A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP COMPARISON STUDY TO DETERMINE THE THERAPEUTIC EQUIVALENCE OF A GENERIC INGENOL MEBUTATE GEL, 0.015% AND PICATO® GEL, 0.015% IN SUBJECTS WITH ACTINIC KERATOSIS ON THE FACE OR SCALP

NCT03200912

SAP dated: November 26, 2016

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STATISTICAL ANALYSIS PLAN

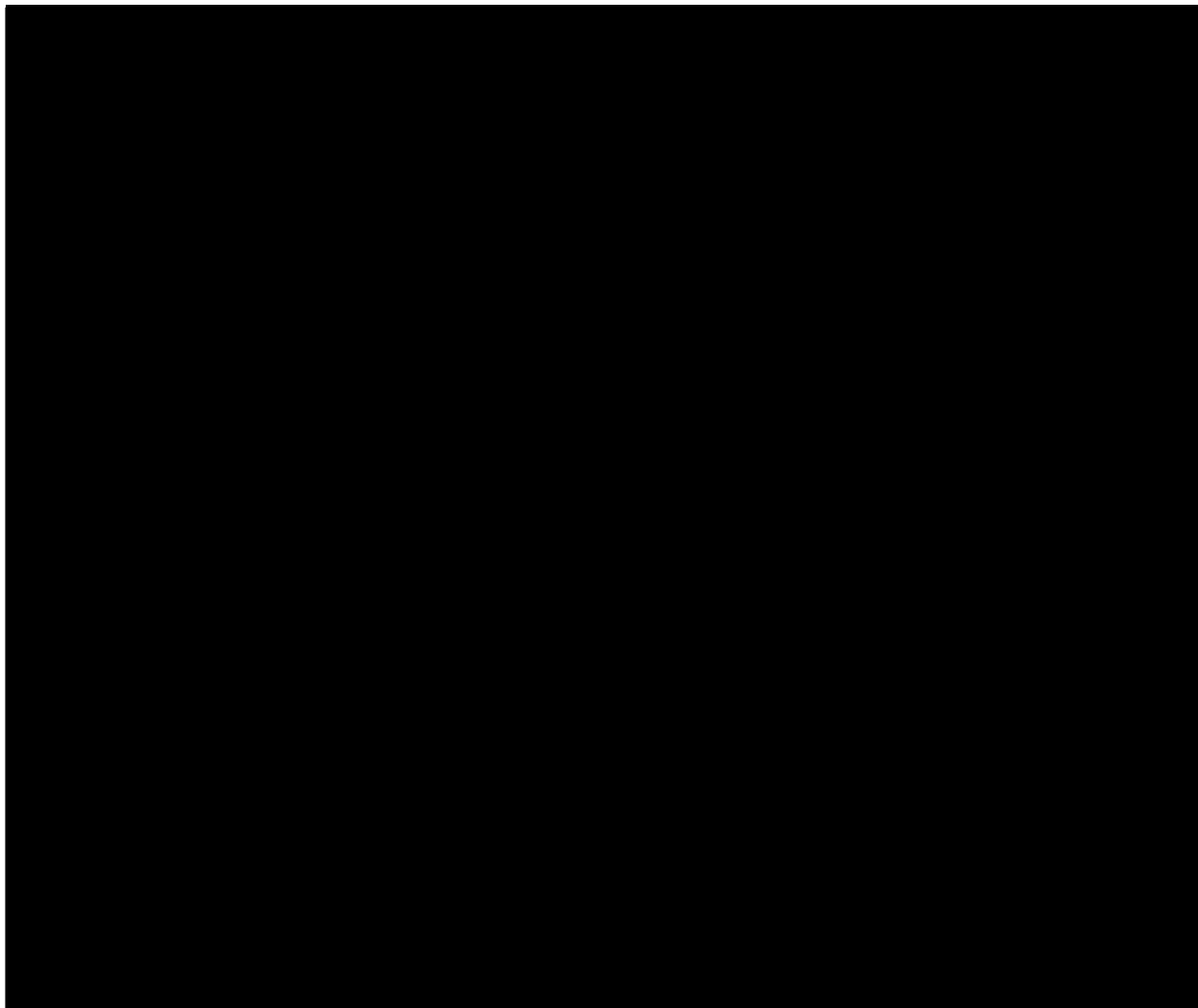|	
Title:	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of a Generic Ingenol Mebutate Gel, 0.015% and Picato® Gel, 0.015% in Subjects with Actinic Keratosis on the Face or Scalp
Protocol Number:	094-8152-301
Sponsor:	Actavis Laboratories UT
██ **Project Number:**	094-8152-301
Date:	29NOV2016
Status:	v1.0

