

**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-
CONTROLLED, PARALLEL GROUP COMPARISON STUDY TO DETERMINE
THE THERAPEUTIC EQUIVALENCE OF GDC 695 AND DICLOFENAC
SODIUM GEL, 3% IN SUBJECTS WITH ACTINIC KERATOSES**

PROTOCOL NUMBER: GDC-695-001

[REDACTED]

[REDACTED]

ORIGINAL PROTOCOL: August 18, 2016

AMENDMENT #1: January 26, 2017

FILENAME:

[REDACTED]

SPONSOR:

Gage Development Company, LLC

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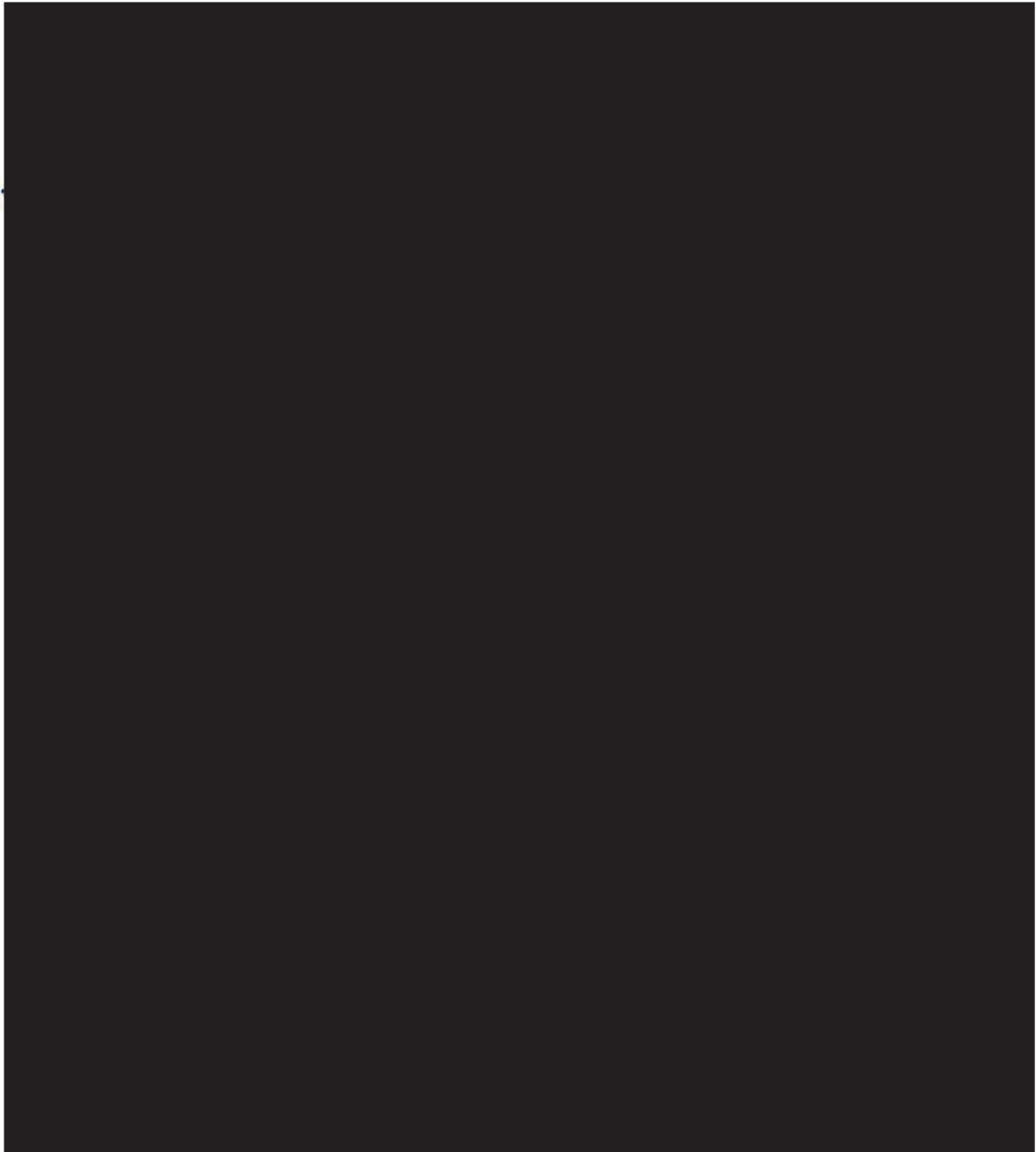
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Product Name: GDC 695
Sponsor Name: Gage Development Company, LLC

Protocol: GDC-695-001
Protocol Date: January 26, 2017, v2.0

PROTOCOL APPROVAL



STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Gage Development Company, LLC, the Sponsor.

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; provided that 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 Gage Development Company, LLC. This condition does not apply to disclosure required by government regulations or laws. However, I agree to give prompt notice to Gage Development Company, LLC of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Gage Development Company, LLC, 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 Gage Development Company, LLC and must be treated in the same manner as the contents of this protocol.

Printed Name of Principal Investigator

Investigator Signature

Date

Protocol number: GDC-695-001

Site number: _____

Version: 2.0

Site address: _____

Date of final version: January 26, 2017

**NAMES AND ADDRESSES OF DEPARTMENTS AND/OR INSTITUTIONS
INVOLVED IN THE STUDY**

Test Article Labeling:

[REDACTED]

Institutional Review Board:

[REDACTED]

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of GDC 695 and Diclofenac Sodium Gel, 3% in Subjects with Actinic Keratoses
Study Type	Bioequivalence with Clinical Endpoint
Test Articles	1. Test product: GDC 695 (Gage Development Company, LLC) 2. Reference Listed Drug (RLD): Diclofenac Sodium Gel, 3% (Fougera) 3. Placebo: vehicle gel (Gage Development Company, LLC)
Study Objective	To evaluate the safety and therapeutic equivalence of GDC 695 to Diclofenac Sodium Gel, 3% and to establish the superiority of the efficacy of these two products over the vehicle gel (i.e., placebo) in the treatment of actinic keratoses (AK).
Study Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group comparison.
Treatment Groups	Eligible subjects will be randomized (1:1:1) to treatment with GDC 695, Diclofenac Sodium Gel, or placebo.
Duration of Treatment	Twice-daily application for 60 days.
Duration of Study	Approximately 90 days (not including a maximum 30-day screening period).
Study Population	Male and/or female subjects, ages 18 years and older with actinic keratoses on the face or bald scalp.
Total Number of Subjects	Approximately 600 subjects will be enrolled to obtain at least 558 modified intent-to-treat (mITT) and at least 417 per-protocol (PP) subjects in the study.
Number of Sites	Approximately 28 sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Is an immunocompetent male and/or non-pregnant female, 18 years of age or older. 2. Has provided written informed consent including consent to photography of the treatment area at Visit 1. 3. Is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study. 4. Has a clinical diagnosis of actinic keratoses with at least five (5) and no more than ten (10) clinically typical, visible, or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, <u>each at least 4 mm in</u>

	<p><u>diameter</u>, contained within a continuous 25 cm² treatment area located on the face (excluding ears) or bald scalp¹.</p> <p>5. 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.</p> <p>6. If female, must be post-menopausal², surgically sterile³, or use an effective method of birth control^{4,5} with a negative urine pregnancy test (UPT)⁶ at the Baseline Visit.</p>
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. Is pregnant, breastfeeding, or is planning to become pregnant or breastfeed during the study. 2. Is currently enrolled in an investigational drug or device study. 3. Has used an investigational drug or investigational device within 30 days prior to the Baseline Visit. 4. Subject has hyperkeratotic, hypertrophic (i.e., Grade 3 AKs), or large AKs of any Grade (e.g., AK >1 cm² in size) within the treatment area. 5. Has >10 AKs of any size within the treatment area. 6. Has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study. 7. Is immunosuppressed (e.g., human immunodeficiency virus, systemic malignancy, graft host disease, etc.) or is taking medications that suppress the immune system. 8. Has experienced an unsuccessful outcome from previous topical diclofenac sodium therapy; an unsuccessful outcome is defined as "after a reasonable therapeutic trial with no compliance issues and the

¹ Bald scalp for the purposes of this study is a scalp where the subject has lost the majority of their hair (well over 50%) within the intended 25 cm² treatment area where the scalp is: a) readily visible and 2) the number of the AKs in the treatment area can be easily seen and counted by the evaluator. It is also important that both the site and subject can repeatedly identify the treatment area to assure accurate repeat therapy by the subject and evaluation by the investigator.

² Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.

³ Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.

⁴ Effective forms of birth control include a) hormonal contraceptives [oral, injectable, transdermal, or intravaginal] for one full cycle (e.g., four to eight weeks) or intrauterine device (IUD) for one week, for injectable (e.g., Depo-Provera) the requirement is at least seven days after injection, prior to test article application, or b) condom and spermicidal, or diaphragm/cervical cap and spermicidal, which are effective as soon as the birth control method is administered properly. Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., a vasectomy performed at least six months prior to the subject's initiation of treatment). 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.

⁵ Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study.

⁶ UPTs must have a minimum sensitivity of 25 mIU β -hCG/mL.

