

Any study drug overdose during the study must be noted on the eCRF.

All AEs associated with overdose should be captured on the Overdose Report Form and the Adverse Event eCRF. If the overdose is associated with an SAE, an SAE Report Form should be completed and sent along with the Overdose Form.

8.2.3 Ocular Exposure

Ocular exposure to study medication will be reported as an event of special interest.

The Ocular Exposure Report Form must be used for reporting. The ocular exposure 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 event. The results of an ophthalmologist's assessment must be provided as a follow-up on the Ocular Exposure Report Form. The contact information for the reporting of ocular exposure is provided in the Investigator File.

Ocular exposure to study medication must be captured on the appropriate eCRF. If the ocular exposure is associated with an AE, the AE must be captured on the Ocular Exposure Report Form and the Adverse Event eCRF. If the ocular exposure is associated with an SAE, an SAE Report Form should be completed and sent along with Ocular Exposure Report Form.

8.2.4 Skin Cancer

During the Treatment and Response Assessment Periods (Days 1 to 57), all skin cancers (including BCC, SCC, and melanoma) will be reported as events of special interest. The location and treatment will be reported. During the Recurrence Follow-up Period, skin cancers (including BCC, SCC, and melanoma) within the treatment area will be reported as events of special interest. The treatment of the skin cancer will be reported.

The Skin Cancer Report Form must be used for reporting. The skin cancer 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 event. The contact information for the reporting of skin cancers is provided in the Investigator File.

The skin cancer must be captured on the Adverse Event eCRF. Any other AEs associated with the skin cancer must be captured on the Skin Cancer Report Form and the Adverse Event eCRF. If the skin cancer is associated with an SAE, an SAE Report Form should be completed and sent along with Skin Cancer Report Form.

8.2.5 Breaking the Blind

The Pharmacovigilance department will maintain a secure copy of the set of sealed envelopes, each containing the subject's treatment allocation for this study. The Investigator may request to unblind the treatment assignment of any subject when this is needed for proper medical management of a medical emergency or SAE. Agreement of the Sponsor's Medical Monitor or designee should be sought prior to unblinding. Instructions for requesting unblinding of a subject will be provided in the Clinical Operations Manual.

The Pharmacovigilance department may unblind individual cases when required for safety reporting. The treatment assignment will be included on the MedWatch or CIOMS form for suspected unexpected serious adverse reaction (SUSAR) reports provided to health authorities.

9 STATISTICAL METHODS

9.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the database is locked and released for unblinding. Database lock, randomization code release, and subsequent data analyses will be performed in 2 steps.

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

For the second step, after the entire study has been completed, the data collected during the Recurrence Follow-up Period will be locked and the randomization code will be released to the study sites as well. Then, the recurrence rate and AEs in the treatment area after Day 57 will be analyzed.

Statistical analyses will be performed using SAS software or other validated statistical software as required. The statistical analyses of the study data are described in this section. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP), which will be written and signed off prior to unblinding of Day 57 data.

If not specified, the baseline value of each assessment will be defined as the latest non-missing value assessed before the first dose of study treatment.

9.1.1 Study Endpoints

9.1.1.1 Primary Endpoint

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

9.1.1.2 Secondary Endpoints

Secondary endpoints are as follows:

- Evaluation of LSRs, pigmentation and scarring in the treatment area, AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs)
- Partial clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with a ≥75% reduction in the number of AK lesions identified at Baseline (Day 1 predose) in the treatment area
- Reduction in AK lesion counts during Days 1 to 57
- Recurrence rate of AK lesions in subjects who achieved complete clearance at Day 57
- AEs within the treatment area after Day 57 and up to 12 months post-Day 57

9.1.2 Definitions of Analysis Sets

Intent-To-Treat (ITT) Population: all randomized subjects. This is the primary efficacy population.

Per-Protocol (PP)/Evaluable Population: all randomized subjects who have received at least 4 of the 5 doses, conformed to the protocol as to entry criteria, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.

Safety Population: all randomized subjects who have received at least one dose of study treatment.