This statistical analysis plan has been reviewed and approved by:
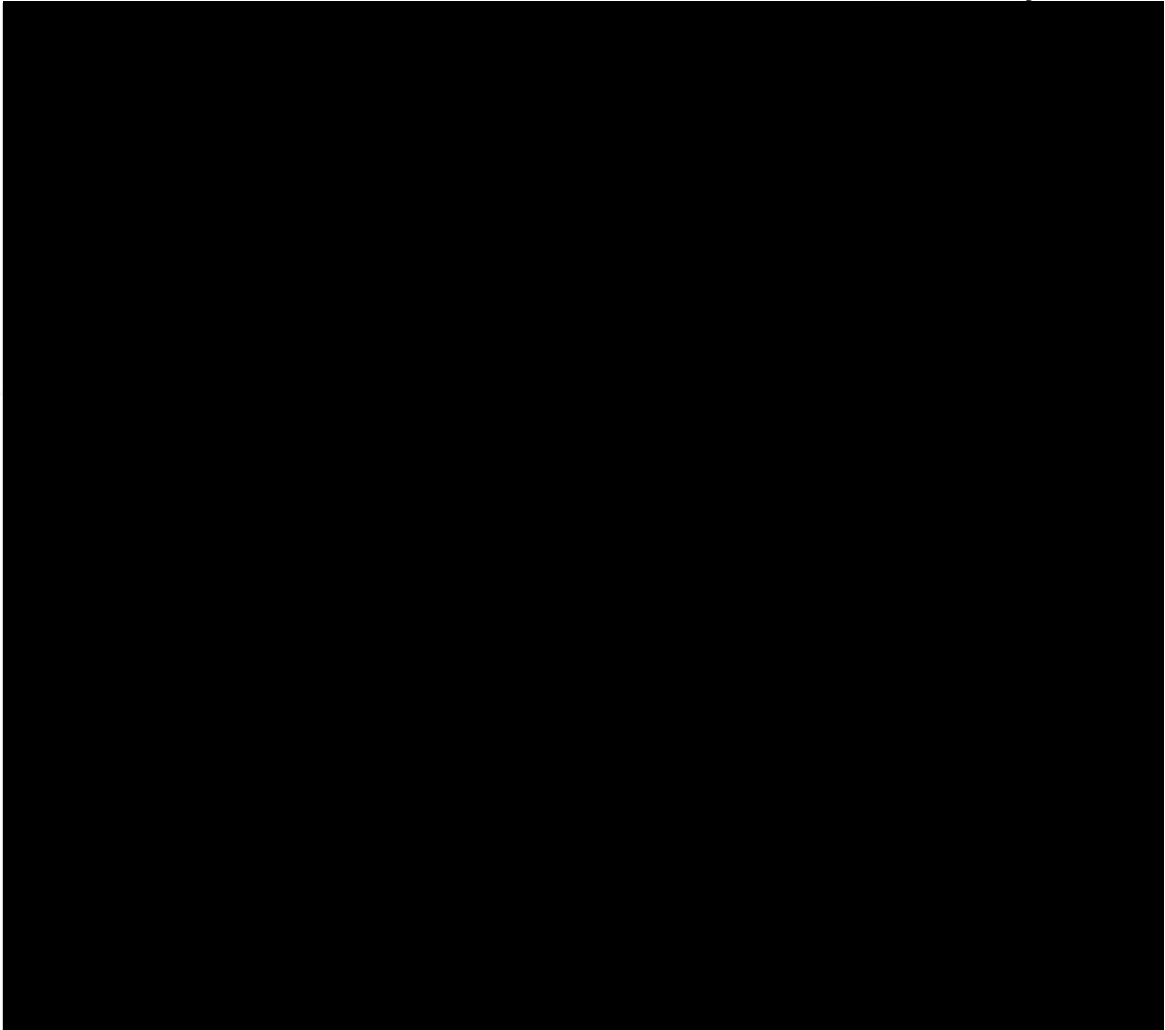
