

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

Protocol dated: May 26, 2016

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IN SUBJECTS WITH ACTINIC KERATOSIS ON THE FACE OR SCALP**

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ORIGINAL PROTOCOL: May 26, 2016
FILENAME: 094-8152-301_pro_26May2016_v1.0
SPONSOR: Actavis Laboratories UT
SPONSOR REPRESENTATIVE: [REDACTED]
Principal Scientist, Clinical R&D
MEDICAL MONITOR: [REDACTED]

PROJECT MANAGER: [REDACTED]

24 Hour Emergency Telephone Number
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Product Name: Generic Ingenol Mebutate Gel, 0.015%
Sponsor Name: Actavis Laboratories UT

Protocol: 094-8152-301
Protocol Date: May 26, 2016

PROTOCOL APPROVAL

The following individuals approve version 1.0 of the 094-8152-301 protocol dated May 26, 2016. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Actavis Laboratories UT Representative:

[REDACTED]
Principal Scientist, Clinical R&D

Signature: _____ Date: _____

[REDACTED]
Medical Monitor

Signature: _____ Date: _____

[REDACTED]
Vice President, Clinical Development

Signature: [REDACTED] Date: [REDACTED]

[REDACTED]
Senior Lead Biostatistician

Signature: [REDACTED] Date: [REDACTED]

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Vice President, Clinical Development

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Senior Lead Biostatistician

Signature: [REDACTED]

Date: [REDACTED]

CONFIDENTIAL
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STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Actavis Laboratories UT.

I have read this protocol and agree that it contains all the details necessary to conduct the study as described. I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from Actavis Laboratories UT. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Actavis Laboratories UT of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Actavis Laboratories UT, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to Actavis Laboratories UT and must be treated in the same manner as the contents of this protocol.

Printed Name of Principal Investigator

Investigator Signature

Date

Protocol number: _____

Site number: _____

Version: 1.0

Date of final version: May 26, 2016

Product Name: Generic Ingenol Mebutate Gel, 0.015%
Sponsor Name: Actavis Laboratories UT

Protocol: 094-8152-301
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PROTOCOL SYNOPSIS

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
Study Type	Bioequivalence with Clinical Endpoint
Test Articles	TEST: Ingenol Mebutate Gel, 0.015% (Actavis) REFERENCE: Picato [®] (ingenol mebutate) Gel, 0.015% (LEO Pharma, Inc.) PLACEBO: Vehicle Gel (Actavis)
Study Objective	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 keratosis on the face and scalp.
Study Design	Multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison.
Treatment Groups	Each enrolled subject will be randomized [REDACTED] to treatment with either generic ingenol mebutate gel, Picato Gel, or vehicle gel. Subjects will apply the test article to the Treatment Area once daily for three days.
Duration of Treatment	Three days.
Duration of Study	Approximately eight weeks for an individual subject.
Study Population	Male or female subjects at least 18 years of age with actinic keratosis (AKs) on the face or scalp. NOTE: Subjects may have AKs on both the face and scalp; however, only one contiguous skin area of approximately 25 cm ² (e.g., 5 cm x 5 cm) will be treated as part of this study.
Total Number of Subjects	Approximately 480 subjects [REDACTED]
Number of Sites	Approximately 26 sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria:

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	<ol style="list-style-type: none">1. Subject is male or non-pregnant female 18 years of age or older.2. Females must be post-menopausal,¹ surgically sterile,² or use an effective method of birth control.^{3,4} Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)⁵ at Visit 1/Baseline.3. Subject has provided written informed consent.4. Subject has a clinical diagnosis of AK at Visit 1/Baseline with at least four, but no more than eight visible and discrete non-hyperkeratotic, non-hypertrophic AK lesions, each at least 4 mm in diameter, within a contiguous 25 cm² treatment area ("the Treatment Area") located on the face or scalp.5. Subject is willing and able to apply the test article as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.6. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of AK lesions or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.
Exclusion Criteria	<p>A subject is ineligible to enter the study if he/she meets one or more of the following criteria:</p> <ol style="list-style-type: none">1. Subject is pregnant, lactating, or is planning to become pregnant during the study.2. Subject has a location of the selected contiguous 25 cm² Treatment Area that (a) is within 5 cm of an incompletely healed wound or (b) is in an area containing a lesion that was previously treated with ingenol mebutate.3. Subject has hyperkeratotic, hypertrophic, or large mat-like AKs (e.g., AK >1 cm² in size) within the contiguous 25 cm² Treatment Area.4. Subject has more than eight AKs, independent of size, within the selected contiguous 25 cm² Treatment Area.5. Subject has atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, xeroderma pigmentosum, or any other possibly confounding skin conditions on the region of the head that contains the Treatment Area (i.e., face or scalp).6. Subject has any skin pathology or condition that, in the investigator's opinion, could interfere with the evaluation of the test article or

¹ Defined as amenorrhea greater than 12 months in women 50 years of age and older.

² Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.

³ Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, or intravaginal], b) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], c) partner vasectomy (performed at least six months prior to study entry), or d) total abstinence. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

⁴ WOCBP taking hormonal therapy must be on treatment prior to study entry and must not change their dosing regimen during the study; treatment must be for (1) oral or transdermal: at least one full cycle (e.g., four to eight weeks); (2) injectable (e.g., Depo-Provera) or intravaginal (e.g., intrauterine device [IUD]): at least one week; and continued per label.

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

	<p>requires the use of interfering topical, systemic, or surgical therapy.</p> <ol style="list-style-type: none"> 7. Subject is immunosuppressed (e.g., human immunodeficiency virus [HIV], systemic malignancy, graft host disease, etc.). 8. Subject has experienced an unsuccessful outcome from previous ingenol mebutate therapy (an unsuccessful outcome is defined as after a reasonable therapeutic trial with no compliance issues and the topical drug did not work). 9. Subject used topical creams, lotions, or gels of any kind within the selected Treatment Area within one day prior to entry into the study. 10. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study or has used artificial tanners within two weeks of Visit 1/Baseline. 11. Subject has used any of the following <u>topical</u> medications on the face or scalp: <ul style="list-style-type: none"> • Corticosteroids within two weeks of Visit 1/Baseline; • Keratolytic-containing therapeutic products or medicated or irritant topical salves within two weeks of Visit 1/Baseline, including, but not limited to, alpha hydroxy acids (e.g., glycolic acid, lactic acid etc. >5%), beta hydroxy acid (salicylic acid >2%), and urea >5%; • Topical retinoids (e.g., tazarotene, adapalene, tretinoin) within two weeks of Visit 1/Baseline; • Light treatments (e.g., psoralen plus ultraviolet A [PUVA] therapy, UVB) within four weeks of Visit 1/Baseline; • Photodynamic therapy within eight weeks of Visit 1/Baseline; • 5-fluorouracil, diclofenac, imiquimod, or ingenol mebutate within eight weeks of Visit 1/Baseline; or • Other topical therapy for actinic keratosis within 2 cm of the selected contiguous 25 cm² Treatment Area within eight weeks of Visit 1/Baseline. 12. Subject has had cryodestruction or chemodestruction, surgical excision, curettage, dermabrasion, chemical peel, or laser resurfacing on the Treatment Area (i.e. face or scalp) within two weeks prior to Visit 1/Baseline. 13. Subject has used any of the following <u>systemic</u> medications: <ul style="list-style-type: none"> • Corticosteroid therapy within one month; • Interferon/interferon inducers, cytotoxic drugs, immunomodulators, or immunosuppressive therapies within one month; • Retinoid therapy within six months prior to Visit 1/Baseline. 14. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the region of the head that contains the Treatment Area (i.e., face or scalp). 15. Subject is currently enrolled in an investigational drug or device study. 16. Subject has used an investigational drug or investigational device treatment within one month prior to Visit 1/Baseline. 17. Subject has a history of sensitivity to any of the ingredients in the test articles (see Section 6.1). 18. Subject has any condition which, in the investigator's opinion, would make it unsafe or preclude the subject's ability to fully participate in this research study.
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	<p>19. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, impaired cerebral function or physical limitations.</p> <p>20. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.</p> <p>21. Subject has been previously enrolled in the same study.</p>
Study Procedures	<p>The study will consist of six clinic visits (see Schedule of Events). Subjects can be screened 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.</p> <p><u>Visit 1 (Screening/Baseline): Day 1.</u> The study requirements and procedures will be reviewed and written informed consent must be obtained prior to the initiation of any study-related procedures. Demographics, inclusion/exclusion criteria, medical/dermatological history, Fitzpatrick Skin Type assessment, and concomitant medications and therapies will be reviewed to determine subject eligibility. If required, the subject will be given adequate washout to discontinue prohibited medications or treatments as specified by the protocol.</p> <p>Once washout has been completed, the following assessments will be performed. A brief physical exam including vital signs and UPT (if applicable) will be performed. The Treatment Area will be defined as a contiguous 25 cm² area on the face or scalp containing at least four, but no more than eight AKs. All AK lesions, independent of size, in the Treatment Area will be counted and evaluated for size. Local skin reactions (LSRs) will be assessed. Subject will be randomized (1:1:1) to treatment and instructed how to apply the test article to the Treatment Area via demonstration using non-medicated samples. Test article (with instructions) and subject diary will be dispensed to the subject. The subject will be instructed to apply the test article to the designated Treatment Area once per day for three days (washing their hands after each application) and to record the date and time of applications in the subject diary. After each application the test article will be washed off after six hours. The subject will be scheduled for follow-up at Visit 2/Day 4.</p> <p><u>Visits 2, 3, and 4 (Follow-Up): Days 4, 8, and 15.</u> The subject will return to the clinic and will be queried for any changes in health status and concomitant medications and therapies. The test article and subject diary will be collected at Day 4. LSRs will be assessed. The subject will be scheduled for the next follow-up visit.</p> <p><u>Visit 5 (Follow-Up): Day 29.</u> The subject will return to the clinic and will be queried for any changes in health status and concomitant medications and therapies. AK lesions, new and pre-existing (i.e., Baseline), will be counted. LSRs will be assessed. The subject will be scheduled for Visit 6/Day 57.</p> <p><u>Visit 6 (End of Study [EOS]): Day 57.</u> The subject will return to the clinic</p>