Recurrence Follow-up Population: all subjects who achieved complete clearance at Day 57, regardless of which treatment they received.

9.1.3 Subject Disposition

All subjects will be tabulated as to study discontinuation and the reasons for discontinuation as described in Section 5.3.

Discontinuations through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.

9.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. For continuous demographic variables, results will be presented as n, mean, standard deviation (SD), median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be summarized for each category.

9.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded using the WHO Drug Dictionary.

Prior medications will be defined as medications/therapies taken 28 days before Day 1. Concomitant medications/therapies will be defined as medications/therapies 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 summary of concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All prior and concomitant medications/therapies will be presented in subject data listings.

9.1.6 Efficacy Analyses

9.1.6.1 Primary Efficacy Endpoint Analysis

To achieve statistical significance in the study as a whole with concordance in both face and scalp, the Day 57 complete clearance rate will be analyzed using a Cochran-Mantel-Haenszel (CMH) model controlling for treatment and treatment location (face and scalp); possible treatment/location interaction will be addressed by analyzing the treatment locations independently to show concordance. The Pearson Chi Square (used to power the study) will be used to demonstrate basic agreement with the CMH.

Prior to unblinding the data, the number of subjects enrolled per site will be reviewed and an investigator site analysis of how low enrollment sites might be combined and the impact of high enrollment sites will be fully discussed.

Exploratory analyses may be conducted to identify outlier study sites. The outlier sites will be discussed and an exploratory analysis excluding the outlier sites may be carried out to estimate the impact of site-by-treatment interactions. This process will be documented.

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

9.1.6.2 Secondary Efficacy Endpoint Analyses

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

The number of AK lesions and the change from baseline at each scheduled visit will be summarized using descriptive statistics (ie, mean, SD, median, minimum and maximum) by treatment group and then contrasted for each treatment group.

Recurrence rate will also be determined at each scheduled visit after Day 57.

9.1.6.3 Missing Data Handling and Sensitivity Analysis

For all efficacy analyses, all missing data caused by subject early discontinuation will be imputed with a last observation carried forward (LOCF) method. For subjects without any post-baseline lesion assessments, the baseline values will be regarded as the Day 57 evaluation results.

A sensitivity analysis with the assumption that all early-terminated subjects are not responders for complete clearance or partial clearance at Day 57 in the ITT population will be used to examine the robustness of the drug efficacy.

9.1.6.4 Subgroup Analysis

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

9.1.7 Safety Analyses

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

Safety data will be summarized by treatment group using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include evaluation of LSRs, pigmentation and scarring in the treatment area,

AEs, SAEs, events of special interest, clinical laboratory data, and other safety assessments (vital signs, PEs, ECGs).

Safety data collected through Day 57 and during the Recurrence Follow-up Period will be analyzed separately.

9.1.7.1 Extent of Exposure

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

9.1.7.2 Adverse Events

For AEs, verbatim terms on the eCRF 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).

All AEs, treatment-emergent or otherwise, will be presented in subject data listings. Only those AEs that are treatment-emergent will be included in summary tables.

Treatment-emergent AEs are defined as:

- either those AEs with an onset after the first dose or
- those pre-existing AEs that worsen after the first dose.

TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT and treatment group. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (by highest mild, moderate or severe rating) and by relationship to study treatment. Treatment-related TEAEs include those events considered by the Investigator to be related (definitely, probably, or possibly related) to study treatment.

By-subject listings of all SAEs and events of special interest will be provided. If any deaths occur in the study, a by-subject listing of all AEs leading to death will be provided.

A subject data listing of all AEs leading to discontinuation from the study will be provided.

For subjects who have treatment-related AEs at Day 57, all safety endpoints observed during any additional follow-up assessments will be listed.

During the Recurrence Follow-up Period, TEAEs in the treatment area will be summarized separately.

9.1.7.3 Laboratory Values

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

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 Day 8 and baseline to Day 15 in each treatment group.

All laboratory data will be listed by subject.