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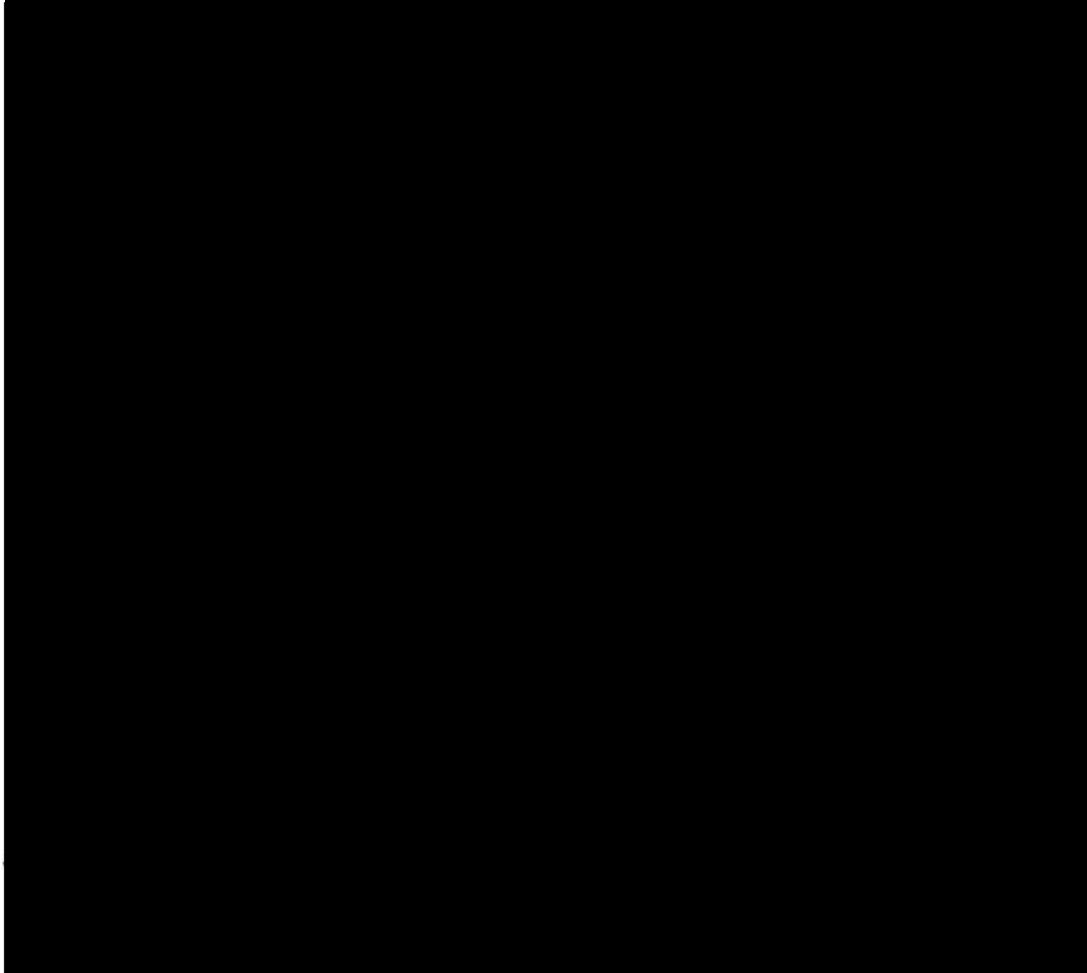