	<p>topical drug did not work”.</p> <ol style="list-style-type: none"> 9. Has a history of sensitivity to any of the ingredients in the test articles including diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 359, hyaluronate sodium, sodium phosphate monobasic anhydrous, sodium hydroxide or other excipients in the test product or RLD. 10. Has signs or symptoms consistent with the aspirin (ASA) triad: asthmatic subjects who experience rhinitis with or without nasal polyps, or who experience severe bronchospasm after taking aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). 11. Used topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, powders, or gels and new brands of make-up) within the selected treatment area within one day prior to the Baseline Visit. 12. Has used topical medications: corticosteroids, alpha hydroxy acids (e.g., glycolic acid, lactic acid, etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >2%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate, aminolevulinic acid (ALA) or prescription retinoids (e.g., tazarotene, adapalene, tretinoin), over-the-counter (OTC) products labeled as scrubs of any kind which are used to smooth the skin (as they contain some form of exfoliant such as nut shells, coffee grounds, polymer particles, etc.) within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit. 13. Has had cryodestruction or chemodestruction, curettage, photodynamic therapy (PDT), surgical excision, or other treatments for AK within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit. 14. Has used systemic corticosteroid therapy (includes intramuscular and intra-articular administration), interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or retinoids within one month prior to the Baseline Visit. 15. Has used oral isotretinoin within six months prior to the Baseline Visit. 16. Has used chemical peels, including but not limited to alphahydroxy acid, betahydroxy acid, bichloroacetic acid, trichloroacetic acid, and phenol within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit. 17. Has had dermatologic procedures or surgeries such as: laser resurfacing, PUVA (Psoralen + ultraviolet A) therapy, ultraviolet B (UVB) therapy, or dermabrasion within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit. 18. Has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the selected treatment area (face or bald scalp). 19. Has any skin pathology or condition within the selected treatment area (the face or bald scalp) such as atopic dermatitis, eczema, psoriasis, rosacea, sunburn, or other confounding skin condition(s) 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. 20. Has active gastrointestinal ulceration or bleeding or has a history of gastrointestinal bleeds due to use of aspirin or other NSAIDs. 21. Has severe renal or hepatic impairment.
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	<p>22. 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.</p> <p>23. Is unable to communicate or cooperate with the investigator due to language problems, poor mental development, impaired cerebral function, or physical limitations.</p> <p>24. 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>25. Has been previously enrolled in the same study.</p>
Study Procedures	<p>Subjects can be screened for the study up to 30 days before Visit 1. During screening, the study requirements will be reviewed, written informed consent obtained, and eligibility confirmed. If applicable, qualified subjects can washout from prohibited medications or treatments prior to their Screening/Baseline Visit once they have been consented. These procedures may be combined with the Baseline Visit.</p> <p>As part of the consent process it is important to:</p> <ol style="list-style-type: none"> 1. Review the IRB-approved informed consent form with each potential subject and provide them with an opportunity to have all questions answered before proceeding. 2. Obtain a signed IRB-approved informed consent from each subject. Written informed consent must be obtained from eligible subjects before they are enrolled into the study. <p>The study will consist of a Screening/Baseline Visit, telephone calls at Day 15 and at Day 45, and follow-up visits at Day 30, Day 60, and Day 90 (30 days after completion of 60 days of treatment).</p> <ol style="list-style-type: none"> 1. <u>Visit 1 - Screening/Baseline Visit (-30 to Day 1):</u> The following will be obtained at this visit: signed written informed consent (or re-consent if washout period exceeds 30 days), confirmation of eligibility, medical history, demographics, review of concomitant medications and therapies/procedures, dermatologic exam, UPT (if applicable), identification of anatomic treatment area (the face [excluding the ears] or the bald scalp), identification of the designated 25 cm² treatment area by creating a "subject specific" template to assist the subject in identifying the treatment area for application of the test article, AK count, and local skin reaction (LSR) assessment. Qualified subjects will be randomly assigned to one of three treatment groups (GDC 695, Diclofenac Sodium Gel, or vehicle gel). Test article application will be demonstrated using the non-medicated samples provided to the site. The subject will be instructed not to open study supplies at the site. Test article will be dispensed, along with application instructions and a subject diary to document any applied, held, or missed doses. Baseline photographs of the designated 25 cm² treatment area will be taken at the site (1 photo to remain in the subject's file at the site and 1 photo given to the subject) in order to help ensure proper application of the test article by the subject. A separate Treatment Area Identification Manual with instructions on how to create the "subject specific"

	<p>template and how to take the Baseline photographs will be provided to the sites for use. The subjects will be instructed to apply the test article twice daily, once in the morning and once in the evening, for 60 days to the entire 25 cm² treatment area. Subjects will be scheduled for the next visit.</p> <p>2. <u>Visit 2 - Phone Call (Day 15 ± 3 days):</u> The site staff will contact the subject on Day 15 to confirm the next visit appointment, review the subject diary and test article compliance, review of concomitant medications and therapies/procedures, and query the subject about adverse events (AEs). The site staff will remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit and to bring their tube of test article with them to their next clinic visit. Subjects with severe tolerability issues or a material AE concern of any type may be seen for an in-office follow-up as an unscheduled visit at the discretion of the investigator.</p> <p>3. <u>Visit 3 (Day 30 ± 3 days):</u> Subjects will return for review of concomitant medications and therapies/procedures, LSRs, and AEs. The subject diary will be reviewed/collected/distributed as necessary and test article compliance will be reviewed and the site staff will remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit. Test article application will be demonstrated if deemed necessary. The subject's tube of test article will be weighed and re-dispensed. The subject will be scheduled for the next follow-up visit.</p> <p>4. <u>Visit 4 - Phone Call (Day 45 ± 3 days):</u> The site staff will contact the subject on Day 45 to confirm the next visit appointment, review the subject diary and test article compliance, review of concomitant medications and therapies/procedures, and query the subject about AEs. The site staff will remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit and to bring their tube of test article with them to their next clinic visit. Subjects with severe tolerability issues or a material AE concern of any type may be seen for an in-office follow-up as an unscheduled visit at the discretion of the investigator. <i>NOTE: The end of treatment visit should be scheduled such that the subject will have had ideally 60 days of treatment.</i></p> <p>5. <u>Visit 5 – End of Treatment [EOT] (Day 60 + 4 days):</u> Subjects will return for review of concomitant medications and therapies/procedures, LSRs, and AEs, UPT (if applicable) as well as AK lesion counts. The subject diary and test article compliance will be reviewed and both the subject diary and test article will be collected. The subject will be scheduled for the end of study visit.</p> <p>6. <u>Visit 6 – End of Study [EOS] (Day 90 ± 4 days):</u> Subjects will</p>
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	<p><i>return 30 days after completion of 60 days of treatment for review of concomitant medications and therapies/procedures, LSRs, and AEs, as well as AK lesion counts. The subject will be discharged from the study.</i></p>
Study Measurements	<p>The primary clinical assessment in the study is based on AK lesion clearing.</p> <p><i>Efficacy</i> The primary efficacy parameter is the number of all visible or palpable AK lesions (baseline and new lesions) in the 25 cm² treatment area as enumerated at Baseline and at all follow-up visits by the investigator or designee.</p> <p><i>Safety</i> All AEs will be recorded. At each visit, subjects will also 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 including erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus will be assessed and recorded separately at each onsite clinic visit by the investigator to allow a comparison between treatment groups.</p>
Study Endpoints	<p><i>Efficacy Endpoint(s)</i> The primary efficacy endpoint is the proportion of subjects in the PP population with treatment success ("Complete Clearance") at Day 90 (30 days after completion of 60 days of treatment). Complete Clearance is defined as 100% clearance of all AK lesions (having a count of zero AKs) in the 25 cm² treatment area (face or bald scalp) at the Day 90 visit. All AKs (those present at baseline and new lesions, if any that may develop) independent of size within the 25 cm² treatment area are to be treated and included in the efficacy lesion count for each visit.</p> <p><i>Safety Endpoint(s)</i> <u>Dosing Compliance</u> Measures of test article compliance will include the total number of applications recorded in the case report forms (CRFs) and verified from the data in the subject diaries. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the expected (120) test article applications, did not miss more than 10 consecutive scheduled applications, and have no other evidence of material dosing noncompliance.</p> <p><u>Adverse Events and Local Skin Reactions</u> Severity and frequency of AEs including LSRs (erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus) will be assessed in the three treatment groups.</p>
Sample Size Calculations	<p>Based on [REDACTED]</p> <p>[REDACTED] probability of demonstrating therapeutic equivalence between the active treatments and at the same time showing that each active treatment is</p>