9.1.7.4 Pregnancy Tests

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

9.1.7.5 Vital Signs

Vital sign values will be listed by subject.

9.1.7.6 Electrocardiograms

All ECG data will be listed for each subject. A by-subject listing of clinically significant ECG abnormality data will be provided.

9.1.7.7 Physical Examinations

Physical examination findings will be listed for each subject.

9.1.7.8 Local Skin Reactions and Pigmentation and Scarring

LSR, hyper- or hypo-pigmentation and scarring assessment results obtained through Day 57 will be displayed and summarized by visit and treatment group. In addition, a composite score, which is defined as the sum of 6 individual LSR scores from the same visit, will be analyzed in the same way.

All LSR, hyper- or hypo-pigmentation, and scarring assessment results during any additional follow-ups after Day 57 will be presented in the by-subject listings.

9.1.8 Determination of Sample Size

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

9.1.9 Interim Analysis

No interim analysis is planned for this study.

9.1.10 Other Statistical/Analytical Issues

Not applicable

9.1.11 Procedure for Revising the Planned Analysis

If the prespecified plans for analysis 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 PROCEDURES AND INSTRUCTIONS

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6[7], Section 4.5).

10.1 Access to Source Data / Documents

The Sponsor's CRA will maintain contact with the Investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and Institutional Review Board (IRB) review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Medical history or other questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRB

In addition to the routine monitoring procedures, qualified personnel designated by the Sponsor may conduct audits of clinical research activities in accordance with the Sponsor's standard operating procedures (SOPs) to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an

inspection during the study or after its completion, the Investigator must inform the Sponsor immediately.

10.2 Quality Control and 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 will 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.

10.2.1 Data Collection

Data required by the protocol will be documented in the participant source documentation and entered into a validated electronic data capture (EDC) system.

Responsible site personnel will enter the information required by the protocol onto the eCRFs in accordance with the eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to verify the data on eCRFs for completeness and accuracy against the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF.

Data that are provided by an external vendor will be transferred and validated according to the procedures specified in the Data Management Plan.

All data derived from the study will be the 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.

10.2.2 Clinical Data Management

There will be a Data Management Plan to detail all relevant data management activities, from eCRF design to database lock.

Quality control for all relevant data management activities and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

10.3 ETHICS

This study will be conducted in accordance with 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 GCP guidelines

- Title 21 of the US Code of Federal Regulations (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

10.3.1 Institutional Review Boards

The protocol, any protocol amendments, and ICF will be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 (GCP), Section 3, and any local regulations. Any protocol amendment and/or revision to the ICF will receive appropriate approval prior to implementation. Verification of unconditional approval of the protocol will be transmitted to the Sponsor prior to the shipment of drug supplies to the investigational site. The Investigators or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

A signed letter of study approval from the IRB chairman must be sent to the Principal Investigator 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 decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

Study progress is to be reported to IRB annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB, 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 of any reportable AEs per ICH guidelines and local IRB standards of practice. Upon completion of the study, the Investigator will provide the IRB with a brief report of the outcome of the study, if required.

At the end of the study, the Sponsor should notify the IRB within 90 days.

In the case of early termination/temporary halt of the study, the Investigator should notify the IRB within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

10.3.2 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator (or designee) 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.

The 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. At the Screening Visit, after the ICF and any other written information to be provided is read and explained, the subject will be asked to sign the ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An approved ICF must be prepared in accordance with ICH E6, and all applicable regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

10.4 Data Handling and Recordkeeping

10.4.1 Recording of Data

An eCRF must be completed for each subject by qualified and authorized personnel. Any correction to entries made on the eCRF must have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

10.4.2 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

10.4.3 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents, ICFs, and IRB correspondence. In addition, the Sponsor will send a list of treatment codes by study subject to the Investigator after the clinical database for this study has been locked. The sites should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

10.5 Publication Policy

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each Investigator and the Sponsor or CRO, as appropriate.

10.6 Other Administrative Policies

10.6.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's Medical Monitor and the IRB for the site(s) must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided the health or regulatory authority and IRBs are immediately notified and appropriate documentation of the urgent protocol change are submitted per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB should be kept informed of such changes as required by local regulations.