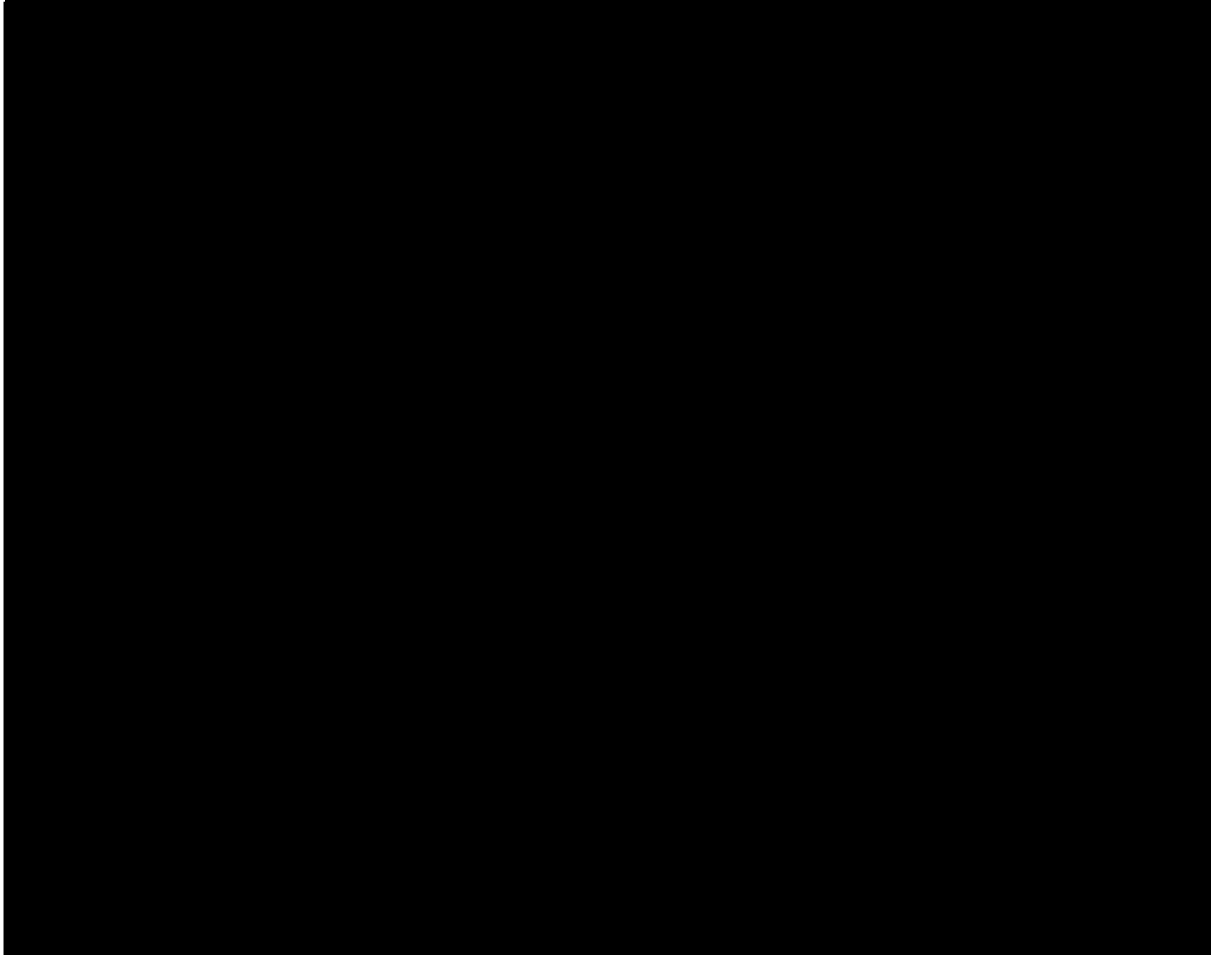**This statistical analysis plan has been reviewed and approved by:**