	superior to the vehicle treatment. Thus, approximately [REDACTED] subjects will be enrolled into the study to obtain [REDACTED] mITT subjects.
Statistical Methods	<p>All statistical processing will be performed using SAS® unless otherwise stated.</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 met all inclusion/exclusion criteria, applied at least one dose of test article, and returned for at least one post-baseline evaluation visit. Randomized subjects who are lost to follow-up after Visit 1, who return for the EOT visit but have not applied any test article, or who are found not to have met the eligibility criteria will be excluded from the mITT population. Subjects will be included in the PP efficacy analyses if they met all the inclusion/exclusion criteria, were compliant with the assigned test articles (applied at least 75% and no more than 125% of the expected (120) test article applications) for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at the EOS visit within the designated visit window (\pm 4 days) with no protocol violations that would affect the treatment evaluation. Subjects who are discontinued from the study due to worsening condition that requires alternate or supplemental therapy for the treatment of AK should be included in the PP population as treatment failures if they meet the mITT criteria. Subjects who are discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using last-observation-carried-forward (LOCF).</p> <p>Efficacy summaries and analyses will be carried out in the mITT and PP populations. All summaries of safety will be carried out in the Safety population. LOCF will be used to impute missing values for efficacy variables in the mITT population.</p> <p>Demographic and baseline characteristics will be summarized by treatment group for all analysis populations. The size of the treatment area in cm² will be summarized by treatment group for the mITT and PP populations. Frequency counts and percentages will be reported for categorical data. Sample size, mean, standard deviation, minimum, and maximum will be reported for the continuous variables.</p> <p>Efficacy Analyses: The 90% Wald's confidence interval with Yate's continuity correction will be constructed on the difference between the proportions of subjects with AK lesion clearance in the Test and Reference treatments to evaluate the therapeutic comparability of the two active treatments. Evaluation in the PP population will be considered primary.</p> <p>At Day 90 (30 days after completion of 60 days of treatment), if the 90%</p>

	<p>confidence interval on the difference between the Test and Reference lesion clearance proportions 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>Two-sided, continuity-corrected Chi-square tests will be used to evaluate the superiority of each active treatment's complete clearance proportion over that of the Vehicle treatment in the mITT population using LOCF.</p> <p>The therapeutic comparability evaluations in the PP population will be considered primary, while those in the mITT population will be considered supportive. The superiority comparisons in the mITT population will be considered primary while those in the PP population will be considered supportive.</p> <p>Safety Analyses: All subjects in the Safety population will be included in summaries of safety data.</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 are defined as those who apply at least 75% and no more than 125% of the expected (120) test article applications, did not miss more than 10 consecutive scheduled applications, and have no other evidence of material dosing noncompliance.</p> <p><u>Adverse Events</u> All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each treatment-emergent AE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, closest relationship to test article, and treatment group. All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome.</p> <p><u>Local Skin Reactions</u> The frequency of the individual LSRs (erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus) will be tabulated by severity and treatment group at each onsite clinic visit.</p>
Interim Analysis	No interim analysis is planned.

SCHEDULE OF EVENTS

Visit/Contact	Visit 1 Screening/ Baseline	Visit 2 Telephone	Visit 3 Follow- up	Visit 4 Telephone	Visit 5 End of Treatment	Visit 6 End of Study ⁷ 30 Days Post- Treatment Follow-up
Day	1	Day 15 (±3 days)	Day 30 (±3 days)	Day 45 (±3 days)	Day 60 (+4 days)	Day 90 (±4 days)
Treatment Period	Test Article Application Twice Daily for 60 Consecutive Days.					
Informed Consent ⁸	X					
Medical History & Demographics	X					
Concomitant Medications and Therapies / Procedures	X	X	X	X	X	X
Dermatology Exam	X					
Eligibility Screening, Inclusion, Exclusion	X					
Identification of 25 cm ² treatment area (Face or Bald Scalp ⁹) - Location & Size	X					
Photography & “Subject Specific” Template ¹⁰	X					
AK Lesion Evaluation & Counting	X				X	X
LSR Assessment	X		X		X	X
Adverse Events	X	X	X	X	X	X

⁷ Subjects who terminate early shall complete all final visit activities designated at Day 90.

⁸ Subjects may have consent signed and if required wash-out from prohibited medications or treatments within 30 days prior to the Baseline Visit.

⁹ Bald scalp for the purposes of this study is a scalp where the subject has lost the majority of their hair (well over 50%) within the intended 25 cm² treatment area where the scalp is: a) readily visible and 2) the number of the AKs in the treatment area can be easily seen and counted by the evaluator. It is also important that both the site and subject can repeatedly identify the treatment area to assure accurate repeat therapy by the subject and evaluation by the investigator.

¹⁰ A Treatment Area Identification Manual will be provided to the sites with instructions on how to perform photography of the treatment area and on how to create the “subject specific” template.

Visit/Contact	Visit 1 Screening/ Baseline	Visit 2 Telephone	Visit 3 Follow- up	Visit 4 Telephone	Visit 5 End of Treatment	Visit 6 End of Study ⁷ 30 Days Post- Treatment Follow-up
Day	1	Day 15 (±3 days)	Day 30 (±3 days)	Day 45 (±3 days)	Day 60 (+4 days)	Day 90 (±4 days)
Pregnancy Testing ¹¹ for WOCBP ¹²	X				X	
Application Instructions Distributed	X					
Test Article Application Demonstration	X					
Randomization	X					
Subject Diary Distributed	X		X			
Subject Diary Reviewed		X	X	X	X	
Subject Diary Collected			X		X	
Test Article Compliance Check		X	X	X	X	
Test Article Accountability (Test Article Dispensing)	X		X			
Test Article Accountability (Test Article Return)					X	

¹¹ UPTs must have a minimum sensitivity of 25 mIU β -hCG/mL.

¹² WOCBP include any female who has experienced menarche or is 10 years of age or older 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 or older). Even women who are using oral, implanted, injectable, intravaginal contraceptive hormones, an IUD, barrier methods (diaphragm/cervical cap and spermicidal, condom and spermicidal) to prevent pregnancy, practicing abstinence, or where the partner is sterile and the subject states she is in a monogamous relationship should be considered to be of childbearing potential. Surgical means of sterilization (e.g., vasectomy, tubal ligation) must be a minimum of six months post-procedure to be considered effective birth control.

ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratoses
ALA	Aminolevulinic Acid
ASA	Acetylsalicylic Acid
β-hCG	Beta-Human Chorionic Gonadotropin
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
cm	Centimeter
COX-2	Cyclooxygenase-2
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GDC 695	Diclofenac sodium gel, 3% (Gage Development Company)
ICH	International Conference on Harmonisation
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
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-the-Counter
PDT	Photodynamic Therapy
PP	Per-Protocol
PT	Preferred Term
PUVA	Psoralen + Ultraviolet A
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SOC	System Organ Class
■	■
UPT	Urine Pregnancy Test
UVB	Ultraviolet B
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, AK(s) may remain unchanged, spontaneously regress, or progress to squamous cell carcinoma. It is unknown which AK(s) will develop into cancer so preventative treatment strategies are warranted. AK treatments include: topical medications, cryosurgery, combination therapies, chemical peels, laser surgery, and photodynamic therapy. Topical medications include: 5-fluorouracil, imiquimod, ingenol mebutate, and diclofenac.

Two important stages in the proposed development of AKs have been identified as a mutation of the p53 tumor suppressor gene and an increase in the cyclooxygenase-2 (COX-2) enzyme (shown at increased levels in premalignant and malignant tumors) [1].

The majority of AKs in the United States are treated by destructive therapies, such as cryosurgery [2]. A limiting factor of these treatment modalities is the focus on treating discrete lesions, which is impractical for use on early or subclinical AKs. Topical agents may be better suited for treating wider photodamaged areas of subclinical lesions.

Diclofenac sodium gel, 3% is a topical nonsteroidal anti-inflammatory agent that is used for the treatment of AKs. This therapy inhibits COX-2 levels thereby blocking the AK development pathway [3]. Diclofenac sodium gel, 3% provides a topical treatment alternative for treating the field of photodamaged skin by inhibiting the formation of new, early AK lesions in addition to providing targeted treatment of clearly visible lesions.

Diclofenac Sodium Gel, 3% (Fougera) was approved by the Food and Drug Administration (FDA) in 2000 for the topical treatment of AK [4]. The FDA-approved regimen for the treatment of AKs is application of diclofenac sodium gel, 3% twice a day to lesion areas with a recommended duration of therapy from 60 days to 90 days.

A generic diclofenac sodium gel, 3% (GDC 695) has been developed by Gage Development Company, LLC for the topical treatment of clinically typical, visible, or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, each at least 4 mm in diameter, contained within a continuous 25 cm² treatment area located on the face (excluding ears) or bald scalp.

2. RATIONALE

Gage Development Company, LLC has developed GDC 695, a generic diclofenac sodium gel, 3% formulation, and the current clinical study is designed to evaluate the

therapeutic equivalence of this formulation with the currently marketed Diclofenac Sodium Gel, 3% formulation (Fougera).

3. OBJECTIVES

The objectives of the study are to evaluate the safety and therapeutic equivalence of GDC 695 to Diclofenac Sodium Gel, 3% (Fougera) and to establish the superiority of the efficacy of these two products over the vehicle gel in the treatment of AKs.

4. STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group comparison study of GDC 695 and Diclofenac Sodium Gel, 3% (Fougera) in subjects with AKs on the face or bald scalp. Approximately 600 subjects with at least five but no more than 10 clinically typical, visible or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, each at least 4 mm in diameter, contained within a continuous 25 cm² treatment area located on the face (excluding the ears) or the bald scalp who fulfill the inclusion/exclusion criteria will be enrolled at approximately 28 sites. Subjects will be randomized to one of three treatment groups on a 1:1:1 basis as follows:

1. GDC 695 (Gage) (generic diclofenac sodium gel)
2. Diclofenac Sodium Gel, 3% (Fougera) (Reference Listed Drug [RLD])
3. Vehicle gel (Gage)

All subjects will be instructed to apply the assigned test article to the entire 25 cm² treatment area (face [excluding ears] or bald scalp) identified by the investigator at Visit 1. The assigned test article will be applied twice daily, once in the morning and once in the evening, for 60 days to the entire 25 cm² treatment area. The study will consist of a Screening/Baseline Visit, telephone calls at Day 15 and at Day 45, and follow-up visits at Day 30, Day 60, and Day 90 (30 days after completion of 60 days of treatment). At the end of the study, safety and efficacy outcome measures will be compared to a) determine if dosing with GDC 695 is clinically equivalent to the currently marketed Diclofenac Sodium Gel, 3% and b) both diclofenac sodium 3% gels are superior in comparison to the vehicle gel.

5. STUDY POPULATION

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. Is an immunocompetent male and/or non-pregnant female, 18 years of age or older.

2. Has provided written informed consent including consent to photography of the treatment area at Visit 1.
3. Is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
4. Has a clinical diagnosis of actinic keratoses with at least five (5) and no more than ten (10) clinically typical, visible, or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, each at least 4 mm in diameter, contained within a continuous 25 cm² treatment area located on the face (excluding ears) or bald scalp¹³.
5. 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.
6. If female, must be post-menopausal¹⁴, surgically sterile¹⁵, or use an effective method of birth control^{16,17} with a negative urine pregnancy test (UPT)¹⁸ at the Baseline Visit.

5.1.2 Exclusion Criteria

1. Is pregnant, breastfeeding, or is planning to become pregnant or breastfeed during the study.
2. Is currently enrolled in an investigational drug or device study.
3. Has used an investigational drug or investigational device within 30 days prior to the Baseline Visit.
4. Subject has hyperkeratotic, hypertrophic (i.e., Grade 3 AKs), or large AKs of any Grade (e.g., AK >1 cm² in size) within the treatment area.
5. Has >10 AKs of any size within the treatment area.

¹³ Bald scalp for the purposes of this study is a scalp where the subject has lost the majority of their hair (well over 50%) within the intended 25 cm² treatment area where the scalp is: a) readily visible and 2) the number of the AKs in the treatment area can be easily seen and counted by the evaluator. It is also important that both the site and subject can repeatedly identify the treatment area to assure accurate repeat therapy by the subject and evaluation by the investigator.

¹⁴ Defined as amenorrhea greater than 12 consecutive 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 [oral, injectable, transdermal or intravaginal] for one full cycle (e.g., four to eight weeks), or intrauterine device (IUD) for one week, for injectable (e.g., Depo-Provera) the requirement is at least seven days after injection, prior to test article application, or b) condom and spermicidal, or diaphragm/cervical cap and spermicidal which are effective as soon as the birth control method is administered properly. Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., a vasectomy performed at least six months prior to the subject's initiation of treatment). 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 Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study.

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

6. Has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study.
7. Is immunosuppressed (e.g., human immunodeficiency virus, systemic malignancy, graft host disease, etc.) or is taking medications that suppress the immune system.
8. Has experienced an unsuccessful outcome from previous topical diclofenac sodium therapy; an unsuccessful outcome is defined as “after a reasonable therapeutic trial with no compliance issues and the topical drug did not work”.
9. Has a history of sensitivity to any of the ingredients in the test articles including diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 359, hyaluronate sodium, sodium phosphate monobasic anhydrous, sodium hydroxide or other excipients in the test product or RLD.
10. Has signs or symptoms consistent with the aspirin (ASA) triad: asthmatic subjects who experience rhinitis with or without nasal polyps, or who experience severe bronchospasm after taking aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).
11. Used topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, powders, or gels and new brands of make-up) within the selected treatment area within one day prior to the Baseline Visit.
12. Has used topical medications: corticosteroids, alpha hydroxy acids (e.g., glycolic acid, lactic acid, etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >2%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate, aminolevulinic acid (ALA) or prescription retinoids (e.g., tazarotene, adapalene, tretinoin), over-the-counter (OTC) products labeled as scrubs of any kind which are used to smooth the skin (as they contain some form of exfoliant such as nut shells, coffee grounds, polymer particles, etc.) within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit.
13. Has had cryodestruction or chemodestruction, curettage, photodynamic therapy (PDT), surgical excision, or other treatments for AK within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit.
14. Has used systemic corticosteroid therapy (includes intramuscular and intra-articular administration), interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or retinoids within one month prior to the Baseline Visit.
15. Has used oral isotretinoin within six months prior to the Baseline Visit.
16. Has used chemical peels, including but not limited to alphahydroxy acid, betahydroxy acid, bichloroacetic acid, trichloroacetic acid, and phenol within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit.
17. Has had dermatologic procedures or surgeries such as: laser resurfacing, PUVA (Psoralen + ultraviolet A) therapy, ultraviolet B (UVB) therapy, or dermabrasion within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit.
18. Has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the selected treatment area (face or bald scalp).
19. Has any skin pathology or condition within the selected treatment area (the face or bald scalp) such as atopic dermatitis, eczema, psoriasis, rosacea, sunburn, or other confounding skin condition(s) 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.
20. Has active gastrointestinal ulceration or bleeding or has a history of gastrointestinal bleeds due to use of aspirin or other NSAIDs.
 21. Has severe renal or hepatic impairment.
 22. 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.
 23. Is unable to communicate or cooperate with the investigator due to language problems, poor mental development, impaired cerebral function, or physical limitations.
 24. 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.
 25. 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

Test article is defined as a pharmaceutical form of an active ingredient or vehicle/placebo being tested or used as reference in the study, whether blinded or unblinded.

6.1 Description

Reference listed drug:	Diclofenac Sodium Gel, 3% (Fougera)
Active ingredient:	Diclofenac sodium
Other ingredients:	Benzyl alcohol, hyaluronate sodium, polyethylene glycol monomethyl ether, and purified water.
Test product:	GDC 695
Active ingredient:	Diclofenac sodium
Other ingredients:	Benzyl alcohol, hyaluronate sodium, polyethylene glycol monomethyl ether, and purified water.
Placebo:	Vehicle gel
Active ingredient:	None
Other ingredients:	Benzyl alcohol, hyaluronate sodium, polyethylene glycol monomethyl ether, sodium phosphate monobasic anhydrous, sodium hydroxide, and purified water.

6.2 Instructions for Use and Application

At Visit 1/Baseline, the investigator will designate the 25 cm² treatment area using a pre-marked 1 cm² gridded transparency to create a “subject specific” template and will take photographs of the treatment area per the instructions provided in the Treatment Area Identification Manual.

Subjects will be instructed to apply the test article twice daily, once in the morning and once in the evening (e.g., approximately 8-12 hours apart), for 60 days to the entire 25 cm² treatment area (the face [excluding the ears] or the bald scalp). Bald scalp for the purposes of this study is a scalp where the subject has lost the majority of their hair (well over 50%) within the intended 25 cm² treatment area where the scalp is: a) readily visible and 2) the number of the AKs in the treatment area can be easily seen and counted by the evaluator. It is also important that both the site and subject can repeatedly identify the treatment area to assure accurate repeat therapy by the subject and evaluation by the investigator. Subjects will be instructed to use the photograph and the “subject specific” template of their 25 cm² treatment area provided to them at Baseline in order to help ensure proper application of the test article. Test article may be applied with the fingertips. Normally 0.5 grams of gel is used on each 25 cm² treatment area (e.g., slightly smaller than the size of a dime; see [Appendix 1](#)) and applied as a thin film to the entire treatment area and rubbed until the gel is no longer visible as instructed by the investigator or site staff. Immediately after application, the hands should be thoroughly washed. Subjects will be cautioned to avoid applying the gel near the eyes, nostrils, and mouth. The test article should be left on the skin for a minimum of four hours prior to washing. Treatment should continue for the full treatment course even if all AKs appear to be gone. The study staff should demonstrate the proper use of the test article using the vehicle gel provided for subject training. See [Appendix 1](#) for the complete Subject Instructions.

6.3 Warnings, Precautions and Contraindications

6.3.1 Contraindications

Diclofenac sodium gel is contraindicated in subjects with a known hypersensitivity to diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 350, and/or hyaluronate sodium.

Diclofenac sodium gel is contraindicated in the following patients:

- In the setting of coronary artery bypass graft surgery.

6.3.2 Warnings

As with other NSAIDs, anaphylactoid reactions may occur in subjects without prior exposure to diclofenac. Diclofenac sodium should be given with caution to subjects with the aspirin triad. The triad typically occurs in asthmatic subjects who experience rhinitis

with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.

6.3.3 Precautions

Diclofenac sodium gel should be used with caution in subjects with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. Diclofenac sodium gel should not be applied to open skin wounds, infections, or exfoliative dermatitis. It should not be allowed to come into contact with the eyes.