10.6.2 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the Investigator, the Investigator's staff, and the IRB, and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/Investigator and the Sponsor/CRO.

10.6.3 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB and provide them with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11 REFERENCE LIST

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

9. Draft Guidance on ingenol mebutate, January 2016. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481827.pdf

12 APPENDICES

APPENDIX 1 INSTRUCTIONS FOR SUBJECTS' SELF-ADMINISTRATION OF STUDY TREATMENT

The study kit contains:

- 5 packets filled with study drug, inside individual plastic bags
- A dosing log

Storage:

Store the study kit at room temperature and in a secure place, out of direct sunlight, and away from food products, children, and pets.

Patient Instructions:

Application of study drug is preferably done early in the day and at approximately the same time every day for a total of 5 days. The first dose will be self-administered in the clinic.

Follow these steps to apply study drug:

- Take the dosing log in the study kit and record the date and time of dosing.
- Open the plastic bag and remove a single-dose packet.
- Tear the packet open along the perforations.
- Squeeze a small amount of ointment from the packet on your fingertip and apply it evenly over the entire treatment area (Note: Each packet contains more than the amount needed for 1 treatment application.).
- Place the used packet (including torn pieces) into the plastic bag in which it came, seal the plastic bag, and put it back into the study kit.
- Wash hands **immediately** with water and soap.
- Place the dosing log back into the study kit and store away the study kit, as instructed above, in a secure place.
- Repeat the above steps for each day of treatment at about the same time each day.
- On Day 5, apply treatment **before** returning to clinic. Bring the study kit (containing all used and unused packets) and the dosing log with you.

Precautions on Treatment Days (Days 1-5):

- Subjects who wear contact lenses should put on their contact lenses BEFORE applying study drug.
- Avoid touching or wetting the treatment area for approximately 12 hours. If you touch the treatment area, wash your hands immediately.
- Avoid activities that might cause excessive sweating, so that the ointment will not get in your eyes.
- If ointment does get into your eyes, flush your eyes with water immediately and extensively. You must immediately contact the study doctor who will give you further instructions. You will be referred to an eye doctor so your eyes can be examined.
- If any severe local skin reaction occurs or persists, let your study doctor know immediately.
- Do not apply study drug more than once each day.
- Do not allow other people or pets to come into contact with the treatment area. If the treatment area is touched, the area of contact on the other person or pet should be washed immediately.
- Do not cover the treatment area with bandages, band aids, tight-fitting scarfs, or caps.

Precautions Throughout the Study:

- When washing the treatment area, wash it gently with a mild, non-abrasive, non-medicated soap or shampoo.
- Do not expose the treatment area to excessive sun light or ultraviolet light, including tanning beds. When outdoors, wear protective loose clothing over the treatment area.
- Do not use moisturizers, sunscreen, artificial tanners, make-up or other over the counter-topical products to the study treatment area until Day 57. If you are unsure of what to use, ask your study doctor. After 15 days, if you are unable to avoid excessive sun light or ultraviolet light to the treatment area, the study doctor may allow you to use sunblock.
- Do not use medications not approved by your study doctor.
- After Day 57, sunblock and non-medicated topical products can be used in the treatment area.

PROTOCOL SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

Study Protocol Number:	KX01-AK-003
Study Protocol Title:	A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp
Investigational Product Name:	KX2-391 Ointment 1%
IND Number:	122464
UTN Number:	U1111-1191-8233

SIGNATURES

Authors:

PPD PPD MD
Medical Monitor
Athenex, Inc.

PPD
Date

PPD , MS
Study Biostatistician
Athenex, Inc.

Date

PROTOCOL SIGNATURE PAGES

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IND Number:	122464
UTN Number:	U1111-1191-8233

SIGNATURES

Authors:

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Medical Monitor
Athenex, Inc.

Date

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Athenex, Inc.

PPD

Date

INVESTIGATOR SIGNATURE PAGE

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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 of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date