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GLOSSARY OF TERMS

Abbreviation	Definition
AE	Adverse Event
AK	Actinic Keratosis
ATC	Anatomical Therapeutic Classification
BSA	Body Surface Area
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
EOS	End of Study
IWRS	Interactive Web Response System
mITT	Modified Intent-to-Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
UPT	Urine Pregnancy Test
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1   INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol 094-8152-301, "A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of a Generic Ingenol Mebutate Gel, 0.015% and Picato® Gel, 0.015% in Subjects with Actinic Keratosis on the Face or Scalp."

This SAP was created using Clinical Protocol 094-8152-301 Version 1.0 dated 26May2016, and the Electronic Case Report Forms (eCRF) for Protocol 094-8152-301 Version 1.0 dated 26Jul2016.

2   PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol 094-8152-301. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3   STUDY OBJECTIVES AND ENDPOINTS

The objectives of the study are to evaluate the safety and therapeutic equivalence of generic ingenol mebutate gel, 0.015% to Picato gel, 0.015% by establishing the therapeutic comparability of the two active products and the superiority of the two active products over the vehicle gel in the treatment of actinic keratoses (AK) on the face and scalp.

Primary efficacy endpoint is the proportion of subjects in each treatment group with complete clearance of AK lesions at Visit 6/Day 57. Complete (100%) clearance is defined as having no (zero) clinically visible AK lesions in the Treatment Area.

Safety endpoints will include assessment of the severity and frequency of Adverse Events (AEs) and Local Skin Reactions (LSRs).

4   STUDY DESIGN

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study of a generic ingenol mebutate gel, 0.015% and Picato® (ingenol mebutate) gel, 0.015% (LEO Pharma, Inc.) in subjects 18 years of age and older with AKs on the face or scalp. Approximately 480 subjects with at least four (4), but no more than 8, visible and discrete nonhyperkeratotic, non-hypertrophic AK lesions, each at least 4 mm in diameter on the face or scalp who fulfill the inclusion/exclusion criteria will be enrolled at approximately 26 study sites.

Subjects will be randomized to one of three treatment groups on a ▓▓▓▓ basis as follows:
- Ingenol mebutate gel, 0.015% (Actavis) [Test, generic]
- Picato® (ingenol mebutate) gel, 0.015% (LEO Pharma Inc.) [Reference]
- Vehicle gel (Actavis) [Placebo]

Subjects who are eligible for enrollment into the study will be randomized by assigning the lowest subject kit number available among kit numbers assigned by IWRS initially at each site. All subjects will apply the assigned test article to the designated Treatment Area once daily for three consecutive days. Subjects will return to the clinic for follow-up on Days 4, 8, 15, 29, and 57. At the end of the study, efficacy outcome measures will be compared to a) determine if dosing with generic ingenol mebutate gel, 0.015% is therapeutically equivalent to the currently marketed Picato® (ingenol mebutate) gel, 0.015% and b) both generic and reference active gel formulations are superior to the vehicle gel.

5 STUDY SCHEDULE OF EVENTS

VISIT	Visit 1[1] Screening/ Baseline	Treatment Period (at home)	Visit 2 End of Treatment	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 4	Visit 6 EOS[2] Week 8
DAY	1	1-3	4	8 ± 2	15 ± 2	29 ± 2	57 ± 2
Informed Consent	X						
Demographics	X						
Inclusion/Exclusion	X						
Medical / Dermatological History	X						
Fitzpatrick Skin Type Assessment	X						
Brief Physical Exam[3]	X						
Vital Signs[4]	X						
UPT[5] for WOCBP[6]	X						X
Definition of Treatment Area[7]	X						
AK Lesion Count and Evaluation	X					X	X
LSR Assessment	X		X	X	X	X	X
Test Article Accountability: Dispense (D), Return (R)	D		R	R[8]			
Subject Diary: Dispense (D), Return (R)	D		R	R[8]			
Test Article Application		X					
Concomitant Medications and Therapies Review	X		X	X	X	X	X
Adverse Events	X		X	X	X	X	X

[1] Screening assessments may be performed up to 30 days prior to Baseline for those subjects that are qualified for enrollment, but require wash-out of prohibited medications and/or therapies. Screening and Baseline may be combined into a single visit for those subjects who do not require washout. Subjects who require washout for longer than 30 days will be re-consented.

[2] Or early discontinuation from the study.

[3] Brief physical exam will include assessment of head and neck, cardiovascular, respiratory, gastrointestinal (abdomen), gross motor and gait.

[4] Vital signs assessment will include height, weight, temperature, blood pressure (systolic and diastolic), heart rate, and respiration rate.

[5] UPT must have minimum sensitivity of 25 mIU β-hCG/mL.

[6] WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal [defined as amenorrheal >12 consecutive months in women 50 years of age and older].

[7] Treatment Area will be defined as a contiguous 25 cm² area on the face or scalp with at least four and no more than eight AKs.

[8] Any "uncollected" test articles or subject diaries will be collected.

6　DEFINITIONS

- End of Study (EOS): Visit 6/Day 57 or Early Termination Visit
- Study Day: The study day is the day of study relative to the date of randomization (Baseline visit/Day 1).
  Study Day = follow-up visit date − first dose date + 1
- Baseline: The baseline assessment is defined as the last non-missing measurement collected at Baseline visit prior to the test article application.