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	and will be queried for any changes in health status and concomitant medications and therapies. A UPT (if applicable) will be performed. AK lesions, new and pre-existing (i.e., Baseline), will be counted. LSRs will be assessed. The subject will exit the study.
Study Measurements	<p><u>Efficacy:</u> The primary clinical assessment is based on complete AK lesion clearance. The number of all visible and discrete non-hyperkeratotic, non-hypertrophic AK lesions (Baseline and new lesions) in the contiguous 25 cm² Treatment Area will be assessed by the investigator at Visit 1/Baseline, Visit 5/Day 29, and Visit 6/Day 57.</p> <p><u>Safety:</u> All adverse events (AEs) will be recorded. At each visit, the subject will be questioned specifically about any AEs associated with the application of the test article as well as the status of any ongoing AEs. In addition, LSRs will be assessed and UPTs (if applicable) will be performed per the Schedule of Events.</p> <p>LSRs including erythema, flaking/scaling, crusting, swelling/edema, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, and scarring will be assessed using a four-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). These LSRs will be collected independently of 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.</p>
Study Endpoints	<p><u>Efficacy Endpoints:</u> Primary efficacy endpoint is the proportion of subjects in each treatment group with complete clearance of AK lesions. Complete clearance is defined as having no (zero) clinically visible AK lesions in the Treatment Area at Visit 6/Day 57.</p> <p><u>Safety Endpoints:</u></p> <ul style="list-style-type: none">• Incidence (including severity and causality) of any local and systemic treatment emergent AEs (TEAEs).• Incidence (by severity) of each individual LSR (erythema, flaking/scaling, crusting, swelling/edema, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, and scarring) at Days 4, 8, 15, 29, and 57.
Sample Size Calculations	<p>Based on conservative assumptions of a complete lesion clearance rate of 50% for both active treatments and a rate of no more than 15% for the vehicle treatment, 480</p> <div></div>

Statistical Methods	<p>All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment group.</p> <p>Study Populations: The Safety population will include all randomized subjects who received the test article. The mITT population will include all randomized subjects who applied at least one dose of test article. The PP population will include all randomized subjects who met all the inclusion/exclusion criteria, were compliant with the assigned test articles (applied all three doses of the test article and no other evidence of material dosing noncompliance), completed the study within the designated visit window (± 2 days), and had no protocol violations that would affect treatment evaluation. 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 population as treatment failures (non-responders). Subjects discontinued prematurely for other reasons will be excluded from the PP population, but included in the mITT population.</p> <p>Efficacy Analyses: The efficacy analyses will be conducted on the mITT and PP populations. Last-observation-carried-forward (LOCF) will be used to impute missing values for efficacy variables in the mITT population.</p> <p><i>Bioequivalence.</i> Evaluations in the PP population will be considered primary. The 90% Wald's confidence interval with Yate's continuity correction will be constructed on the difference between the proportion of subjects with complete (100%) lesion clearance in the Test and Reference treatments to evaluate bioequivalence of the two active treatments. If the 90% confidence intervals on the difference between the proportion of subjects with complete lesion clearance in the Test and Reference treatments are contained within the interval -0.20 to +0.20, then the Test and Reference products will be considered to be therapeutically equivalent.</p> <p><i>Superiority.</i> To determine study sensitivity, two-sided, Fisher's exact test with an alpha of 0.05 will be used to evaluate the superiority of each active treatment over the vehicle for the proportion of subjects with complete (100%) lesion clearance using mITT population and LOCF. This test will be repeated on the PP population.</p> <p>Safety Analyses: The analysis of safety will be conducted on the Safety population.</p> <p><u>Dosing Compliance</u> Descriptive statistics will be used to summarize test article compliance for the mITT and PP populations. Measures of test article compliance will include the total number of applications as determined from the data recorded in the subject diaries. Compliant subjects will be defined as those</p>
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	<p>who applied all three test article applications and had no other evidence of material dosing non-compliance.</p> <p><u>Local Skin Reactions</u> Severity of LSRs (erythema, flaking/scaling, crusting, swelling/edema, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, and scarring) will be recorded. LSRs will be summarized for each treatment group by frequency and severity of each individual LSR at Baseline, and Days 4, 8, 15, 29, and 57. LSRs will also be summarized for each treatment group by the most intense score of each individual LSR and by the total score (sum of all LSRs) at Baseline, and Days 4, 8, 15, 29, and 57.</p> <p><u>Adverse Events</u> All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms on the electronic case report forms (eCRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the MedDRA mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment.</p>
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SCHEDULE OF EVENTS

VISIT	Visit 1 ⁶ 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 ⁷ 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 ⁸	X						
Vital Signs ⁹	X						
UPT ¹⁰ for WOCBP ¹¹	X						X
Definition of Treatment Area ¹²	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 ¹³			
Subject Diary: Dispense (D), Return (R)	D		R	R ¹³			
Test Article Application		X					
Concomitant Medications and Therapies Review	X		X	X	X	X	X
Adverse Events	X		X	X	X	X	X

⁶ 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.

⁷ Or early discontinuation from the study.

⁸ Brief physical exam will include assessment of head and neck, cardiovascular, respiratory, gastrointestinal (abdomen), gross motor and gait.

⁹ Vital signs assessment will include height, weight, temperature, blood pressure (systolic and diastolic), heart rate, and respiration rate.

¹⁰ UPT must have minimum sensitivity of 25 mIU β -hCG/mL.

¹¹ 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].

¹² 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.

¹³ Any "uncollected" test articles or subject diaries will be collected.

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ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis or Keratoses
β-HCG	Beta-Human Chorionic Gonadotropin
cm	Centimeter
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mL	Milliliter
OTC	Over-the-Counter
PP	Per-Protocol
PT	Preferred Term
PUVA	Psoralen + UltraViolet Light A
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
[REDACTED]	
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia
UVB	Ultraviolet Light B
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

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1. BACKGROUND

Actinic keratoses (AKs) are common skin lesions which appear as scaly or crusty growths on the bald scalp, face, ears, lips, backs of the hands and forearms, shoulders, neck or any other areas of the body frequently exposed to the sun. The lesions appear as invisible or subclinical lesions as well as visible ones on the skin surface. Without treatment, AKs may spontaneously regress or progress to squamous cell carcinoma. It is unknown which AKs will develop into cancer so preventative treatment strategies are warranted. AK treatments include: topical medications (e.g., 5-fluorouracil, imiquimod, diclofenac, and ingenol mebutate), cryosurgery, combination therapies, chemical peels, laser surgery, and photodynamic therapy.

Ingenol mebutate is a pleiotropic effector which possesses a novel, dual mechanism of action as a topical therapy for skin cancer and pre-cancerous skin lesions. The anti-tumor activity of ingenol mebutate is associated with a direct cytotoxic effect on tumor cells and an enhanced innate and acquired immune response. Initially, ingenol mebutate rapidly induces necrosis, resulting in the debulking of locally-affected tumor cells. Secondly, it induces a tumor cell-specific innate immune response characterized by antibody dependent cellular cytotoxicity, which results in removal of residual disease. More recently, ingenol mebutate has been shown to also stimulate an acquired immune response through induction of tumor-specific cluster of differentiation CD8⁺ T-cell and CD4⁺ T-cell responses, resulting in further anti-tumor activity and possible long-term immunity.

Picato[®] (ingenol mebutate) gel is the first and only ingenol mebutate product approved by the FDA in 2012 for the topical treatment of AKs on the face and scalp (0.015% formulation) and on the trunk and extremities (0.05% formulation). The FDA approved regimen for ingenol mebutate gel, 0.015% for the treatment of AKs on the face and scalp is once-daily application of one unit dose tube for 3 consecutive days applied to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm).

A generic ingenol mebutate gel, 0.015% has been developed by the Sponsor for the topical treatment of clinically typical, visible, and discrete non-hyperkeratotic, non-hypertrophic AK lesions on the face and scalp.

2. RATIONALE

The Sponsor has developed a generic ingenol mebutate gel, 0.015% formulation. This trial is designed to evaluate the therapeutic equivalence of the generic formulation with the currently marketed Picato[®] (ingenol mebutate) gel, 0.015% (LEO Pharma, Inc.) formulation.

3. OBJECTIVE

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 keratosis on the face and scalp.

4. STUDY DESIGN

This is a multicenter, 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 will be enrolled at approximately 26 study sites.

Subjects will be randomized [REDACTED] to one of three treatment groups:

- **TEST:** Ingenol mebutate gel, 0.015% (Actavis)
- **REFERENCE:** Picato[®] (ingenol mebutate) gel, 0.015% (LEO Pharma Inc.)
- **PLACEBO:** Vehicle gel (Actavis)

Subjects will apply the test article to the designated Treatment Area once daily for three consecutive days. The Treatment Area will be defined as a contiguous 25 cm² area on the face or scalp with at least four, but no more than eight, visible and discrete non-hyperkeratotic, non-hypertrophic AK lesions, each at least 4 mm in diameter. Subjects will return to the clinic for follow-up on Days 4, 8, 15, 29, and 57. At the end of the study, safety and 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 POPULATION

Approximately 480 male or female subjects at least 18 years of age and older with AKs on the face or scalp will be enrolled in the study.