The safety of the concomitant use of sunscreens, cosmetics or other topical medications, and diclofenac sodium gel is unknown.

Although low, there is systemic exposure to diclofenac following labeled use of diclofenac sodium gel. Therefore, concomitant administration of diclofenac sodium gel with oral NSAIDs or aspirin may result in increased NSAID adverse effects.

6.3.4 Other Considerations

These test articles are for topical use only (not for oral, ophthalmic, or intravaginal use). Contact with eyes, lips, and nostrils should be avoided. If contact with the mouth or eyes occurs, rinse thoroughly with water right away.

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

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

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 who are eligible for enrollment into the study will be randomized by assigning the lowest subject kit number available at the site. Subjects will be randomized to one of three treatments on a 1:1:1 basis [GDC 695 (Gage), Diclofenac Sodium Gel, 3% (Fougera), or vehicle gel (Gage), respectively].

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Screening/Baseline, Visit 1) will be recorded as prior/concomitant medications

with the dose and corresponding indication. The medications to be recorded include prescription and OTC medications (except vitamins and dietary supplements). All medications taken on a regular basis should be recorded on this page prior to commencing the use of the test article. Any changes in concomitant medications during the study must be recorded on the CRFs.

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 may be continued. All concomitant therapies during the study must be recorded on the Concomitant Therapy case report form (CRF).

The reason for any changes in concomitant medications or therapies/procedures should be reported and should reflect either a baseline medical condition documented in the medical history of the CRF or an adverse event (AE).

8.1 Prohibited Medications or Therapies

Prohibited medications or therapies during the study include:

- Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, powders, or gels of any kind and new brands of make-up) within the selected treatment area within one day prior to the Baseline Visit.
- Topical medications: corticosteroids, alpha hydroxy acids (e.g., glycolic acid, lactic acid, etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >2%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate, ALA or prescription retinoids (e.g., tazarotene, adapalene, tretinoin), OTC products labeled as scrubs of any kind which are used to smooth the skin (as they contain some form of exfoliant such as nut shells, coffee grounds, polymer particles, etc.) within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit.
- Cryodestruction or chemodestruction, curettage, PDT, surgical excision, or other treatments for AK within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit.
- Systemic corticosteroid therapy (includes intramuscular administration, see [Section 8.2](#) for guidance regarding intra-articular corticosteroids), interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or retinoids within one month prior to the Baseline Visit.
- Oral isotretinoin within six months prior to the Baseline Visit.
- Chemical peels, including but not limited to alphahydroxy acid, betahydroxy acid, bichloroacetic acid, trichloroacetic acid, and phenol within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit.

- Dermatologic procedures or surgeries such as: laser resurfacing, PUVA therapy, UVB therapy, or dermabrasion within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit.
- Areas treated with the test article should not be covered with any type of bandage or occlusive dressings.

8.2 Allowed Medications or Therapies

The use of any of the following allowed medications or therapies should be documented in the subject's CRF.

- Any medications not intended or beneficial for the treatment of AKs may be used unless specifically excluded or prohibited by this protocol (see [Section 8.1: Prohibited Medications or Therapies](#) above).
- NOTE: Ideally, treatment of AKs at a body site exclusive of the HEAD should be avoided during the study period **unless** the treatment is deemed to be a material medical necessity for the subject by the investigator. In such cases, the **ONLY** allowed treatments for AKs, at any body site exclusive of the HEAD, are focal and limited treatment to the AK site only using surgical excision, cryotherapy, and curettage ± pin point focal electrodesiccation. Use of any other treatment methods is prohibited (see [Section 8.1](#)), as are the treatment of any AKs on the HEAD using any method.
- In the event that treatment of an AK on the HEAD, but outside the treatment area, is deemed necessary by the investigator, such a procedure may only be performed after discussion and the approval by the Medical Monitor.
- Intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders, or other conditions.
- A single intra-articular corticosteroid injection is allowed during the study. Additional treatments are allowed only with the approval of the Medical Monitor.
- Protective clothing (e.g., a hat) is encouraged to reduce exposure of the treatment area to sunlight.
- Use of a light bodied bland moisturizer in the treatment area as an aid to managing local skin reactions is allowed ONLY with the approval of the Medical Monitor. Examples of light bodied moisturizers are Cetaphil, Lubriderm (without alpha hydroxy acid), and other bland moisturizers that do not contain any "active" ingredients (e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient that could irritate or cause a keratolytic effect). Moisturizers should not be applied within four (4) hours after test article application. NOTE: moisturizers, if allowed and used in the treatment area, shall be recorded as a concomitant therapy.

9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

9.1 Visit 1 (-30 to Day 1): Screening/Baseline

Informed consent may be collected from study subjects up to 30 days before Visit 1. If applicable, qualified subjects can washout from prohibited medications or treatments (see [Section 8.1](#)) prior to their Screening/Baseline Visit once informed consent has been obtained. If washout period exceeds 30 days, re-consent is required. The Screening and Baseline Visit may be completed on the same day, if no washout is required.

At this visit, the investigator or designee will:

- Obtain a signed, written informed consent, and update the Subject Screening and Enrollment Log.
- Confirm the subject meets the inclusion/exclusion criteria.
- Document the information required on the Medical History form.
- Document the information required on the Demographics form.
- Record the subject's prior and/or concomitant medications and therapies/procedures.

If the subject requires washout from previous medications, the remaining activities will be performed after washout is completed and must be completed within 30 days of first visit, or the subject needs to be re-consented.

- Perform a dermatologic exam. Consistent with Exclusion Criterion #18, any subject with a suspicious lesion within the treatment area should not be enrolled prior to confirmation that the lesion is not skin cancer. In the event that a biopsy is warranted to make such a determination per the investigator, such a procedure is considered outside the scope of this study and therefore will be the responsibility of the potential subject. In the event that a biopsy is needed and it is not available for review, the subject shall be considered a screen failure.
- Identify the 25 cm² treatment area on either the face (excluding ears) or bald scalp. NOTE: Use the procedure as detailed in the Treatment Area Identification Manual to create and label the transparency to record the designated treatment area.
- Create a "subject specific" template per the instructions provided in the Treatment Area Identification Manual to assist the subject in the identification of the treatment area prior to application of the test article. A copy of the template will also be retained in the subject's site file for use by the site to properly identify the treatment area at future visits.
- Take Baseline photographs of the designated 25 cm² treatment area per the instructions provided in the Treatment Area Identification Manual and store one photo in the subject's file at the site and give one photo to the subject in order to help ensure proper application of the test article by the subject.
- Record the size of the designated treatment area.

- Perform the AK lesion count as described in [Section 10.1](#), which includes any AKs ≥ 4 mm in diameter, as well as any smaller lesions. NOTE: A minimum of five to a maximum of 10 AKs ≥ 4 mm in diameter in the 25 cm² treatment area is required to qualify.
- Document the diameter of each AK lesion in the treatment area.
- Perform the LSR assessment as described in [Section 10.2](#).
- Reaffirm the Inclusion/Exclusion criteria.
- Perform a UPT for all WOCBP. The UPT must be negative for subjects to continue.
- Assign the subject the next available (lowest) subject number in ascending order. Assign the subject the lowest available test article kit number and dispense test article. NOTE: Test article will be weighed prior to being dispensed and the subject will be instructed not to open study supplies at the site.
- Review and dispense a Subject Instruction Sheet to the subject (see [Appendix 1](#)). Instruct the subject to apply test article twice daily, once in the morning and once in the evening, and demonstrate proper test article application using vehicle gel provided for subject training.
- Explain and issue the subject diary.
- Confirm the next appointment.

9.2 Visit 2 (Day 15 \pm 3 days): Phone Call

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate. NOTE: If severe tolerability issues or a material AE concern of any type are noted, the subject may be scheduled for an in-office visit at the investigator's discretion.
- Record any changes in the subject's concomitant medications and therapies/procedures.
- Review the subject diary and test article compliance.
- Remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit and to bring their tube of test article with them to their next clinic visit.
- Confirm the next appointment and instruct subject to not apply the study medication to the treatment area prior to any study visits.

9.3 Visit 3 (Day 30 \pm 3 days): Follow-Up

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate.

- Record any changes in the subject's concomitant medications and therapies/procedures.
- Use the transparency and the Baseline photo as necessary to locate the selected treatment area.
- Perform the LSR assessment as described in [Section 10.2](#).
- Review/collect/distribute the subject diary as necessary.
- Review test article compliance. Test article application will be demonstrated if deemed necessary. As necessary, the Baseline photograph and the template may be used as a visual aid to re-instruct subject on proper application of the test article to the treatment area.
- The subject's tube of test article will be weighed and re-dispensed.
- Remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit.
- Confirm the next appointment.

9.4 Visit 4 (Day 45 ± 3 days): Phone Call

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate. NOTE: If severe tolerability issues or a material AE concern of any type are noted, the subject may be scheduled for an in-office visit at the investigator's discretion.
- Record any changes in the subject's concomitant medications and therapies/procedures.
- Review the subject diary and test article compliance.
- Remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, to the skin of the 25 cm² treatment area until the next clinic visit and to bring their tube of test article with them to their next clinic visit.
- Confirm the next appointment and instruct subject to not apply the study medication to the treatment area prior to any study visits.