7　CLINICAL EVALUATIONS

7.1　Efficacy Measurements

7.1.1　*AK Lesion Evaluation and Counting*

AK lesion counts will be performed at Visit 1/Baseline, Visit 5/Day 29, and Visit 6/Day 57. At the Baseline Visit (Visit 1) all AK lesions in the selected contiguous 25 cm^2 Treatment Area, independent of size, will be identified, counted, recorded on the transparency, and measured for size (i.e., diameter). At Visits 5 and 6, the number of total AK lesions, independent of size, in the selected Treatment Area will be counted including Baseline AKs and new AKs; a new AK is defined as a lesion that was not present at Visit 1/Baseline.

The AK clearance rate within treatment area for a subject at post-baseline follow-up visits will be calculated as follows:

$$\{1 - [\frac{\#AKs\ at\ follow-up}{\#AKs\ at\ Baseline}]\} * 100.$$

Therefore, if the AK count at follow-up visits is 0, the clearance rate will be 100%, i.e., complete clearance of AK lesions.

7.2　Safety and Baseline Measurements

7.2.1　*Adverse Events*

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A treatment emergent AE (TEAE) is defined as an AE that started on or after the first dose date.

Serious adverse events (SAE) are defined as any untoward medical occurrence that at any dose in the view of either the Investigator or Sponsor results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/birth defect.

The severity of an AE will be recorded as mild, moderate or severe. The relationship between an AE and the test article will be classified as related, possibly related or not

related. The AE outcome will be specified as not recovered/resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, fatal, or unknown.

7.2.2 *Local Skin Reactions Assessments*

At every visit, LSRs will be assessed in the Treatment Area and adjacent surrounding skin using a four-point ordinal scale of 0 = absent, 1= mild (slight, barely perceptible), 2=moderate (distinct presence) and 3 = severe (marked, intense) for the following:
- Erythema
- Flaking/scaling
- Crusting
- Swelling/edema
- Vesiculation/pustulation
- Erosion/ulceration
- Hyperpigmentation
- Hypopigmentation
- Scarring

These LSRs will be collected independently of adverse events (AEs). Only LSRs that require medical intervention (e.g., prescription medication), require withholding of the application of the test article), or extend beyond 2 cm outside of the Treatment Area will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.

7.2.3 *Fitzpatrick Skin Type Assessment, Brief Physical Exam and Vital Signs*

Fitzpatrick skin type (I-VI) assessment will be performed at the Baseline Visit.

Fitzpatrick Skin Phototype		
Skin Phototype	**Typical Features**	**Tanning Ability**
I	Pale white skin, blue/Hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

In addition, a brief physical examination will be performed at the Baseline Visit. The physical examination will include head and neck, cardiovascular, respiratory, gastrointestinal (abdomen), gross motor and gait with findings recorded in the medical history. Vital signs including temperature, blood pressure (diastolic and systolic), heart rate, and respiration rate, as well as height and weight, will be assessed at the Baseline Visit.

7.2.4 *Laboratory Tests*

Urine Pregnancy Tests (UPTs) will be performed on all WOCBP at the Baseline Visit prior to randomization and at the EOS visit.

7.2.5 *Prior/Concomitant Medications and Concurrent Therapies/Procedures*

Details of prior and concomitant medication use and concurrent therapies/procedures will be collected for each subject.