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is male or non-pregnant female 18 years of age or older.

2. Females must be post-menopausal,¹⁴ surgically sterile,¹⁵ or use an effective method of birth control.^{16,17} Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)¹⁸ at Visit 1/Baseline.
3. Subject has provided written informed consent.
4. Subject has a clinical diagnosis of AK at Visit 1/Baseline with at least four, but no more than eight visible and discrete non-hyperkeratotic, non-hypertrophic AK lesions, each at least 4 mm in diameter, within a contiguous 25 cm² treatment area ("the Treatment Area") located on the face or scalp.
5. Subject is willing and able to apply the test article as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
6. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of AK lesions or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has a location of the selected contiguous 25 cm² Treatment Area that (a) is within 5 cm of an incompletely healed wound or (b) is in an area containing a lesion that was previously treated with ingenol mebutate.
3. Subject has hyperkeratotic, hypertrophic, or large mat-like AKs (e.g., AK >1 cm² in size) within the contiguous 25 cm² Treatment Area.
4. Subject has more than eight AKs, independent of size, within the selected contiguous 25 cm² Treatment Area.
5. Subject has atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, xeroderma pigmentosum, or any other possibly confounding skin conditions within the region of the head that contains the selected Treatment Area (i.e., face or scalp).
6. Subject has any skin pathology or condition that, in the investigator's opinion, could interfere with the evaluation of the test article or requires the use of interfering topical, systemic, or surgical therapy.

¹⁴ Defined as amenorrhea greater than 12 months in women 50 years of age and older.

¹⁵ Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.

¹⁶ Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, or intravaginal], b) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], c) partner vasectomy (performed at least six months prior to study entry), or d) total abstinence. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

¹⁷ WOCBP taking hormonal therapy must be on treatment prior to study entry and must not change their dosing regimen during the study; treatment must be for (1) oral or transdermal: at least one full cycle (e.g., four to eight weeks); (2) injectable (e.g., Depo-Provera) or intravaginal (e.g., intrauterine device [IUD]): at least one week; and continued per label.

¹⁸ UPT must have a minimum sensitivity of 25 mIU β -hCG/mL.

7. Subject is immunosuppressed (e.g., human immunodeficiency virus [HIV], systemic malignancy, graft host disease, etc.).
8. Subject has experienced an unsuccessful outcome from previous ingenol mebutate therapy (an unsuccessful outcome is defined as after a reasonable therapeutic trial with no compliance issues and the topical drug did not work).
9. Subject used topical creams, lotions, or gels of any kind within the selected Treatment Area within one day prior to entry into the study.
10. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study or has used artificial tanners within two weeks of Visit 1/Baseline.
11. Subject has used any of the following topical medications on the face or scalp:
 - Corticosteroids within two weeks of Visit 1/Baseline;
 - Keratolytic-containing therapeutic products or medicated or irritant topical salves within two weeks of Visit 1/Baseline, including, but not limited to, alpha hydroxy acids (e.g., glycolic acid, lactic acid etc. >5%), beta hydroxy acid (salicylic acid >2%), and urea >5%;
 - Topical retinoids (e.g., tazarotene, adapalene, tretinoin) within two weeks of Visit 1/Baseline;
 - Light treatments (e.g., psoralen plus ultraviolet A [PUVA] therapy, UVB) within four weeks of Visit 1/Baseline;
 - Photodynamic therapy within eight weeks of Visit 1/Baseline;
 - 5-fluorouracil, diclofenac, imiquimod, or ingenol mebutate within eight weeks of Visit 1/Baseline; or
 - Other topical therapy for actinic keratosis within 2 cm of the selected contiguous 25 cm² Treatment Area within eight weeks of Visit 1/Baseline.
12. Subject has had cryodestruction or chemodestruction, surgical excision, curettage, dermabrasion, chemical peel, or laser resurfacing on the Treatment Area (i.e. face or scalp) within two weeks prior to Visit 1/Baseline.
13. Subject has used any of the following systemic medications:
 - Corticosteroid therapy within one month;
 - Interferon/interferon inducers, cytotoxic drugs, immuno-modulators, or immunosuppressive therapies within one month;
 - Retinoid therapy within six months prior to Visit 1/Baseline.
14. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the selected contiguous 25 cm² Treatment Area on the face or scalp.
15. Subject is currently enrolled in an investigational drug or device study.
16. Subject has used an investigational drug or investigational device treatment within one month prior to Visit 1/Baseline.
17. Subject has a history of sensitivity to any of the ingredients in the test articles (see Section 6.1).
18. Subject has any condition which, in the investigator's opinion, would make it unsafe or preclude the subject's ability to fully participate in this research study.

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Sponsor Name: Actavis Laboratories UT

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19. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, impaired cerebral function or physical limitations.
20. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
21. Subject has been previously enrolled in the same study.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will not be replaced.

6. TEST ARTICLES AND REGIMEN

6.1 Description

Test articles will be supplied in single unit tubes, one tube (each, 0.47 grams with a 0.25 grams deliverable weight) for each application.

Test article name: Ingenol mebutate, gel 0.015% (Actavis) [TEST]
Active ingredient: Ingenol mebutate
Other ingredients: [REDACTED]

Test article name: Picato[®] (ingenol mebutate) gel, 0.015% (LEO Pharma, Inc.) [REFERENCE]
Active ingredient: Ingenol mebutate
Other ingredients: Isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

Test article name: Vehicle gel (Actavis) [PLACEBO]
Active ingredient: None
Other ingredients: [REDACTED]

6.2 Instructions for Use and Application

At Visit 1/Baseline, the investigator will designate the Treatment Area [REDACTED]

[REDACTED]



Subjects will be provided with an instruction sheet detailing how to apply the test article (see Appendix 2) and a study staff member will demonstrate how to dispense and apply the test article using non-medicated samples. Subjects will be instructed to store the test article in a refrigerator at 36°F-42°F (2°C-8°C) and protect from freezing. Subjects will be instructed to keep the empty test article tube(s) and returned them to the study site after a single use application.

Subjects will be instructed to wash their hands before and after test article application. Subjects will apply the test article once daily for three consecutive days to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm) designated as the Treatment Area on the face or scalp using the provided template. The test article should be applied evenly over the skin area to be treated (i.e., the entire 25 cm² Treatment Area) using a fingertip; **in most cases, this requires the use of the entire unit of a single dose tube.** The treated areas should be allowed to dry for 15 minutes. Subjects will be instructed to record the date and time of each application in a Subject Diary (see Appendix 3).

Subjects should avoid touching the Treatment Area or doing activities that may cause a lot of sweating for six hours after application or covering the treated area with bandages or other dressings. Subjects should wash the Treatment Area with mild soap and water approximately six hours following each application of the test article. Subjects should not apply moisturizers, sunscreen, make-up, creams, lotions, powders, or any other topical product of any kind other than the assigned test article to the Treatment Area for 15 days after treatment.

6.3 Warnings, Precautions and Contraindications

The test articles are for topical use only.

Care should be taken to avoid contact with eyes and all mucous membranes. Subjects should wash their hands immediately after test article application to minimize transfer of the test article. If contact with eyes occurs, flush them with large amounts of water and get medical care as soon as possible. Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema can occur after exposure to ingenol mebutate.

Subjects with a known sensitivity to any of the ingredients in the test articles should not participate in this study.

Severe LSRs in the treated area, including erythema, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, can occur after topical application of ingenol mebutate gel. Application of ingenol mebutate gel to open wounds, infections, or exfoliative dermatitis is not recommended.

Areas treated with the test article should not be covered with any type of bandage or occlusive dressings.

In case of accidental ingestion, subjects should contact the investigator immediately.

The effects of the test article in nursing mothers, pregnant women and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the study period.

7. RANDOMIZATION ASSIGNMENT

Subjects will be randomized to one of three treatments on a [REDACTED] basis (Test [generic gel, Actavis]: Reference [Picato[®] Gel, LEO Pharma, Inc.]: Placebo [vehicle gel, Actavis]). The study will use a block randomization scheme by investigational site, which reduces the probability of imbalance in treatment allocation [REDACTED] at any given time point. Subjects who are eligible for enrollment into the study will be randomized by assigning the lowest subject kit number available at the site. Treatment group designation will remain blinded until the final database is locked (unless unblinding is required, see Section 15).

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Visit 1/Baseline) will be recorded as prior/concomitant medications with the dose and corresponding indication. The medications to be recorded include prescription, over-the-counter (OTC) medications, and vitamins, minerals, and dietary supplements being taken for a therapeutic indication. All medications taken on a regular basis should be recorded on the electronic case report forms (eCRFs) prior to commencing the use of the test article. All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Visit 1/Baseline may be continued, but must be recorded.

Any changes to concomitant medications or therapies during the study must be recorded. The reason for any change in concomitant medications and/or therapies should be evaluated and, if appropriate, reported as, or in conjunction with, an AE.