9.5 Visit 5 (Day 60 + 4 days): End of Treatment

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate.
- Record any changes in the subject's concomitant medications and therapies/procedures.
- Use the transparency and the Baseline photo as necessary to locate the selected treatment area.

- Perform the AK lesion count as described in [Section 10.1](#), which includes any AKs ≥ 4 mm in diameter, as well as any smaller lesions.
- Perform the LSR assessment as described in [Section 10.2](#).
- Review and collect the subject diary and test article compliance.
- The subject's tube of test article will be weighed and collected.
- Perform a UPT for all WOCBP.
- Confirm the next appointment.

9.6 Visit 6 (Day 90 \pm 4 days): End of Study

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate.
- Record any changes in the subject's concomitant medications and therapies/procedures.
- Use the transparency and the Baseline photo as necessary to locate the selected treatment area.
- Perform the AK lesion count as described in [Section 10.1](#), which includes any AKs ≥ 4 mm in diameter, as well as any smaller lesions.
- Perform the LSR assessment as described in [Section 10.2](#).
- Discharge the subject from the study.

9.7 Unscheduled Visit

The investigator may see the subject at an unscheduled visit to manage any AEs or LSRs.

At this visit, the investigator or designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the CRF, as appropriate.
- Use the transparency and the Baseline photo as necessary to locate the selected treatment area.
- Perform the LSR assessment as described in [Section 10.2](#).
- Record any changes in the subject's concomitant medications.
- Review subject diary and the requirements for test article application, if applicable.
- Confirm the next appointment.

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 Baseline, Day 60/EOT, and Day 90/EOS. At the Baseline Visit (Visit 1), all AK lesions in the 25 cm² treatment area, independent of size, will be identified, counted, and recorded on the transparency. The number and location of AK lesions to be treated that are ≥ 4 mm in diameter and the diameter of each AK lesion in the 25 cm² treatment area will also be documented at the Baseline Visit. The suggested procedure for AK counting and definition of face (excluding ears) and bald scalp will be detailed in a separate document. At the Baseline Visit, the 25 cm² treatment area must include at least five and no more than 10 clinically typical, visible, or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, each at least 4 mm in diameter, contained within a continuous 25 cm² treatment area located on the face (excluding ears) or bald scalp. At the EOT and EOS visits, the number of total AK lesions in the 25 cm² treatment area will be counted and the number of new AKs will be identified. A new AK is defined as a lesion that was not present at the Baseline Visit.

NOTE: To ensure accurate identification of the treatment area, the site must use the transparency and the Baseline photo as necessary to locate the selected treatment area.

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 CRF that the AK count was unable to be obtained due to a LSR.

10.2 Local Skin Reaction Assessment

At Baseline, Day 30 follow-up, Day 60/EOT, Day 90/EOS, and Unscheduled Visits (if applicable), the investigator or designee will assess the 25 cm² treatment area and rate on a scale of 0 = absent, 1 = mild (slight, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense) the following LSRs:

- Erythema
- Dryness/flaking/scaling
- Burning/stinging
- Erosion/ulceration
- Edema
- Pain (within the last 24 hours)
- Pruritus (itching) (within the last 24 hours)

These LSRs will be collected independently of AEs. Any LSR that occurs **within the 25 cm² treatment area (face [excluding the ears] or bald scalp) and extends to adjacent surrounding skin (defined to be up to a 5 cm border around the 25 cm² treatment area)** will be considered LSRs. LSRs that require medical intervention

(prescription medication) or extend beyond the 5 cm surrounding skin should be documented as an AE.

11. PHOTOGRAPHY

Photography documentation is required in this study. Photographs taken as part of this study will be used to document proper identification of the treatment area to help ensure proper application of the test article by the subject. Photographs may also be used to document the effects of treatment, AEs, or other findings during the study. The site will be provided with suggested guidelines to assist them in taking standardized photographs. 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 who decline to have Baseline photographs taken will not be eligible to be in the study. Additional details regarding taking Baseline photographs are provided in a separate photo guide (i.e., the Treatment Area Identification Manual) provided to the site.

12. LABORATORY TESTS

12.1 Urine Pregnancy Tests

UPTs must be performed on all WOCBP at Baseline prior to randomization and at the Day 60/EOT visit. All WOCBP must have a negative UPT at 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 60-day treatment and all of the EOS visit evaluations at Day 90 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:

- AEs
- Death

- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy (if applicable)
- Progressive disease
- Protocol deviation
- 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 reason that may affect the outcome of the study or safety of subjects)

If a subject withdraws prematurely for any reason, the site should make every effort to have the subject return for; a) their next scheduled visit to perform all required visit activities and to collect and reconcile all test article AND b) return for the EOS visit (Day 90) to perform all required visit activities and complete the EOS CRF. If the subject will not agree to return for the EOS visit, the site should complete the EOS CRFs during the last visit that the subject will complete. Subjects who withdraw prematurely will not be replaced. When a subject is withdrawn from the study for a treatment-related AE (i.e., as defined in [Section 14](#)), when possible, the subject should be followed until resolution or stabilization of the AE. If a subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed (see [Section 14.5](#)).

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 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with any drug) and with any route of administration, formulation, or dose, including an overdose.

Suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. For the purposes of prescription drug labeling, the term adverse reaction is defined to mean "an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action or may be unpredictable in its occurrence. This definition does not include all AEs observed during use of a drug, only those AEs for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the AE".

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the RLD package insert or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the RLD package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the RLD package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the RLD package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists [REDACTED] in identifying any untoward medical occurrence, thereby allowing:

- 1) protection of the safety of study subjects;
- 2) a greater understanding of the overall safety profile of the test article;
- 3) recognition of dose-related test article toxicity;
- 4) appropriate modification of study protocols;
- 5) improvements in study design or procedures; and
- 6) adherence to worldwide regulatory requirements.

14.2 Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE CRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as serious adverse events (SAEs, see [Section 14.3](#)). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the investigator to be related to the test article, should be reported.

Information on the medical condition of subjects should begin following the subject's written consent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore, AE data should be collected from the date of the first dose of test article until the date of the final study visit. These data are considered treatment-emergent AEs.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

Mild - The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate - The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe - The AE interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Related - There is a strong medical evidence to suggest that the AE is related to test article usage.

Possibly Related - There is medical evidence to suggest that the AE may be related to test article usage.

Not Related - There is no medical evidence to suggest that the AE may be related to test article usage.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

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

14.3 Serious Adverse Event

An event that is serious must be recorded on the AE CRF and on the [REDACTED] SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered “serious” if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening AE; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.

- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be serious AEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen, and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of “serious” given above and not resulting in hospital admission.

AEs classified as “serious” by either the investigator or the Sponsor 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 by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or RLD Package Insert and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of a SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to [REDACTED] if available.

Upon receiving such notices, the investigator must review and retain the notice with the RLD Package Insert and promptly 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.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA) within seven calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

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 outcome.

14.5 Pregnancy

WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [at least six months prior to initiation of treatment], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women 50 years of age and older). Even women who are using one of the effective forms of birth control per protocol will be considered of childbearing potential.

WOCBP must have a UPT prior to study enrollment and must use an effective¹⁹ method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

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 a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study.

If following initiation of study treatment, it is subsequently discovered that a study subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event, and record the

¹⁹ Effective forms of birth control include a) hormonal contraceptives [oral, injectable, transdermal or intravaginal] for one full cycle (e.g., four to eight weeks), or IUD for one week, for injectable (e.g., Depo-Provera) the requirement is at least seven days after injection, prior to test article application, or b) condom and spermicidal, or diaphragm/cervical cap and spermicidal which are effective as soon as the birth control method is administered properly. Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., a vasectomy performed at least six months prior to the subject's initiation of treatment). 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.

pregnancy on the appropriate pregnancy surveillance form. The form will be sent to [REDACTED]. The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to [REDACTED], on the appropriate [REDACTED] pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE and details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as a SAE.

15. BLINDING/UNBLINDING

This is a double-blind, randomized, placebo-controlled study. Blinding is important for the integrity of this clinical drug study. 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). If possible, the need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability, etc. of the test article is included in [Appendix 2](#).

16.2 Supplies Provided by [REDACTED]

- CRFs
- Site regulatory binder
- UPT kits
- Transparencies (pre-marked 1 cm² grid) and markers to identify the treatment area
- Treatment Area Identification Manual

16.3 Supplies Provided by Investigator

- Urine collection containers

16.4 Supplies Provided by Gage Development Company, LLC

- Samples for demonstration to subjects of test article application
- Digital camera, photo printer, and supplies.

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

Based on [REDACTED]
[REDACTED]
probability of demonstrating therapeutic equivalence between the active treatments and at the same time showing that each active treatment is superior to the vehicle treatment. Thus, approximately [REDACTED] subjects will be enrolled into the study to obtain [REDACTED] mITT subjects.

17.2 Endpoints

17.2.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects in the PP population with treatment success ("Complete Clearance") at Day 90 (30 days after completion of 60 days of treatment). Complete Clearance is defined as 100% clearance of all AK lesions (having a count of zero AKs) in the 25 cm² treatment area (face or bald scalp) at the Day 90 visit. All AKs (those present at baseline and new lesions, if any that may develop) independent of size within the 25 cm² treatment area are to be treated and included in the efficacy lesion count for each visit.

17.2.2 Safety Endpoints

Dosing Compliance

Measures of test article compliance will include the total number of applications recorded in the CRFs and verified from the data in the subject diaries. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the expected (120) test article applications, did not miss more than 10 consecutive scheduled applications, and have no other evidence of material dosing noncompliance.

Adverse Events and Local Skin Reactions

Severity and frequency of AEs including LSRs (erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus) will be assessed in the three treatment groups.

17.3 Statistical Methods

All statistical processing will be performed using SAS® unless otherwise stated.

The Safety population will include all randomized subjects who received the test article. The mITT population will include all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of test article, and returned for at least one post-baseline evaluation visit. Randomized subjects who are lost to follow-up after Visit 1, who return for the EOT visit but have not applied any test article, or who are found not to have met the eligibility criteria will be excluded from the mITT population. Subjects will be included in the PP efficacy analyses if they met all the inclusion/exclusion criteria, were compliant with the assigned test articles (applied at least 75% and no more than 125% of the expected (120) test article applications) for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at the EOS visit within the designated visit window (± 4 days) with no protocol violations that would affect the treatment evaluation. Subjects who are discontinued from the study due to worsening condition that requires alternate or supplemental therapy for the treatment of AK should be included in the PP population as treatment failures if they meet the mITT criteria. Subjects who are discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using last-observation-carried-forward (LOCF).

Efficacy summaries and analyses will be carried out in the mITT and PP populations. All summaries of safety will be carried out in the Safety population. LOCF will be used to impute missing values for efficacy variables in the mITT population.

Demographic and baseline characteristics will be summarized by treatment group for all analysis populations. The size of the treatment area in cm^2 will be summarized by treatment group for the mITT and PP populations. Frequency counts and percentages will be reported for categorical data. Sample size, mean, standard deviation, minimum, and maximum will be reported for the continuous variables.

17.3.1 Efficacy Analyses

The 90% Wald's confidence interval with Yate's continuity correction will be constructed on the difference between the proportions of subjects with AK lesion clearance in the Test and Reference treatments to evaluate the therapeutic comparability of the two active treatments. Evaluation in the PP population will be considered primary.

At Day 90 (30 days after completion of 60 days of treatment), if the 90% confidence interval on the difference between the Test and Reference lesion clearance proportions

are contained within the interval -0.20 to +0.20, then the Test and Reference products will be considered to be therapeutically equivalent.

Two-sided, continuity-corrected Chi-square tests will be used to evaluate the superiority of each active treatment's complete clearance proportion over that of the Vehicle treatment in the mITT population using LOCF.

The therapeutic comparability evaluations in the PP population will be considered primary, while those in the mITT population will be considered supportive. The superiority comparisons in the mITT population will be considered primary while those in the PP population will be considered supportive.

17.3.2 Safety Analyses

All subjects in the Safety population will be included in summaries of safety data.

17.3.2.1 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 are defined as those who apply at least 75% and no more than 125% of expected (120) test article applications, did not miss more than 10 consecutive scheduled applications, and have no other evidence of material dosing noncompliance.

17.3.2.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each treatment-emergent AE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, closest relationship to test article, and treatment group. All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome.

17.3.2.3 Local Skin Reactions

The frequency of the individual LSRs (erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus) will be tabulated by severity and treatment group at each onsite clinic visit.

17.4 Subgroup Analyses

No subgroup analysis is planned.

17.5 Interim Analyses

No interim analysis is planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical 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. Correct contact information for each site and any vendors used in the study will be kept in a separate reference document.

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 (if applicable), 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 EDC software to collect data. All requested information must be entered on the electronic CRFs (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.

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.

Each site will be required to randomly select reserve samples from the shipment of test articles. Instructions on the number of kits to select and how to document the kit numbers selected as reserve samples will be included in the shipment. Each site will then store the reserve samples. 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 from which the reserve samples were obtained.

The investigator must contact [REDACTED] or the Sponsor in writing to obtain consent 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]

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

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APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

Copies of the following subject instructions will be provided to the study site. The investigator must give each subject a copy of this instruction sheet at the Baseline Visit.

Sample Subject Instruction Sheet

The study staff has identified the treatment area where you should apply study medication:

Face (excluding ears) **or**
Bald scalp

Apply the study medication twice a day, once in the morning and once in the evening, for 60 consecutive days to the entire 25 cm² treatment area. Use the photograph and template provided to you by the study staff at your first visit to help you identify the area to apply the study medication.

Most subjects will experience local skin reactions in and around the treatment area. Local skin reactions may include: skin redness, scabbing or crusting, flaking, scaling, pain, itching, or dryness, and in some cases swelling, sores or blisters, and/or draining (weeping) may develop. The skin responses can vary from mild to severe. You may also see an increase in the number of AK growths as previously hidden AK growths may become visible with treatment.

NOTE: It is important for you to continue to use the study medication twice daily during the prescribed 60-day treatment period unless directed to do otherwise by the study doctor. Do not discontinue the use of the medication unless directed so by the study staff. Talk to the study staff about any side effects that you experience.

Please follow these instructions carefully. Contact the study staff at the telephone number below if you have any questions about the study.

Name: _____ Phone: _____

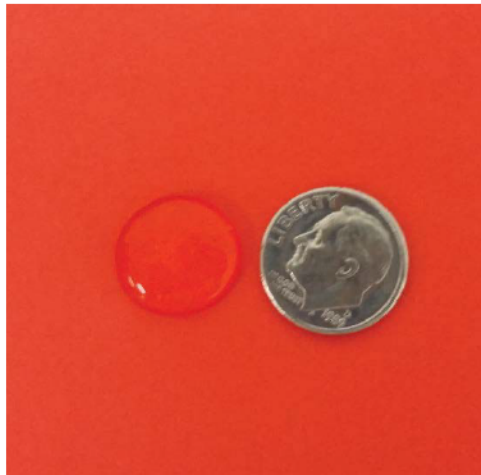
- The site staff will instruct you to apply the gel twice daily, once in the morning and once in the evening, for 60 consecutive days using the photograph and template provided to you to help you identify the correct area to treat at each application.
- Do not apply any moisturizers, sun screen, make-up, creams, lotions, powders, or any topical product other than the study medication gel to the treatment area.
- Do not cover the treatment area with bandages or other closed dressings.
- Do not use sunlamps, ultraviolet lights or tanning beds, and avoid sunlight as much as possible during treatment with the study medication. Use protective clothing if you go outside during daylight.
- If you miss a dose, apply the next dose at the regular time.
- Record any missed doses in your study diary.
- If you get the study medication in your mouth or eyes, rinse well with water right away.
- Do not allow anyone else to use this study medication.
- Keep study medication out of reach from children.
- Do not use any other topical products (e.g., powders, ointment, creams, lotions, solutions, sun screen, etc.) on the treatment area without approval from your study doctor.
- Do not apply the study medication to the treatment area prior to any study visits.
- Store the study medication at room temperature.

Subject Instructions for Application of Gels

Before Each Use: Wash your hands. Remove the cap from the tube.

Application:

1. Use the study medication twice a day as instructed by your study doctor. Use it only on your skin.
2. Use the photograph and template given to you by study staff at your first visit to identify the correct area to apply the study medication.
3. Dispense the required amount of study medication into the palm of your hand. Up to 0.5 gram (e.g., slightly smaller than the size of a dime) of study medication should be used to treat the entire treatment area at each application.



- Using the other hand, apply small aliquots (“dots”) of study medication over the entire 25 cm² treatment area.
4. Using your fingers, gently rub the study medication into your skin so that a uniform thin coat covers the entire 25 cm² treatment area (face or bald scalp).
 5. Care should be taken not to apply study medication near the eyes, nostrils, and mouth.
 6. Be absolutely sure that lesions identified at the Baseline Visit are adequately covered.
 7. Wash your hands as soon as you finish putting the study medication on your skin.
 8. Avoid transferring the study medication to other household members using common towels, skin to skin contact after application, etc.

For Each Application: Rub the study medication into your skin until you can no longer see the gel. Do not get the study medication in or near your eyes, in or on your nostrils, lips or, for women, in the vagina. Wash your hands with mild soap and water. Record the application of study medication in your study diary. **Do not** take a bath, wash, or get the treatment area wet for at least 4 hours after application.

Study Visit Schedule:

Visit	Calendar Day	Date	Time
2 (Phone Call)			
3			
4 (Phone Call)			
5			
6			

Bring this instruction sheet, used and unused study medications and your diary to each study visit.

APPENDIX 2 TEST ARTICLE INFORMATION

A 2.1 Test Article Packaging and Labeling

GDC 695 and vehicle gel formulations will be manufactured by [REDACTED] and Diclofenac Sodium Gel, 3% will be purchased by [REDACTED]. The test articles will be blinded by packaging GDC 695 and vehicle gel in tubes that are indistinguishable from the Diclofenac Sodium Gel, 3% tube. All test article tubes will have identical labels as described below. [REDACTED] will label the test articles.