8 STATISTICAL METHODS

8.1 General Considerations

All statistical processing will be performed using SAS® Version 9.4 or higher, unless otherwise stated. For continuous variables, descriptive statistics will include the number of subjects with non-missing data (n), and mean, median, standard deviation, minimum and maximum values. For categorical variables, the number and percentage of subjects within each category will be presented. Subject data listings will be sorted by treatment group, study site and subject number. Summaries will be provided as specified below.
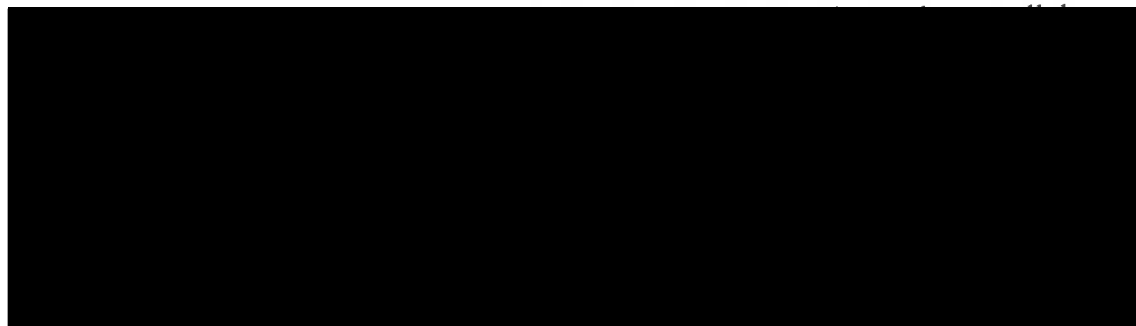
8.2 Analysis Populations

8.2.1 *Safety Population*

The Safety population will include all randomized subjects who received the test article.
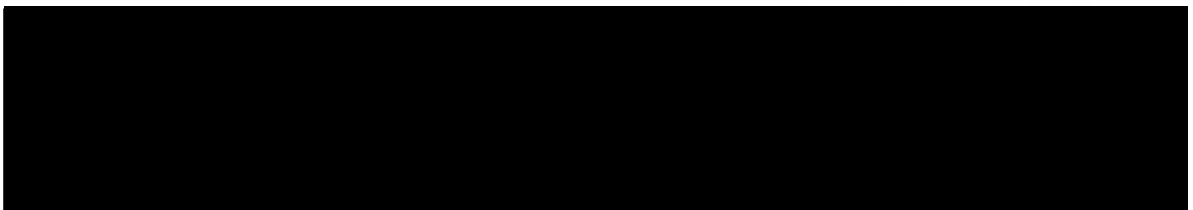
8.2.2 *mITT Population*

The modified Intent-to-Treat (mITT) population will include all randomized subjects who applied at least one dose of test article.

8.2.3 *PP Population*

8.3 Methods for Handling Missing Data

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8.4   Subject Disposition

Subjects who complete the three consecutive days of treatment and all of the Visit 6/Day 57 evaluations will be considered to have completed the study.

The number and percent of subjects who were enrolled in the study, who completed the study, and who withdrew from the study will be tabulated by treatment group for the Safety, mITT and PP populations along with their reasons for discontinuation.

Subjects who are excluded from the PP population with their reasons for exclusion will be listed.

The number of subjects who were screen failures will be tabulated by site and reason for screen failure.

8.5   Screening and Baseline Assessments

8.5.1   *Demographic and Baseline Characteristics*

Gender, age, race, ethnicity and Fitzpatrick Skin Phototype will be summarized by treatment group for the Safety, mITT and PP populations.

Characteristics of the AK lesions in the Treatment Area at Baseline will be summarized including the location, total number of AK lesions and the number of AK lesions at least 4 mm in diameter.

Informed consent information and subject eligibility status will be provided in a listing.

8.5.2   *Medical History and Physical Exam*

Medical/dermatological history will be coded into system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary version 19.0. The number and percentage of unique subjects reporting each medical history will be summarized by SOC and PT for the Safety population. Start and end dates with ongoing status will be presented in a subject data listing. Abnormalities noted during the physical exam will be collected in the medical history.

8.5.3   *Vital Signs*

Systolic and diastolic blood pressures (mm Hg), pulse rate (beats/minute), temperature (°F), and respiration rate (breaths/minute), as well as, height (in) and weight (lbs) will be summarized by treatment group for the Safety population.

8.5.4   Prior Medications/Therapies/Procedures Identified in the Exclusion Criteria

Listings will be provided for the prior medications and therapies/procedures that needed a washout period prior to the subjects' enrollment.

8.6   Efficacy Analyses

8.6.1   Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of subjects in the PP population with treatment success (complete clearance of AK lesions) at Day 57, where complete clearance of AK lesions is defined as having no (zero) clinically visible AK lesions in the Treatment Area.

Subjects who discontinued early from the study due to lack of treatment effect or who worsen and require alternate or supplemental therapy will be included in the PP and the mITT populations as treatment failures (non-responders). For subjects who are discontinued prematurely for any other reasons, LOCF imputation will be used to impute missing AK lesion counts in the mITT population.