8.1 Prohibited Medications or Therapies

Prohibited medications or therapies during the study include:

- Topical creams, lotions, or gels of any kind within the selected Treatment Area and the surrounding 2 cm border area for 15 days after treatment.
- Topical medications within the region of the head that contains the selected Treatment Area (i.e., face or scalp):
 - Corticosteroids [except stable doses of intranasal, inhaled, or ophthalmic steroids used for the management of allergies, pulmonary disorders, or other conditions];
 - Keratolytic-containing therapeutic products or medicated or irritant topical salves, including, but not limited to, alpha hydroxy acids (e.g., glycolic acid, lactic acid etc. >5%), beta hydroxy acid (salicylic acid >2%), and urea >5%;
 - Topical retinoids (e.g., tazarotene, adapalene, tretinoin).
- Topical AK treatments including, but not limited to, 5-fluorouracil, diclofenac, imiquimod, or ingenol mebutate, and other at-home AK treatments at any body site.
- Any AK therapy including, but not limited to, topicals, cryodestruction or chemodestruction, surgical excision, curettage, photodynamic therapy, dermabrasion, chemical peel, or laser resurfacing on the head. NOTE: See Section 8.2 for professionally administered medical therapies of AKs deemed to be a medical necessity at a body site or in rare circumstances those on the head outside of the Treatment Area by at least a 5 cm radius.
- Artificial tanners and/or tanning devices, excessive sunlight, or light treatments (e.g., PUVA therapy, UVB).
- Systemic medications:
 - Corticosteroid therapy;
 - Interferon/interferon inducers, cytotoxic drugs, immuno-modulators, or immunosuppressive therapies;
 - Retinoid therapy.
- Investigation drug or devices.

8.2 Allowed Medications or Therapies

Ideally, treatment of AKs on the head must be avoided during the study period UNLESS the treatment is deemed by the investigator to be a material medical necessity for the subject. In such cases, the ONLY allowed treatments for AKs on the anatomic unit of the head, exclusive of the selected Treatment Area plus a 5 cm perimeter, which are focal and limited to the site of the AK using surgical excision, cryotherapy, curettage ± pin

point focal electrodesiccation. **The investigator should discuss these cases with the Medical Monitor prior to proceeding with any treatment.**

For AKs at body sites outside of the head, professionally administered medical therapies limited to cryodestruction or chemodestruction, surgical excision, curettage, photodynamic therapy, dermabrasion, or laser resurfacing are permitted, but must be recorded as concurrent procedures/therapies. Use of any other treatment methods are prohibited, as are the treatment of AKs on the head using any method.

Allowed medications or therapies during the study must be documented and include:

- Any medications not intended or beneficial for the treatment of AK, unless specifically excluded (see Section 8.1).
- Intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders, or other conditions.
- Light bodied bland moisturizer (e.g., Cetaphil, Lubriderm [without alpha hydroxy acid]) in the selected Treatment Area as an aid to managing LSRs ONLY with the approval of the Medical Monitor. NOTE: Moisturizers should not be applied within six hours of test article application.

9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

9.1 Visit 1 (Day 1): Screening/Baseline

Subject can be screened up to 30 days prior to Baseline for those subjects that are qualified for enrollment, but require washout 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 reconsented.

At Screening, the investigator or designee will:

- Obtain a signed, written informed consent.
- Record demographics.
- Confirm inclusion/exclusion criteria.
- Record medical/dermatological history.
- Perform Fitzpatrick Skin Type Assessment (Section 10.3).
- Record prior and/or concomitant medications and therapies.

If the subject requires washout from previous medications, the remaining activities will be performed after washout is complete.

- Perform a brief physical exam, with vital signs (including height and weight).
- Perform a UPT for all WOCBP (Section 12.1). Results must be negative for the subject to be enrolled in the study.

- Designate the Treatment Area as a contiguous 25 cm² area on the face or scalp which contains at least four, but no more than eight clinically typical AKs, which are ≥ 4 mm in diameter. NOTE: Use the procedure as detailed in Appendix 1 to create and label the transparency to record the designated Treatment Area.
- Create a “subject specific” template to assist the subject in the identification of the Treatment Area prior to application of the study medication (Section 6.2).
- Perform AK lesion counts (Section 10.1). NOTE: AKs measuring ≥ 4 mm in diameter should be counted for inclusion/exclusion and must be between four and eight (inclusive), but smaller lesions should also be counted, recorded such the total of all AKs in the Treatment Area does not exceed eight AK lesions.
- Evaluate the size (i.e., diameter) of each AK lesion in the selected Treatment Area.
- Document LSRs (Section 10.2).
- Randomize the subject by assigning the next available (lowest) subject number in ascending order and dispense the corresponding test article kit.
- Review and dispense a Subject Instruction Sheet (Appendix 2) to the subject. Instruct the subject to apply the test article once per day for three consecutive days at home. NOTE: Application should not be immediately after a shower or within two hours of bedtime.
- Demonstrate the proper test article application using the non-medicated samples provided for subject training and the provided Treatment Area template. Remind the subject to return all used and unused tubes of the test article at the next visit.
- Dispense the Subject Diary and provide completion instructions (Appendix 3).
- Record any AEs, if applicable.
- Schedule Visit 2/Day 4 follow-up visit.

9.2 Visits 2 (Day 4), 3 (Day 8 \pm 2), and 4 (Day 15 \pm 2): Follow-Up

At this visit, the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Use the transparency to locate the selected Treatment Area (Appendix 1).
- Document LSRs (Section 10.2).
- Collect all used and unused tubes of the test article and document in the Test Article Accountability Log [at Visit 2/Day 4].
- Collect the Subject Diary and review compliance [at Visit 2/Day 4].
- Schedule the next follow-up visit.

NOTE: Any “uncollected” test articles or subject diaries will be collected at Visit 3/Day 8.

9.3 Visit 5 (Day 29±2): Follow-Up

At this visit, the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Use the transparency to locate the selected Treatment Area (Appendix 1).
- Perform AK lesion counts (Section 10.1). NOTE: Lesions that were not present at Visit 1/Baseline will be defined as “new” AKs and will be identified, counted, and recorded.
- Document LSRs (Section 10.2).
- Schedule Visit 6/Day 57 EOS visit.

9.4 Visit 6 (Day 57±2): End of Study

At this visit, the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Perform a UPT for all WOCBP (Section 12.1).
- Use the transparency to locate the selected Treatment Area (Appendix 1).
- Perform AK lesion counts (Section 10.1). NOTE: Lesions that were not present at Visit 1/Baseline will be defined as “new” AKs and will be identified, counted, and recorded.
- Document LSRs (Section 10.2).
- Exit the subject from the study.

9.5 Unscheduled Visit(s)

A subject may have additional clinic visit(s), per discretion of the investigator, to manage any AEs or LSRs.

At this visit, the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Document LSRs, as applicable.
- Confirm the next visit.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

10.1 Actinic Keratoses Lesion Counts

AK lesions will be counted at Visit 1/Baseline, Visit 5/Day 29, and Visit 6/Day 57. At Visit 1/Baseline, AK lesions will be evaluated for size. To qualify for the study, the subject must have four to eight visible and discrete non-hyperkeratotic, non-hypertrophic, AK lesions, each at least 4 mm in diameter, within a contiguous 25 cm² treatment area ("the Treatment Area") on the face or scalp.

The Treatment Area will be defined using the three-point landmark technique (see Appendix 1). At Visit 1/Baseline, all AK lesions in the selected contiguous 25 cm² Treatment Area, independent of size, will be identified, counted, recorded on the transparency, and measured for size (i.e., diameter). AK lesions will be assigned a numeric designation (i.e., 1, 2, 3, ..., 8) to be maintained throughout the study, with qualifying (≥ 4 mm in diameter) AK lesions assigned first and smaller AK lesions assigned subsequently. The number of qualifying (≥ 4 mm in diameter) AK lesions and the total number of lesions, independent of size, will be recorded.

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.

If the subject has a LSR that prevents the investigator or designee from performing the AK count at a visit, the investigator or designee should document in the source document and eCRF that the AK count was unable to be obtained due to a LSR.

10.2 Local Skin Reactions

LSRs will be assessed in the Treatment Area and adjacent (2 cm border) surrounding skin at every clinic visit using a four-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). The following LSRs will be assessed:

- Erythema
- Flaking/scaling
- Crusting
- Swelling/edema
- Vesiculation/pustulation
- Erosion/ulceration
- Hyperpigmentation
- Hypopigmentation
- Scarring

These LSRs will be collected independently of 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.

10.3 Fitzpatrick Skin Type Assessment

The investigator or designee will document the subject's skin phototype (I-VI) at Visit 1/Baseline using the Fitzpatrick Skin Type Assessment.

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

11. PHOTOGRAPHY

Photography documentation is not required in this study. However, the investigator may elect to photograph the subject to help identify the Treatment Area location or to document the effects of treatment, AEs, or other findings during the trial. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment.

Note: Subjects may decline to have photographs taken during the conduct of the study. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

12. LABORATORY TESTS

12.1 Urine Pregnancy Tests

UPTs will be performed on all WOCBP at Visit 1/Baseline and Visit 6/Day 57 (EOS or early discontinuation). All WOCBP must have a negative UPT at Visit 1/Baseline to be eligible for study entry. The UPTs will be performed at the study site, if the site is registered and conforms to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the CRFs, in the subject's medical records, and

in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β -HCG/mL.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

13.1 Completion of the Study

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.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AE
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject: Note: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE.
- Other (e.g., any other reason that may affect the outcome of the study or the safety of subjects)

If a subject withdraws or is withdrawn from the study prematurely for any reason, the site should make every effort to have the subject return for an EOS visit to perform all of the required visit activities and to collect and reconcile all test articles (if applicable). If the subject will not agree to return for the EOS visit, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up. When a subject is withdrawn from the study for a treatment-related AE, when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed (see Section 14.5).

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

14.1 Definitions

The following definitions will be utilized:

Adverse Event (AE) - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs include any unintended sign, symptom, or disease that appears to worsen after the subject signs the informed consent for a clinical study. AEs may also include any changes in physical examination or laboratory parameters that are, in the investigator's opinion, clinically significant changes.

No causal relationship with the study drug is implied by the use of the term "adverse event". An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may also be AEs. If the event meets the criteria for a serious AE, such as an extended hospitalization, it will be considered a serious AE.

Serious Adverse Event (SAE) - Any AE that, in the view of either the investigator or the Sponsor, results in any of the following outcomes:

- Death
- Is life-threatening (Note: the term life-threatening refers to any AE that places the subject, in the view of either the investigator or Sponsor, at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events (Note: Important medical events refer to AEs that may not result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Unexpected Adverse Drug Reaction: An AE, whether serious or non-serious, is designated an unexpected (unlabeled) drug related event if it is not consistent with the risk information in the Investigator Brochure, general investigational plan or Package Insert (marketed drugs) or if the event is shown to have a materially greater frequency or severity than previously reported; then such event(s) will be reported to the investigators if, in the opinion of the Medical Monitor, such findings represent a material drug related event.

Test Article: A pharmaceutical form of an active ingredient (or “primary operational component” for devices) or vehicle/placebo being tested or used as a reference in the study, whether blinded or unblinded.

14.2 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject, observed by the Investigator, and those elicited by asking general, non-leading questions. AEs will be recorded at each visit throughout the study on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Subjects should be asked whether, since the time of the last observation or visit, they had any of the following:

- Experienced any changes in well-being
- Used any new medications
- Changed medication regimens (both prescription and OTC)
- Were admitted to a hospital or had any accidents

All questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, relevant medical evaluations should be carried out and appropriate treatment provided. Additional follow-up will be done as necessary and recorded in the subject's source documents, and the results will be provided to the

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Sponsor. Follow-up information should be accompanied by the completed SAE form and sent to the sponsor using the contact information provided in the protocol.

14.3 Reporting of Adverse Events

AEs that occur from the time of informed consent through completion of the last study visit should be reported. Any SAE that the Investigator becomes aware of that occurs within 30 days of study completion or withdrawal should also be reported.

The investigator is responsible for reporting SAEs and AEs of special interest to the Institutional Review Board (IRB) according to agreements and instructions from that board or committee that oversees this research, as well as according to applicable regulations.

Any SAEs, AE of special interest, or pregnancy occurring in a subject receiving study drug must be reported to [REDACTED] within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be done by faxing or emailing the appropriate completed form (SAE Form or pregnancy reporting form) to [REDACTED]. Any pertinent follow-up information should be provided in a similar manner. [REDACTED] must then report the SAE to the Sponsor within 24 hours using the contact information below. The Sponsor will generate the MedWatch form and communicate it back to [REDACTED].

Actavis Inc.
Pharmacovigilance



The most common AEs reported with the use of ingenol mebutate gel include LSRs, application site pain, application site pruritus, application site irritation, application site infection, periorbital edema, nasopharyngitis, and headache. Less common AEs include eyelid edema, eye pain, and conjunctivitis. LSRs occurring within the Treatment Area will be assessed at each visit and documented as detailed in Section 10.2. Any LSR that requires medical intervention (prescription medication) or extends beyond the 2 cm surrounding skin should be documented as an AE.

14.3.1 Adverse Event and Serious Adverse Event Reporting Period

The AE and SAE reporting period starts following the subject's written consent to participate in the study with the first study related procedure and ends after the subject's last study visit.

AEs classified as "serious" require expeditious handling and reporting to [REDACTED] to comply with regulatory requirements. All SAEs whether related or unrelated to test article must



be immediately reported to [REDACTED] by telephone or confirmed facsimile transmission to the Medical Monitor or Project Manager listed on the first page of the protocol. Follow-up of AEs and SAEs is to occur as described in Section 14.3.

14.3.2 Assessment of Adverse Events

The investigator must assess all AEs using the following criteria:

14.3.2.1 Intensity

“Intensity” of the AE refers to the extent to which an AE affects the subject’s daily activities and differs from “serious”, which is a regulatory classification. Intensity will be categorized according to the following criteria:

- **Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- **Severe**: medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

14.3.2.2 Relationship to Study Treatments

“Causality” refers to the relationship of the AE to the study drug. The investigator must include assessment of causality (whether there is a reasonable possibility the drug caused the event) for each AE. Causality will be categorized according to the following criteria:

- **Not Related**: There is no medical evidence to suggest that the AE may be related to study drug usage.
- **Possibly Related**: There is medical evidence to suggest that the AE may be related to study drug usage.
- **Related**: There is a strong medical evidence to suggest that the AE is related to study drug usage.

14.3.2.3 Outcome

An AE outcome is defined as follows:

- **Fatal** - Termination of life as a result of an AE.
- **Not Recovered/Not Resolved** - AE has not improved or recuperated.
- **Recovered/Resolved with Sequelae** - Subject recuperated but retained the pathological conditions resulting from the prior disease or injury.
- **Recovered/Resolved** - AE has improved or recuperated.
- **Recovering/Resolving** - AE is improving.

- **Unknown** - Not known, not observed, not recorded or refused.

14.3.2.4 Treatment Required

- **Yes** (if yes, specify on concomitant therapy page of the CRF)
- **No**

14.3.3 Adverse Event Follow-Up

Follow-up of AEs will continue through the last day of the study, until the investigator determines outcome, stabilization, and/or resolution of the event, or not-relatedness to study medication, or up to 30 days after the last dose of the test article. For SAEs, this can occur before or after day 30. In the event of death, if an autopsy is performed, a copy of the report should be sent to [REDACTED]

If subjects have unresolved treatment emergent AEs or LSRs at Visit 6, site visits are recommended every 7 to 28 days until resolution or until investigator deemed clinically stable. Subjects with pigment related changes or scarring should return every 28 days until resolution or for a period of 6 months from Day 1, unless deemed by the investigator to be clinically insignificant.

AEs that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter. Investigators and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any AE determined to be clinically significant by the Investigator will remain under medical supervision until the Investigator or the Medical Monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

14.3.4 Procedure for Reporting of Serious Adverse Events

14.3.4.1 Notification by Investigator to [REDACTED]

A SAE form must be completed by the investigator and faxed to the Medical Monitor or Project Manager noted on page 1 of the protocol within 24 hours after becoming aware of the event. The investigator will keep the original of this SAE form on file at the study site. The Medical Monitor will inform the Sponsor within one business day of their notification of the event (see Section 14.3). At the time of the initial report, the following information should be provided at a minimum:

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- | | |
|---|--|
| ○ Study identifier | ○ Whether study treatment was discontinued |
| ○ Study Center | ○ The reason why the event is classified as serious |
| ○ Subject Number | ○ Investigator assessment of the association between the event and trial treatment |
| ○ A description of the event | ○ Blinding status (randomization code broken or not) of subject |
| ○ Date of onset | ○ If the Test Article was administered and date of the administration |
| ○ Date investigator was informed of the event | |
| ○ Current status | |

Even if all the information is not known, an initial report should be made. The investigator is obliged to provide follow-up information within three days of the initial report on a SAE form, and any other diagnostic information that will assist the understanding of the event.

Significant new information on ongoing SAEs should be provided promptly to the Medical Monitor or Project Manager as a follow-up report.

Documents relevant to the diagnosis, treatment and course of the event must be submitted (e.g., technical investigation reports, histology findings, eCRFs, hospital discharge documents). All documents must be blinded with respect to subject's name.

When the investigator determines that there is no more information likely to be available, a final report should be provided.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome, if possible (see Section 14.3). Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported to the Medical Monitor within 24 hours.

14.3.5 Institutional Review Board Notification by Investigator

Reports of all SAEs (including follow-up information) must be submitted to the IRB according to local requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's Regulatory binder.

As required, [REDACTED] will notify all participating investigators of all AEs that are serious (regardless of whether the event is considered drug related), unexpected, and certainly, probably, or possibly related to the test article, as soon as possible, but in no case later than 15 calendar days after becoming aware of its occurrence. This notification will be in the form of a Safety Update to the Investigator Brochure (i.e., "15-day letter").

Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of Safety Updates by the investigator to Health Authorities should be handled according to local regulations.

14.3.6 FDA Notification by Sponsor

The study Sponsor shall notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than seven calendar days from the Sponsor's original receipt of the information followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

Serious, unexpected reactions that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that the case meets the minimum criteria for expedited reporting.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study Sponsor will submit the AE in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

14.4 Laboratory Test Abnormalities

Although there are no specific labs required in this study, if an abnormal laboratory result indicated as clinically significant by the Investigator is the reason for a subject being withdrawn from the study or requires treatment for the abnormality, this abnormal result must also be reported as an AE. In addition, any laboratory test result that meets the criteria for a SAE (see Section 14.3) must also be reported as a SAE so [REDACTED] can collect additional information about that abnormality, including information regarding relationship to test article or other causes, any action taken, and resolution.

14.5 Pregnancy

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 amenorrhea >12 consecutive months in women 50 years of age and older]. In cases where a woman's partner is sterile (e.g., she is considered to be of childbearing potential). Even women who are using effective methods of contraception to prevent pregnancy, including those practicing abstinence, are considered to be of childbearing potential. Post-menopausal women who have fertilized eggs implanted are considered to be of childbearing potential.

All WOCBP participating in the study must use an appropriate method of birth control or continuous abstinence from heterosexual contact during the course of the study until the *onset of the first menses after the last dose of study medication*, in a manner such that risk of failure is minimized. Effective forms of birth control include a) hormonal contraceptives [e.g., oral or transdermal (for at least one full cycle), injectable or intravaginal (for at least one week)], b) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], c) partner vasectomy (performed at least six months prior to study entry), or d) total abstinence. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

Prior to study enrollment, all WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risks if pregnancy were to occur. The subject must sign an informed consent form documenting this discussion.

If a subject or investigator suspects that the subject may be pregnant prior to test article administration, the study medication must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study medication and must not be enrolled in the study. Female subjects must have a negative UPT at Visit 1/Baseline. UPTs will also be performed at Visit 6/EOS or when a subject prematurely withdraws from the study.

During the study, WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that the subject may be pregnant at any time before or during the study, the test article must immediately be withheld until the result of laboratory pregnancy testing having a minimum sensitivity of at least 25 mIU/mL for hCG are available. The Sponsor and site monitor must be notified and available information captured on a Pregnancy Reporting form (see Section 14.2). If pregnancy is confirmed, the test article must be permanently discontinued and the subject must be withdrawn from the study and the Sponsor and site monitor must be notified. Additional relevant information about the confirmed pregnancy will be recorded on the appropriate form(s), but the pregnancy will not be captured as an AE.

The subject should be followed until the outcome of the pregnancy is known.

14.5.1 Reporting Procedure

The investigator must report any pregnancy associated with exposure to test article within 24 hours of becoming aware of the pregnancy using the appropriate [REDACTED] pregnancy surveillance form(s) to the Medical Monitor or Project Manager listed on page 1 of the protocol. If pregnancy was associated with an AE, procedures for AE reporting should be followed. If pregnancy was associated with a SAE, procedures for SAE reporting must be

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followed. Spontaneous abortion is always considered a SAE. The investigator must report information regarding the course of the pregnancy, including perinatal and neonatal outcome on the [REDACTED] pregnancy surveillance form(s). The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

15. BLINDING/UNBLINDING

This is a double-blind, randomized, vehicle-controlled study. Blinding is important for the integrity of this clinical drug trial. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. If possible, before breaking the blind, contact the responsible Medical Monitor.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability etc. is included in Appendix 4.

16.2 Supplies Provided by [REDACTED]

[REDACTED] will provide the following additional supplies to the study sites:

- eCRFs
- Source document draft templates
- Site regulatory binder
- UPT kits
- Transparencies (pre-marked 1 cm² grid) and markers to identify the Treatment Area

16.3 Supplies Provided by Investigator

- Urine collection containers

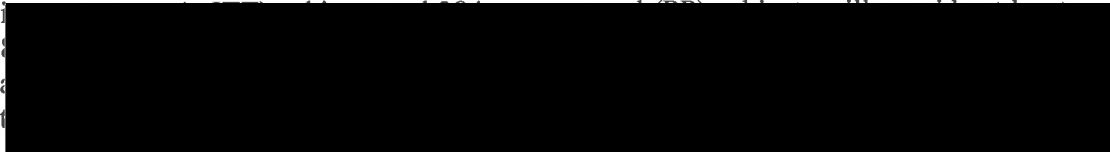
16.4 Supplies Provided by the Sponsor

- Non-medicated samples for demonstration of test article application

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

Based on conservative assumptions of a complete lesion clearance rate of 50% for both active treatments and a rate of no more than 15% for the vehicle treatment, 480 modified



17.2 Endpoints

17.2.1 Efficacy Endpoints

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

17.2.2 Safety Endpoints

Safety endpoints will include assessment of the severity and frequency of AEs and LSRs.

17.3 Statistical Methods

All statistical processing will be performed using SAS[®]. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment group.

Study Populations

The Safety population will include all randomized subjects who received the test article. The mITT population will include all randomized subjects who applied at least one dose of test article. The PP population will include all randomized subjects who met all the inclusion/exclusion criteria, were compliant with the assigned test articles (applied all three doses of the test article and no other evidence of material dosing noncompliance), completed the study within the designated visit window (± 2 days), and had no protocol violations that would affect treatment evaluation. 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 population as treatment failures (non-responders). Subjects discontinued prematurely for other reasons will be excluded from the PP population, but included in the mITT population.

17.3.1 Efficacy Analyses

The efficacy analyses will be conducted on the mITT and PP populations. Last-observation-carried-forward (LOCF) will be used to impute missing values for efficacy variables in the mITT population.

Bioequivalence. Evaluations in the PP population will be considered primary. The 90% Wald's confidence interval with Yate's continuity correction will be constructed on the difference between the proportion of subjects with complete (100%) lesion clearance in the Test and Reference treatments to evaluate the bioequivalence of the two active treatments. If the 90% confidence intervals on the difference between the proportion of subjects with complete lesion clearance in the Test and Reference treatments are contained within the interval -0.20 to +0.20, and each of these proportions is greater than, and statistically different ($p < 0.05$) from, the Placebo proportion, then the Test and Reference products will be considered to be therapeutically equivalent.

Superiority. To determine study sensitivity, two-sided, Fisher's exact test with an alpha of 0.05 will be used to evaluate the superiority of each active treatment over the vehicle for the proportion of subjects with complete (100%) lesion clearance using mITT population and LOCF. This test will be repeated on the PP population.

17.3.2 Safety Analyses

The analysis of safety will be conducted on the Safety population.

Dosing Compliance

Descriptive statistics will be used to summarize test article compliance for the mITT and PP populations. Measures of test article compliance will include the total number of applications as determined from the data recorded in the subject diaries. Compliant subjects will be defined as those who applied all three test article applications and had no other evidence of material dosing non-compliance.

Local Skin Reactions

Severity of LSRs (erythema, flaking/scaling, crusting, swelling/edema, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, and scarring) will be recorded. LSRs will be summarized for each treatment group by frequency and severity of each individual LSR at Baseline, and Days 4, 8, 15, 29, and 57. LSRs will also be summarized for each treatment group by the most intense score of each individual LSR and by the total score (sum of all LSRs) at Baseline, and Days 4, 8, 15, 29, and 57.

Adverse Events

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC)

using the MedDRA mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment.

17.4 Subgroup Analyses

No subgroup analyses are planned.

17.5 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

18.2 Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects and any updates. The investigator will submit documentation of the IRB approval to [REDACTED]

The IRB-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

■ must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to ■

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of ■ and/or the Sponsor must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff and facilities.

The investigator should immediately notify ■ of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

The study will utilize validated 21CFR Part 11 compliant electronic data capture (EDC) software to collect data, all requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRFs.

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The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from [REDACTED] and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify [REDACTED] in the event of a FDA site audit.

18.9 Records Retention

According to 21CFR § 312.62, an investigator is required to maintain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

In accordance with 21CFR § 320.38, each reserve sample (retain) shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least five years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least five years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used.

The investigator must contact [REDACTED] or the Sponsor prior to destroying any records or reserve samples associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to [REDACTED]

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18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring by [REDACTED] or the Sponsor, the FDA or other regulatory authority, or the IRB.

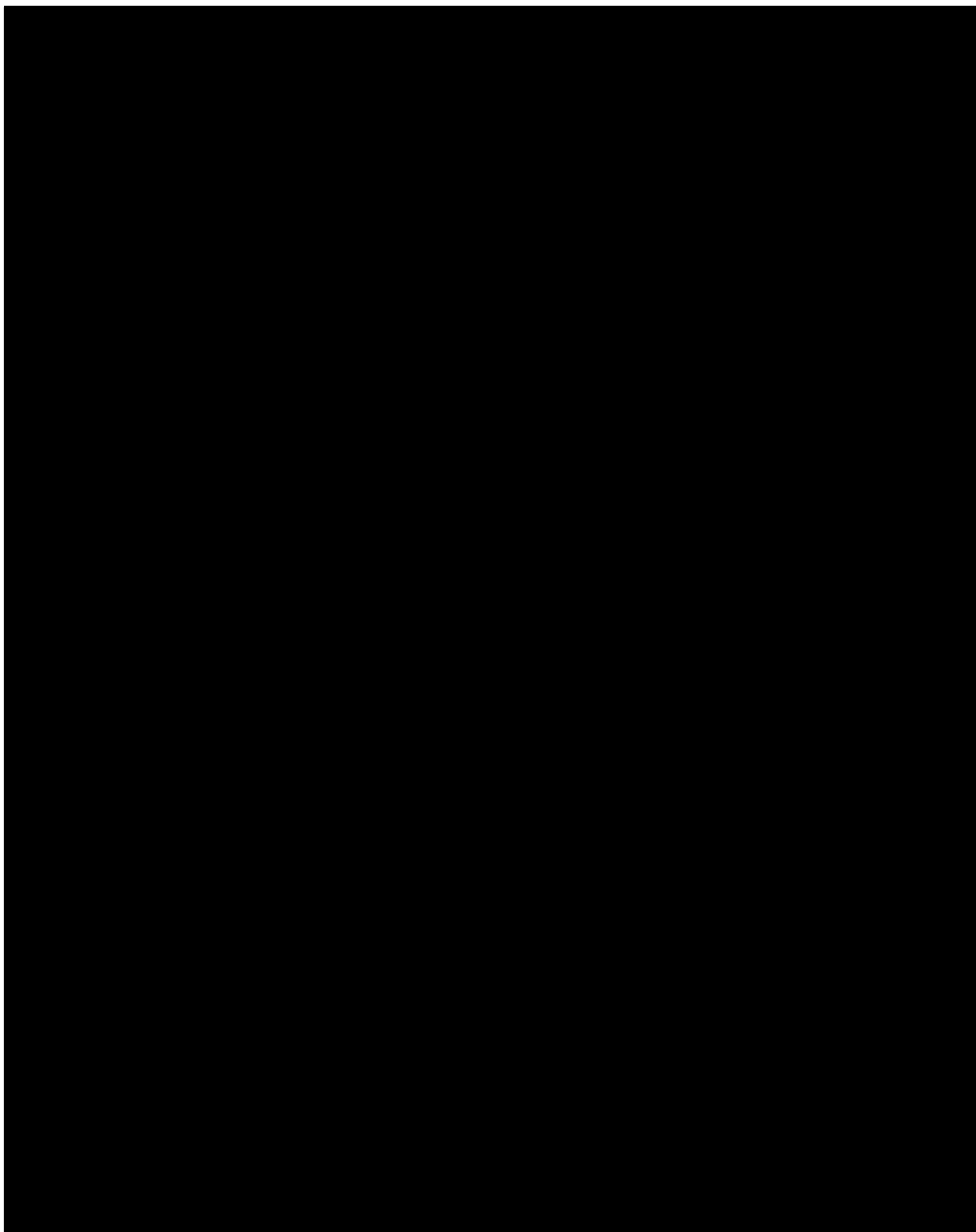
The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from [REDACTED] or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

19. REFERENCES

None.

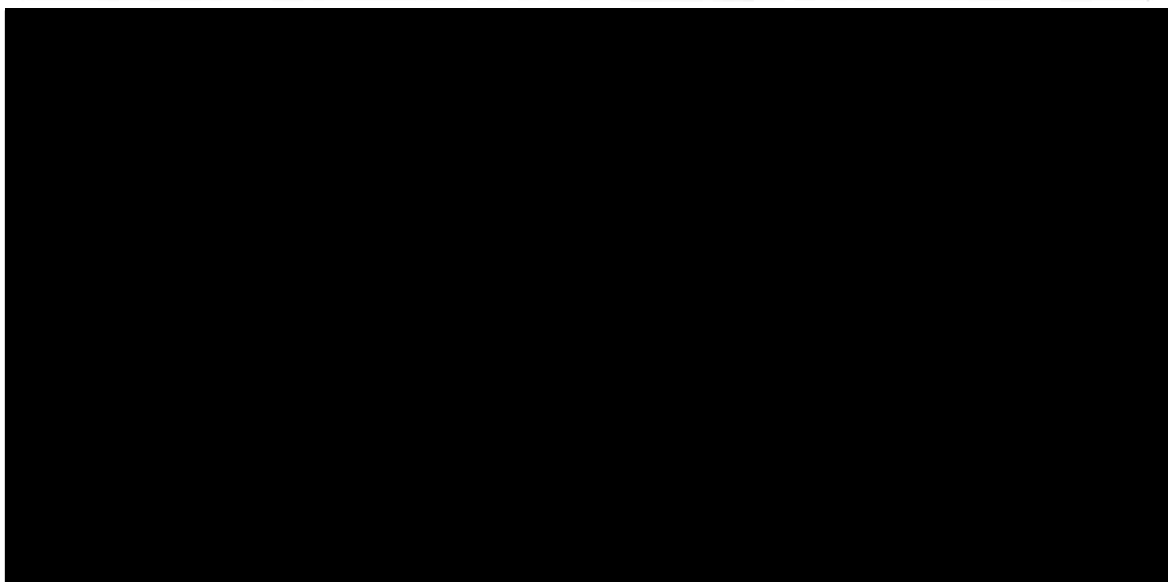
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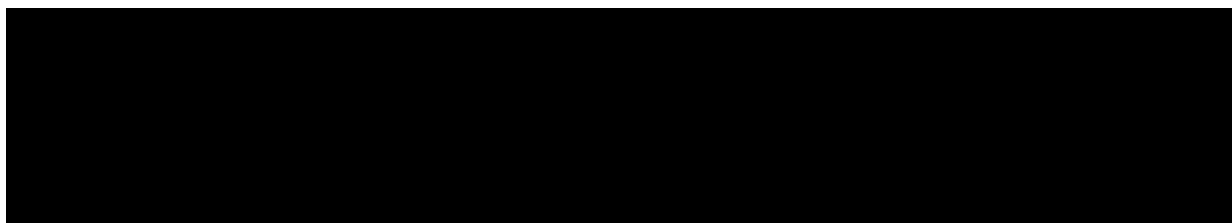
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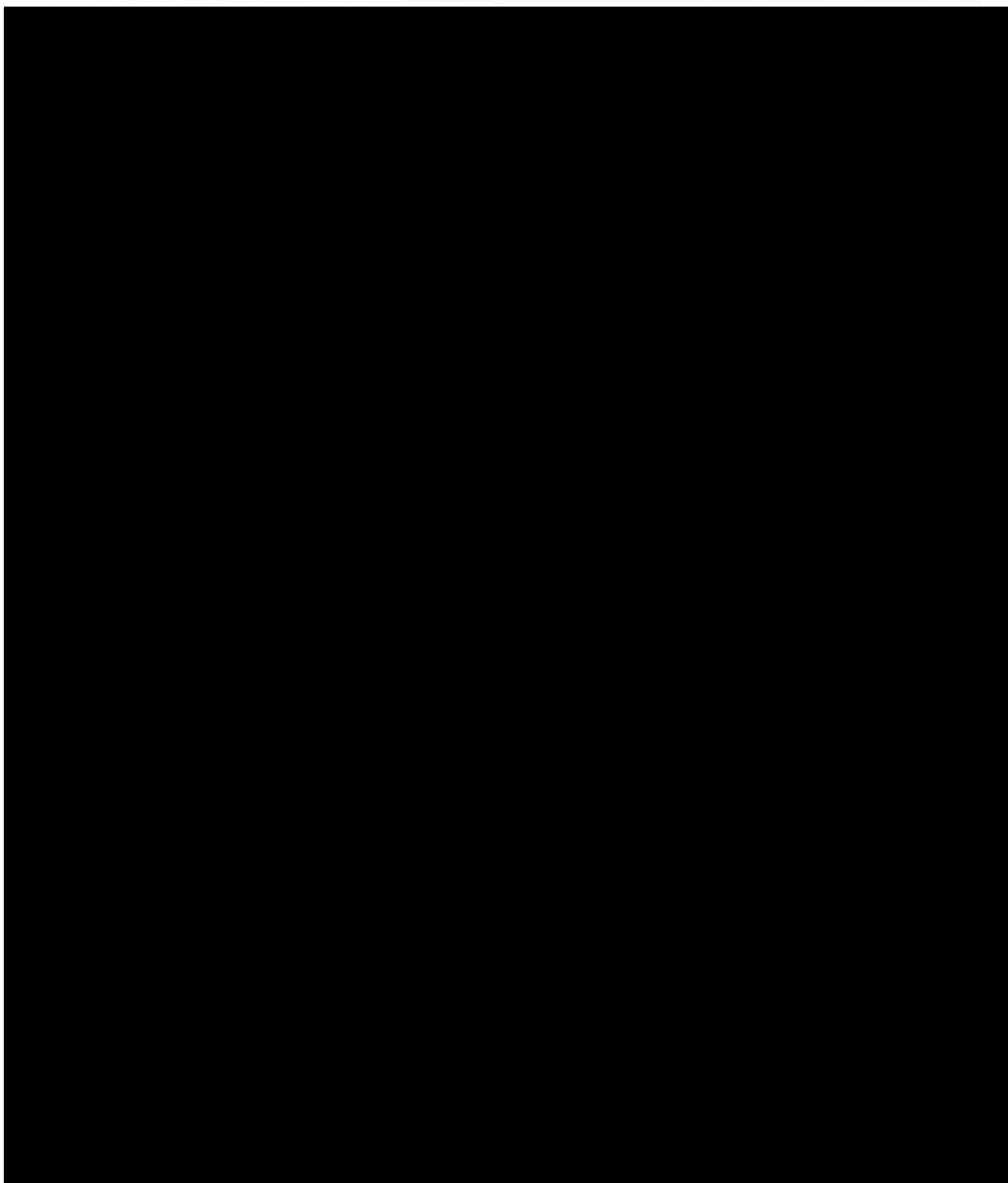
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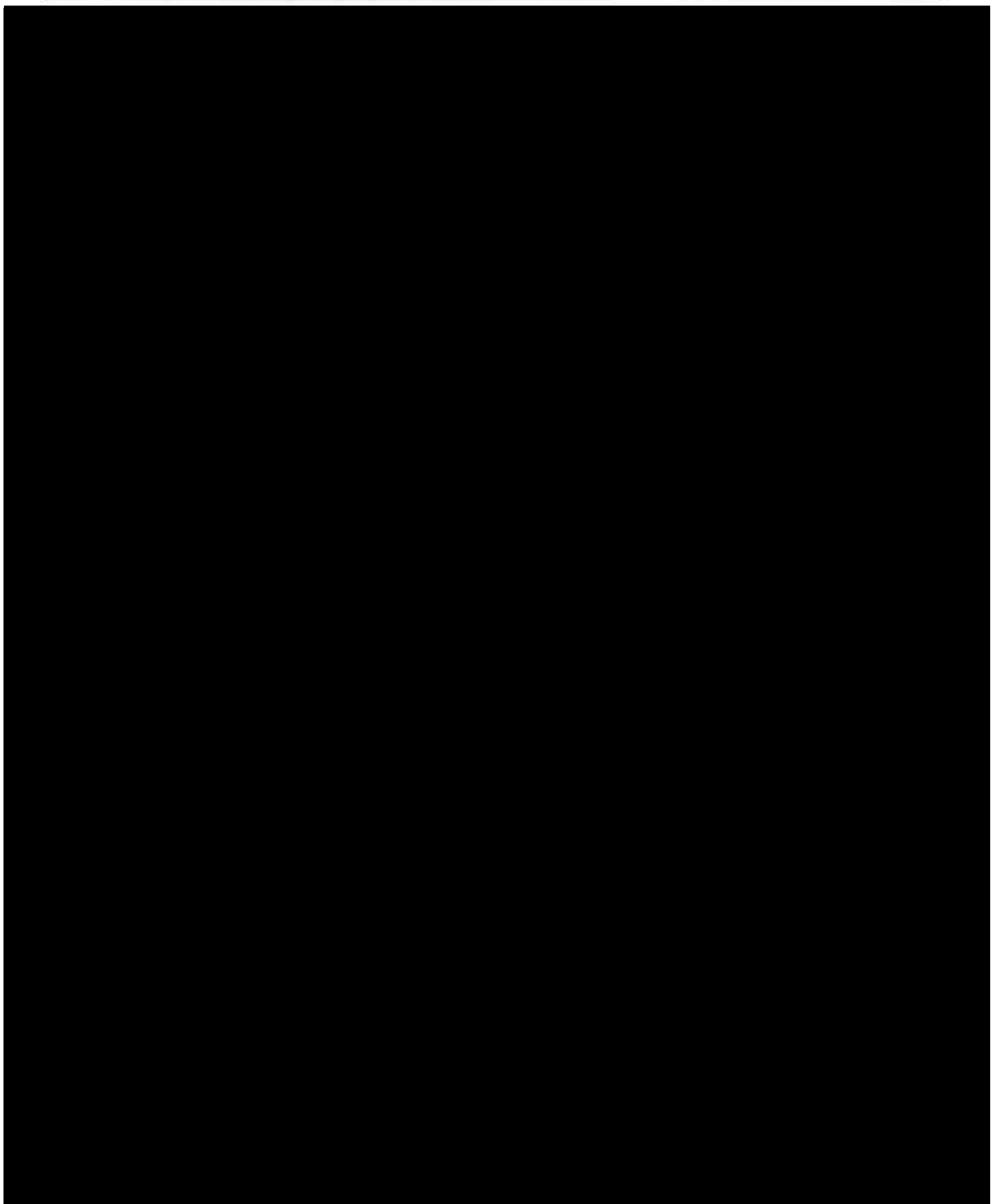
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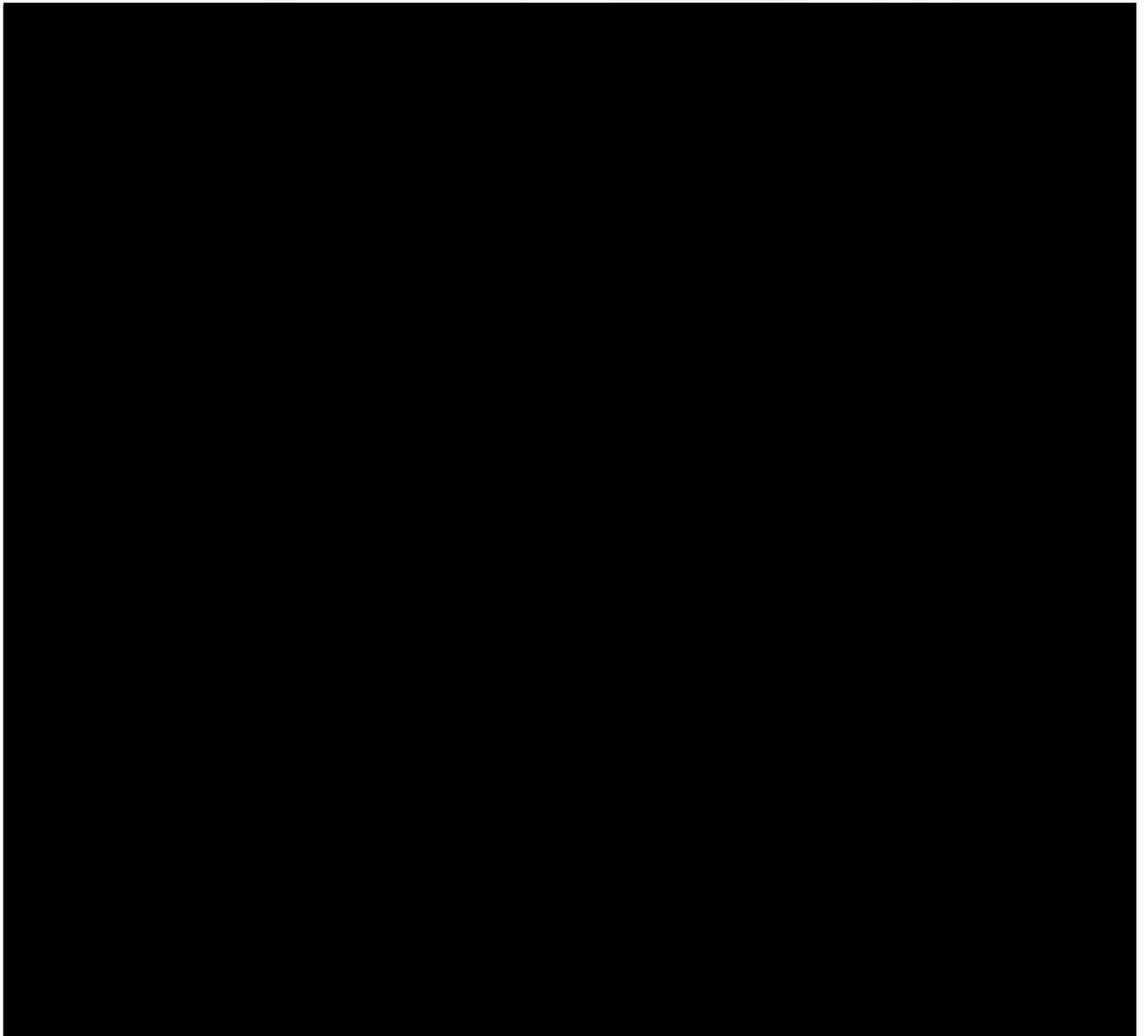
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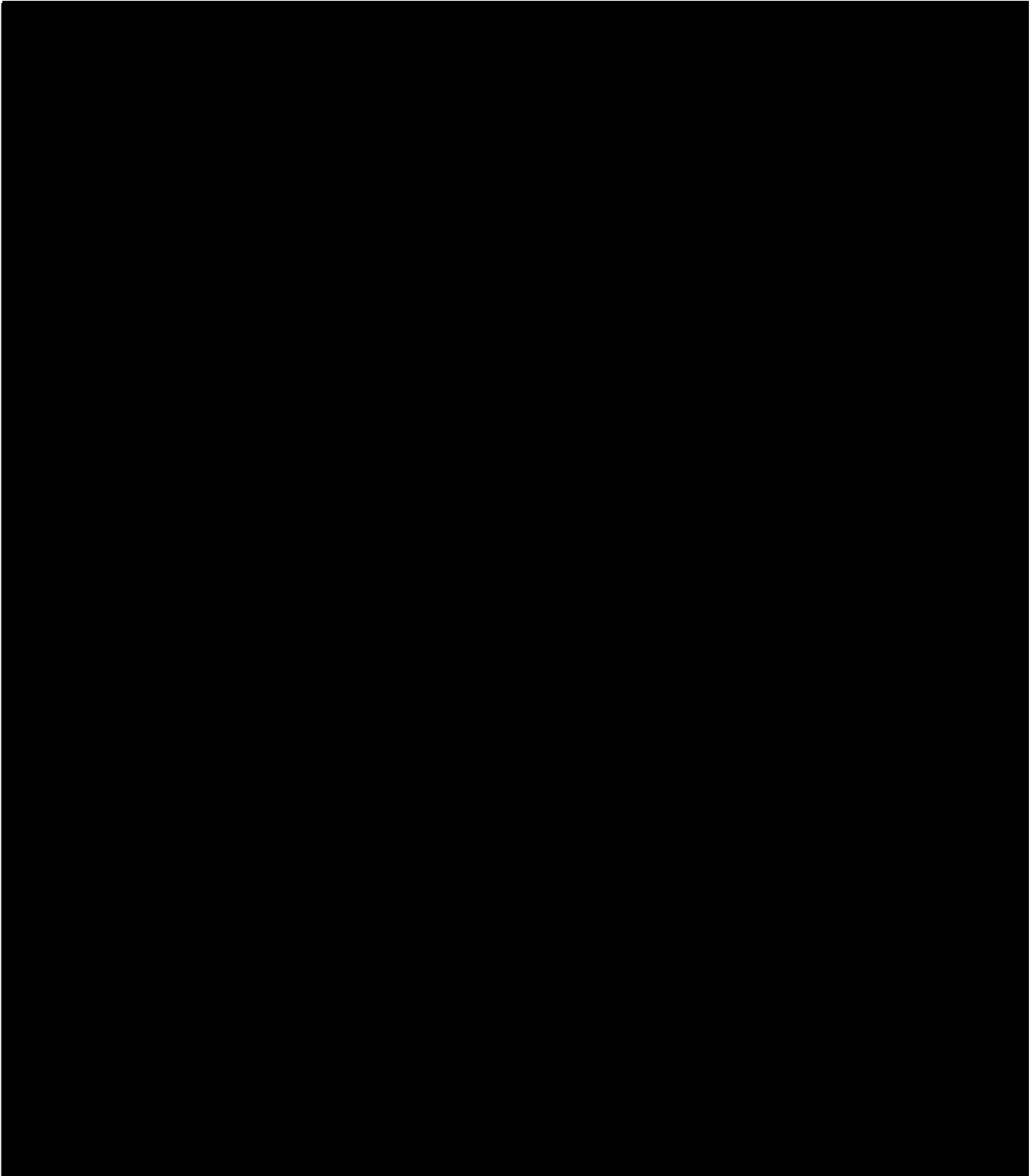
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Protocol: 094-8152-301
Protocol Date: May 26, 2016