Sites will be provided with samples for demonstration use only to train subjects on the application of the test article.

Tube Label

Tubes will be labeled with a two-part label that will have a scratch-off panel that contains the identity of the study medication. In the event of emergency, the identity of the test article can be revealed by scratching this section of the label. The 2-part label will contain at least the following information:

- Protocol GDC-695-001
- Kit No.:
- Subject No: ____ _
- Initials: ____ _
- Contents: GDC 695 or Diclofenac Sodium Gel, 3% or Vehicle Gel.
- Apply as directed.
- Store at Controlled Room Temperature 20 to 25° C (68 to 77° F).
- Keep out of reach of children.
- Caution: New Drug - Limited by United States law to investigational use.
- Manufactured for Gage Development Company, LLC [REDACTED]

A 2.2 Retains

Each site will be required to randomly select reserve samples from the shipment of test articles. Instructions on the number of kits to select and how to document the kit numbers selected as reserve samples will be included in the shipment. Each site will then store the reserve samples 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 from which the reserve samples were obtained.

A 2.3 Test Article Storage and Preparation

Test article should be stored at controlled room temperature 20 to 25° C (68 to 77° F), excursions permitted between 15 to 30° C (59 to 86° F), in a secure area according to local regulations.

A 2.4 Dispensing Test Article

The test article must be dispensed only to study subjects and only at study sites specified on the form FDA 1572 by authorized personnel as required by applicable regulations and guidelines.

A 2.5 Test Article Supply Records at Study Sites

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers. The tubes will be weighed prior to being dispensed and also after they are returned.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.
- Retain samples sent to third party for bioavailability/bioequivalence.

■ will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

A 2.6 Dose Modifications

Dosing modifications should be noted on the subject diary and documented in the subject's CRF.

A 2.7 Documentation of Application and Compliance

Subjects will be instructed to document the application of test article and any missed or held doses on the subject diary.

A 2.8 Return and Destruction of Test Article Supplies

At the completion or termination of the study, all unused and/or partially used test articles must be returned by a traceable method. All missing tubes must be explained on the completed Test Article Accountability Log. The investigator must keep the original Label pages and Test Article Accountability Log in the site study file. Photocopies of the original Test Article Accountability Log and Label pages will be kept with the study records at [REDACTED]. All shipment of returned test article must be labeled with the investigator's name, address, and the protocol number. Return all test articles in the original containers by a traceable means (e.g., 2-day FedEx shipping) to:



Upon receipt of the test articles, a Sponsor representative will perform a final reconciliation. [REDACTED] will be notified of any missing test article.

APPENDIX 3 PROTOCOL AMENDMENTS

PROTOCOL AMENDMENT #1

Date of Amendment: January 26, 2017

Summary:

The protocol was amended as follows:

1. Updated second signatory for Gage Development, LLC on protocol approval page.
2. Washouts and prohibition of oral steroid use was changed to systemic steroid use.
3. The description of AKs was modified in exclusion criterion #4 given that a few sites had issues with the language pertaining to “mat-like”.
4. Removed “ALA-PDT” from exclusion criterion #17 given that it conflicts and/or is redundant to exclusion criterion #13.
5. Inserted definition for what is meant by “twice daily” other than once in the morning and once in the evening by inserting “(e.g., approximately 8-12 hours apart)” in the test article application section of the protocol (Section 6).
6. A definition of bald scalp was added as a footnote to inclusion criterion #4 in the synopsis and Section 5.1.1 as well as in schedule of events and was added in the text of Section 6.2 (Instructions for Use and Application).

SPECIFIC CHANGES: Specific changes to the protocol are listed below; new or revised sections are included (*Added text has been **bolded** & deleted text has been ~~redlined~~*). Minor typographical errors, grammatical, and wording changes are not included in this section.

Section # / Name	Revised Text
Inclusion Criterion #4	4. Has a clinical diagnosis of actinic keratoses with at least five (5) and no more than ten (10) clinically typical, visible, or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, <u>each at least 4 mm in diameter</u> , contained within a continuous 25 cm ² treatment area located on the face (excluding ears) or bald scalp.
Exclusion Criteria #s 4, 14, and 17	4. Subject has hyperkeratotic, hypertrophic (i.e., Grade 3 AKs), or large mat-like AKs of any Grade (e.g., AK >1 cm ² in size) within the treatment area. 14. Has used oral systemic corticosteroid therapy (includes intramuscular and intra-articular administration), interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or retinoids within one month prior to the Baseline Visit. 17. Has had dermatologic procedures or surgeries such as:

	laser resurfacing, PUVA (Psoralen + ultraviolet A) therapy, ultraviolet B (UVB) therapy, ALA-PDT , or dermabrasion within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit.
Section 6.2 Instructions for Use and Application	Subjects will be instructed to apply the test article twice daily, once in the morning and once in the evening (e.g., approximately 8-12 hours apart), for 60 days to the entire 25 cm ² treatment area (the face [excluding the ears] or the bald scalp). Subjects will be instructed to use the photograph and the “subject specific” template of their 25 cm ² treatment area provided to them at Baseline in order to help ensure proper application of the test article. Test article may be applied with the fingertips. Normally 0.5 grams of gel is used on each 25 cm ² treatment area (e.g., slightly smaller than the size of a dime; see Appendix 1) and applied as a thin film to the entire treatment area and rubbed until the gel is no longer visible as instructed by the investigator or site staff. Immediately after application, the hands should be thoroughly washed. Subjects will be cautioned to avoid applying the gel near the eyes, nostrils, and mouth. The test article should be left on the skin for a minimum of four hours prior to washing. Treatment should continue for the full treatment course even if all AKs appear to be gone. The study staff should demonstrate the proper use of the test article using the vehicle gel provided for subject training. See Appendix 1 for the complete Subject Instructions.
8.1 Prohibited Medications or Therapy	<p>Prohibited medications or therapies during the study include:</p> <ul style="list-style-type: none"> • Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, powders, or gels of any kind and new brands of make-up) within the selected treatment area within one day prior to the Baseline Visit. • Topical medications: corticosteroids, alpha hydroxy acids (e.g., glycolic acid, lactic acid, etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >2%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate, ALA or prescription retinoids (e.g., tazarotene, adapalene, tretinoin), OTC products labeled as scrubs of any kind which are used to smooth the skin (as they contain some form of exfoliant such as nut shells, coffee grounds, polymer particles, etc.) within the selected treatment area (face or bald scalp) within one month prior to the Baseline Visit. • Cryodestruction or chemodestruction, curettage, PDT, surgical excision, or other treatments for AK within the

	<p>selected treatment area (face or bald scalp) within one month prior to the Baseline Visit.</p> <ul style="list-style-type: none"> • Systemic oral corticosteroid therapy (includes intramuscular administration, see Section 8.2 for guidance regarding intra-articular corticosteroids), interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or retinoids within one month prior to the Baseline Visit. • Oral isotretinoin within six months prior to the Baseline Visit. • Chemical peels, including but not limited to alphahydroxy acid, betahydroxy acid, bichloroacetic acid, trichloroacetic acid, and phenol within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit. • Dermatologic procedures or surgeries such as: laser resurfacing, PUVA therapy, UVB therapy, ALA PDT, or dermabrasion within the selected treatment area (face or bald scalp) within six months prior to the Baseline Visit. • Areas treated with the test article should not be covered with any type of bandage or occlusive dressings.
Section 8.2 Allowed Medications and Therapies	<p>The use of any of the following allowed medications or therapies should be documented in the subject's CRF.</p> <ul style="list-style-type: none"> • Any medications not intended or beneficial for the treatment of AKs may be used unless specifically excluded or prohibited by this protocol (see Section 8.1: Prohibited Medications or Therapies above). • NOTE: Ideally, treatment of AKs at a body site exclusive of the HEAD should be avoided during the study period unless the treatment is deemed to be a material medical necessity for the subject by the investigator. In such cases, the ONLY allowed treatments for AKs, at any body site exclusive of the HEAD, are focal and limited treatment to the AK site only using surgical excision, cryotherapy, and curettage ± pin point focal electrodesiccation. Use of any other treatment methods are is prohibited (see Section 8.1), as are the treatment of any AKs on the HEAD using any method. • In the event that treatment of an AK on the HEAD, but outside the treatment area, is deemed necessary by the investigator, such a procedure may only be performed after discussion and the approval by the Medical Monitor. • Intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders, or other conditions. • A single intra-articular corticosteroid injection is allowed

	during the study. Additional treatments are allowed only with the approval of the Medical Monitor.
Footnote to inclusion criterion #4 in Synopsis and Section 5.1.1, footnote in Schedule of Events, and text of Section 6.2 (Instructions for Use and Application)	Bald scalp for the purposes of this study is a scalp where the subject has lost the majority of their hair (well over 50%) within the intended 25 cm² treatment area where the scalp is: a) readily visible and 2) the number of the AKs in the treatment area can be easily seen and counted by the evaluator. It is also important that both the site and subject can repeatedly identify the treatment area to assure accurate repeat therapy by the subject and evaluation by the investigator.