Test for bioequivalence of test and reference treatments

To establish bioequivalence for the proportion of subjects with treatment success, the following hypotheses will be tested in the PP population:

H_0: $\pi_T - \pi_R \leq -0.2$ or $\pi_T - \pi_R \geq 0.2$
H_A: $-0.2 < \pi_T - \pi_R < 0.2$

,where π_T is the proportion of subjects with treatment success in test treatment group (generic ingenol mebutate gel (Actavis)) and π_R is the proportion of subjects with treatment success in reference treatment group (Picato® gel).

The null hypothesis, H_0, is rejected with a type I error (alpha) of 0.05 (two one-sided tests) if the estimated 90% Wald's confidence interval with Yate's continuity correction for the difference of the success rates between test and reference treatment groups ($\pi_T - \pi_R$) is contained within the interval [-0.2, 0.2]. Rejection of the null hypothesis supports the conclusion of equivalence of the test and reference treatments.

This analysis will be repeated for mITT population as a supportive analysis.

Test for superiority of each active treatment over vehicle treatment

To establish that the study is sufficiently sensitive to detect difference between treatments, two-sided, continuity-corrected chi-square tests with an alpha of 0.05 will be used to test the superiority of each active treatment group's treatment success rate over

that of the Vehicle treatment in the mITT population. If any cells have an expected frequency of less than 5, then Fisher's exact tests will be used instead.

This analysis will be repeated for PP population as a supportive analysis.

8.7 Dosing Compliance and Test Article Exposure

Test article compliance will be determined by the total number of test article applications verified from the data in the subject diaries. Compliant subjects are defined as those who applied all three test article applications and had no other evidence of material dosing non-compliance.

Frequency tables of the total number of applications and the duration of treatment by treatment group will be presented for the mITT and PP populations.

8.8 Safety Analyses

8.8.1 *Adverse Events*

AE terms will be coded into SOC and PT using MedDRA Coding Dictionary version 19.0. Tabulations of the number and percent of unique subjects reporting each TEAE will be presented by SOC, PT, and treatment group for (a) AEs, (b) serious AEs, (c) AEs by maximum severity, (d) AEs by closest relationship to study drug and (e) AEs within treatment area. AEs will be counted only once for a subject within each PT and SOC. If a subject reports a PT multiple times with differing severities/relationships to study medication, the subject is counted once for the PT with the maximum severity and the closest relationship, respectively.

All adverse events will be listed.

8.8.2 *Local Skin Reactions*

The frequency of the individual LSRs will be tabulated by severity and treatment group at each visit. LSRs will also be summarized for each treatment group by the total score (sum of all LSRs) at Baseline, and Days 4, 8, 15, 29, and 57 and by the worst score of each individual LSR.

8.8.3 *Urine Pregnancy Tests*

Results of UPT tests will be provided in a subject data listing.

8.8.4 *Concomitant Medications and Concurrent Therapies/Procedures*

Concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary (version 01Sep2015). The medications will be tabulated by treatment group and Drug Class (pharmacological level, ATC3).

Prior and Concomitant medications and concurrent therapies/procedures will be provided in separate subject listings.

8.9   Sample Size

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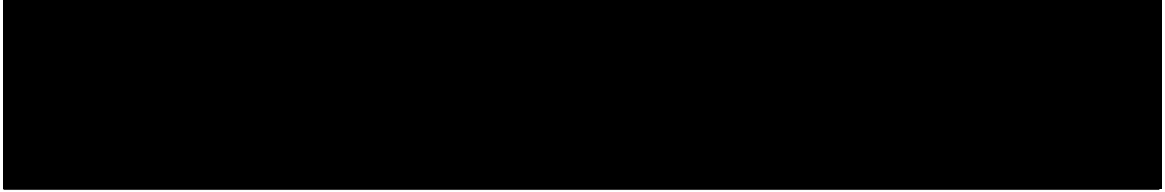
8.10   Protocol Deviations

Protocol deviations will be provided in a subject listing.

8.11   Interim Analysis

No interim analyses are planned.

8.12   Subgroup Analyses

No subgroup analyses are planned.

List of Tables: