Clinical Study Protocol

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP COMPARISON STUDY TO DETERMINE THE THERAPEUTIC EQUIVALENCE OF GENERIC IMIQUIMOD CREAM, 2.5% AND ZYCLARA® (IMIQUIMOD) CREAM, 2.5% IN SUBJECTS WITH ACTINIC KERATOSES

Study Number 094-3153-301

NCT02120898

Protocol Approval Date: 30 July 2013

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP COMPARISON STUDY TO DETERMINE THE THERAPEUTIC EQUIVALENCE OF GENERIC IMIQUIMOD CREAM, 2.5% AND ZYCLARA® (IMIQUIMOD) CREAM, 2.5% IN SUBJECTS WITH ACTINIC KERATOSES

PROTOCOL NUMBER:	094-3153-301
[redacted] **PROJECT NUMBER:**	094-3153-301
ORIGINAL PROTOCOL:	July 30, 2013
FILE NAME:	094-3153-301_pro_30July2013_v1.0
SPONSOR:	Actavis, LLC
SPONSOR REPRESENTATIVE:	[redacted]
MEDICAL MONITOR:	[redacted] (office) (cell) (fax) (email)
CLINICAL PROJECT MANAGER:	[redacted] (office) (fax) (email)

24 Hour Emergency Telephone Number

[redacted]

PROTOCOL APPROVAL

The following individuals approve version 1.0 of the 094-3153-301 protocol dated July 30, 2013. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Actavis Representative(s):

[redacted]

Signature: _____ Date: _____

[redacted]

Signature: _____ Date: _____

[redacted]

Signature: _____ Date: _____

[redacted]

Signature: _____ Date: _____

[redacted]

Signature: _____ Date: _____

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Actavis, LLC.

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

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

I understand the study may be terminated or enrollment suspended at any time by Actavis, 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 Actavis, 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: 094-3153-301 Site number: _____

Version: 1.0

DATE OF FINAL VERSION: July 30, 2013

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of Generic Imiquimod Cream, 2.5% and Zyclara® (imiquimod) Cream, 2.5% in Subjects with Actinic Keratoses
Study Type	Bioequivalence with Clinical Endpoint
Test Articles	1. Imiquimod cream, 2.5% (Actavis) (generic imiquimod) 2. Zyclara® (imiquimod) Cream, 2.5% (Medicis) (Reference Listed Drug) 3. Vehicle cream (Actavis)
Study Objective	To evaluate the safety and therapeutic equivalence of generic imiquimod cream, 2.5% to Zyclara (imiquimod) Cream, 2.5% and to establish the superiority of the efficacy of these two products over the vehicle cream in the treatment of actinic keratoses (AK).
Study Design	Multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison.
Treatment Groups	After enrollment in the study, each subject will be randomized [redacted] to treatment with Zyclara, generic imiquimod, or vehicle control.
Duration of Treatment	Two 2-week treatment cycles separated by a 2-week no-treatment period and an 8-week follow-up period.
Duration of Study	Approximately 14 weeks (not including up to 30-day screening period).
Study Population	Male or female subjects, age 18 years or older with actinic keratoses on the face or balding scalp.
Total Number of Subjects	Approximately 435 subjects will be enrolled.
Number of Sites	Approximately 25 sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is a male or female, 18 years of age or older. 2. Subject has provided written informed consent. 3. Subject is willing and able to apply the test article as directed, comply with study instructions and commit to all follow-up visits for the duration of the study. 4. Subject has a clinical diagnosis of actinic keratoses (AK) with at least five (5) and no more than twenty (20) clinically typical, visible or palpable AK lesions, each at least 4 mm in diameter, in an area greater than 25 cm^2 on the face (excluding ears) or balding scalp, but not both. 5. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of AK lesions or

	which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation. 6. Females must be post-menopausal[1], surgically sterile[2] or use an effective method of birth control[3,4] with a negative urine pregnancy test (UPT)[5] at the Baseline Visit.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject has hyperkeratotic, hypertrophic or atypical AKs (e.g., AK > 1 cm^2 in size) in the treatment area. 3. Subject is currently enrolled in an investigational drug or device study. 4. Subject plans to be exposed to artificial tanning devices or excessive sunlight during the trial. 5. Subject is immunosuppressed (e.g., HIV, systemic malignancy, graft vs. host disease, etc.). 6. Subject has experienced an unsuccessful outcome from previous imiquimod therapy (an unsuccessful outcome is defined as after a reasonable therapeutic trial with no compliance issues and the topical drug did not work). 7. Subject has used an investigational drug or investigational device within 30 days prior to the Baseline Visit. 8. Subject has had dermatologic procedures or surgeries such as: laser resurfacing, PUVA (Psoralen + ultraviolet A) therapy, UVB therapy, chemical peels or dermabrasion on the face or balding scalp within six (6) months prior to the Baseline Visit. 9. Subject has had cryodestruction or chemodestruction, curettage, photodynamic therapy, surgical excision or other treatments for actinic keratosis on the designated treatment area (face or scalp) within one month prior to the Baseline Visit. 10. Subject has used oral corticosteroid therapy, interferon, cytotoxic drugs, immunomodulators, immunosuppressive therapies or retinoids within one month prior to the Baseline Visit. 11. Subject has used topical medications; corticosteroids, alpha hydroxy

[1] Defined as amenorrhea greater than 12 consecutive months.
[2] Hysterectomy, bilateral tubal ligation (at least 6 months prior to initiation of baseline treatment) or bilateral oophorectomy.
[3] Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal], intrauterine device (IUD), condom and spermicidal or diaphragm and spermicidal). IUD must be in place for at least one week prior to the Baseline Visit. 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., vasectomy performed at least 6 months prior to the Baseline Visit). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.
[4] Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment for at least 12 weeks prior to the Baseline Visit and must not change their dosing regimen during the study.
[5] Urine pregnancy tests must have a minimum sensitivity of 25mIU ß-hCG/mL.

	acids (e.g., glycolic acid, lactic acid etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >5%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate or prescription retinoids (e.g., tazarotene, adapalene, tretinoin) to the face or balding scalp within one month prior to the Baseline Visit. 12. Subject has used topical creams, lotions or gels of any kind to the selected treatment area within one day prior to the Baseline Visit. 13. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the selected treatment area (face or scalp). 14. Subject has a history of sensitivity to any of the ingredients in the test articles (see **Section 6.1**). 15. Subject has any skin pathology or condition (e.g., facial/scalp psoriasis, atopic dermatitis, acne, rosacea, etc.) that, in the investigator's opinion, could interfere with the evaluation of the test article, worsen due to the treatment or requires the use of interfering topical, systemic or surgical therapy. 16. Subject has any condition which, in the investigator's opinion, would make it unsafe or precludes the subject's ability to fully participate in this research study. 17. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Study Procedures	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, the washout from prohibited medications or treatments will be determined and implemented. These procedures may be combined with the Baseline Visit. 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, review of concomitant medications, brief physical exam including dermatologic exam and vital sign assessment, urine pregnancy test (if applicable), identification of treatment area (the entire face excluding the ears, or the entire balding scalp, but not both), % body surface area (BSA) of the treatment area, AK count, and local skin reaction (LSR) assessment. Qualified subjects will be randomly assigned to one of three treatment groups. Test article application will be demonstrated using the non-medicated samples provided to the site. Test article will be dispensed, along with application instructions and a subject diary to document any applied, held or missed doses. The subjects will be instructed to apply up to two (2) pump actuations of test article once daily in the evening for 14 days to the entire treatment area. Subjects will be scheduled for Visit 3. **NOTE: The subject will apply the assigned test article once daily for 14 consecutive days followed by a two week no treatment period followed by a second once daily regimen for 14 consecutive days.**

	2. Visit 2 - Phone Call (Day 8 ± 2): The site staff will contact the subject on Day 8 to confirm the next visit appointment, review application instructions and query about adverse events (AEs). Remind the subject to continue to apply up to two (2) pump actuations of test article once daily in the evening and to stop after the Day 14 application, even if Visit 3 is scheduled on Day 16 through 18. 3. Visit 3 (Day 15 + 3): Subjects will return for LSR and AE assessment. Compliance with test article application and concomitant medications will be reviewed. The subject diary card will be reviewed and collected. Test article will be returned and collected. Subjects will be scheduled for the next visit. **NOTE: Day 15 (+ 3 days) through Day 29 (± 2 days): Subject will not apply test article.** 4. Visit 4 (Day 29 ± 2): Subjects will return for LSR and AE assessment. Concomitant medications will be reviewed. The subject diary card for treatment cycle 2 will be dispensed. Test article for treatment cycle 2 will be dispensed. Any uncollected test article from treatment cycle 1 will be collected. Subjects will be scheduled for the next visit. NOTE: Visit 6 should be scheduled 14 to 17 days after Visit 4. 5. Visit 5 - Phone Call (Day 36 ± 2): The site staff will contact the subject on Day 36 to confirm the next visit appointment, review application instructions and query about AEs. Remind the subject to continue to apply up to two (2) pump actuations of test article once daily in the evening and to stop after the subject has treated for 14 consecutive days after Visit 4, even if Visit 6 is scheduled after 14 consecutive application days have elapsed. 6. Visit 6 (14-17 Days after Visit 4): Subjects will return for an AK lesion count, LSR and AE assessment. Compliance with test article application and concomitant medications will be reviewed. The subject diary card and test article will be reviewed and collected. Subjects will be scheduled for the next visit. 7. Visit 7 (Day 99 ± 4): Subjects will return for the final AK lesion count, LSR and AE assessment. Concomitant medications will be reviewed. A UPT, if applicable, will be obtained. Any uncollected test article or diaries will be collected.
Study Measurements	Efficacy: The primary efficacy parameter is the number of all visible or palpable AK(s) (baseline and new lesions) in the treatment area as enumerated at Visits 1, 6 and 7 by the investigator. Safety: 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 AEs. In addition, LSRs including erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration, pain and pruritus) will be assessed separately at each visit by the investigator as detailed in **Section 10.2**.
Study Endpoints	***Efficacy Endpoint(s)*** Complete clearance rate (treatment success), defined as the proportion of subjects in each treatment group at Visit 7 (Week 14/ End of Study Visit) in the per-protocol (PP) population with a count of zero AK lesions in the treatment area. All AKs (baseline and new lesions) independent of size within the treatment area will be included in the efficacy lesion count for each visit. ***Safety Endpoint(s)*** <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 test article applications and no other evidence of material dosing noncompliance. <u>Adverse Events:</u> Assessment of the severity and frequency of adverse events including LSRs in the three treatment groups.
Sample Size Calculations	[redacted] Bioequivalence was concluded if the 90% continuity-corrected confidence interval on the difference in active treatment complete clearance rates was between -0.20 and +0.20 in the per protocol (PP) population, and each active treatment was found to be statistically superior to the vehicle by independent continuity-corrected Z-tests in the intent-to-treat (ITT) population. [redacted] A total of 435 ITT subjects [redacted] for demonstrating superiority of each active treatment over the vehicle treatment. [redacted]
Statistical Methods	All statistical processing will be performed using SAS® unless otherwise stated. [redacted]

	[redacted] Efficacy summaries and analyses will be carried out in the ITT and PP populations. All summaries of safety will be carried out in the Safety population. Last-observation-carried-forward (LOCF) will be used to impute missing values for efficacy variables in the ITT population. Demographic and baseline characteristics will be summarized by treatment group for the ITT and PP populations. The size of the treatment area (in centimeters) at baseline will be determined from an estimate of the % BSA treated. BSA will be determined from the subject's height and weight using the Mosteller formula. Frequency counts and percentages will be reported for categorical data. Sample size, mean, standard deviation, and minimum and maximum will be reported for the continuous variables. **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. Two-sided, continuity-corrected Z-tests will be used to evaluate the superiority of each active treatment's clearance proportion over that of the Vehicle 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, and each of these proportions is greater than, and statistically different ($p<0.05$) from, the Vehicle proportion, then the Test and Reference products will be considered to be therapeutically equivalent. The therapeutic comparability evaluations in the PP population will be considered primary while those in the ITT population will be considered supportive. The superiority comparisons in the ITT population will be considered primary while those in the PP population will be considered supportive. **Safety Analyses:** All subjects in the safety population will be included in summaries of safety data. <u>Dosing Compliance</u> Descriptive statistics will be used to summarize test article compliance for the ITT 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 test article applications and no other evidence of material dosing noncompliance.

	Adverse Events All adverse events will be coded using the 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 study drug, 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. Local Skin Reactions LSRs will be summarized by treatment group by the most intense score for each LSR and by the sum score at each visit and over the course of the study. The frequency of the individual LSRs will be tabulated by severity and treatment group at each visit.

SCHEDULE OF EVENTS

Visit	Visit 1	Visit 2 Telephone	Visit 3	Visit 4	Visit 5 Telephone	Visit 6	Visit 7
Week	Screening/ Baseline	Week 1	Week 2	Week 4	Week 5	Week 6	Week 14/ EOS
Day	Day 1	Day 8 (± 2 days)	Day 15 (+ 3 days)	Day 29 (± 2 days)	Day 36 (± 2 days)	14-17 Days After Visit 4	Day 99 (± 4 days)
Treatment Period	**Treatment Cycle = Test Article Application Once Daily for 14 Consecutive Days Treatment Cycle 1-Visit 1 to Visit 3 Treatment Cycle 2-Visit 4 to Visit 6**						
Informed Consent[1]	X						
Medical History, Demographics	X						
Concomitant Medications	X		X	X		X	X
Brief Physical Exam including Dermatologic Exam and Vital Sign Assessment	X						
Inclusion/Exclusion Criteria	X						
Treatment Area (Face or Balding Scalp) ID - Location & Size	X						
AK Lesion Count	X					X	X
Local Skin Reaction Assessment	X		X	X		X	X
Confirm Next Visit Appointment, Review Dosing Instructions and Query About AEs.		X			X		
Pregnancy Testing[2]for WOCBP[3]	X						X
Issue Subject Diary	X			X			
Collect & Review Subject Diary for Compliance			X			X	
Adverse Events	X	X	X	X	X	X	X
Dispense/Return/Weigh Test Article (Perform Drug Accountability)	X		X	X		X	

[1] Informed consent may be obtained within 30 days prior to the Baseline Visit.
[2] Urine pregnancy tests must have a minimum sensitivity of 25 mIU ß-hCG/mL of urine and must be performed within 24 hours prior to the start of test article at baseline.
[3] See **Section 14.4** for definition of woman of childbearing potential (WOCBP).

ABBREVIATIONS

5-FU	5-Fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
AHA	Alpha Hydroxy Acid
AK	Actinic Keratosis or Keratoses
BSA	Body Surface Area
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
CRF	Case Report Form
EOS	End of Study
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
NFκB	Nuclear Factor κB
OTC	Over-the-Counter
PDT	Photodynamic Therapy
PP	Per-Protocol
PT	Preferred Term
PUVA	Psoralen + Ultraviolet A
QA	Quality Assurance
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SAS	Statistical Analysis Software
SOC	System Organ Class
[redacted]	[redacted]
TLR	Toll-like Receptor
TNF	Tumor Necrosis Factor
UPT	Urine Pregnancy Test
UVB	Ultraviolet B
WHO	World Health Organization

WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

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 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 (PDT). Topical medications include: 5-fluorouracil (5-FU), imiquimod cream 5%, 3.75% and 2.5%, ingenol mebutate and diclofenac.

Imiquimod is an immune response modifier that acts via stimulation of toll-like receptor 7 (TLR-7) on plasmacytoid and myeloid dendritic cells. TLR-7 is part of a family of 11 TLRs that are important in the innate immune system's recognition of various microbial antigens. Stimulation of TLR-7 most notably results in dissociation of nuclear factor κB (NFκB) away from its inhibitor, thereby freeing it to diffuse into the nucleus and transcribe genes for various cytokines including tumor necrosis factor α (TNFα), interferon γ (IFNγ), interferon α (IFNα), and interleukin-12 (IL–12), among others. These cytokines upregulate cell mediated Th1 responses that have antitumor and antiviral effects and downregulate Th2 (humoral) responses. Imiquimod may also directly affect cell death through various pathways including via IFNγ modulation of the p53 apoptotic pathway.

Aldara® (imiquimod) Cream, 5% was the first imiquimod product approved by the FDA and is now available in a generic formulation. Imiquimod cream 5% is approved for the topical treatment of AK(s), superficial basal cell carcinoma and external genital and perianal warts. The FDA approved regimen for the treatment of AK is application of 250 mg of cream twice a week for 16 weeks to a 25-cm^2 area. In 2010, a lower strength imiquimod cream, Zyclara (imiquimod) Cream, 3.75% was approved by the FDA. In 2011, Zyclara (imiquimod) Cream, 2.5% was approved by the FDA. When used for the treatment of AK, both of these Zyclara formulations are applied for a shorter duration and in an expanded treatment area (e.g., face or scalp) in comparison to Aldara®.

A generic imiquimod cream, 2.5% has been developed by Actavis, LLC for the topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp.

2. RATIONALE

Actavis, LLC has developed a generic imiquimod cream, 2.5% formulation and the current clinical study is designed to evaluate the therapeutic equivalence of this

formulation with the currently marketed Zyclara (imiquimod) cream, 2.5% formulation (Medicis).

3. OBJECTIVE

The objective is to evaluate the safety and therapeutic equivalence of generic imiquimod cream, 2.5% to Zyclara (imiquimod) Cream, 2.5% and to establish the superiority of the efficacy of these two products over the vehicle cream in the treatment of actinic keratoses (AK).

4. STUDY DESIGN

This is a multicenter, double-blind, vehicle-controlled, parallel group comparison study of a generic imiquimod cream, 2.5% and Zyclara (imiquimod) cream, 2.5% (Medicis) in subjects with actinic keratoses on the full face or balding scalp. Approximately 435 subjects with at least five (5) but no more than 20 clinically typical, visible or palpable AK lesions at least 4 mm in diameter involving the face (excluding the ears) or the balding scalp who fulfill the inclusion/exclusion criteria will be enrolled at approximately 25 U.S. study sites. Subjects will be randomized to one of three treatment groups on a [redacted] basis as follows:

- Imiquimod cream, 2.5% (Actavis)
- Zyclara (imiquimod) cream, 2.5% (Medicis)
- Vehicle cream (Actavis)

All subjects will apply the assigned test article to the designated treatment area (full face or balding scalp) identified by the investigator at Visit 1. The assigned test article will be applied once daily for two, 2-week treatment cycles separated by a 2-week no treatment interval. Subjects will also return for an End of Study (EOS) Visit, 8 weeks post-treatment. At the end of the study, safety and efficacy outcome measures will be compared to a) determine if dosing with generic imiquimod cream, 2.5% is clinically equivalent to the currently marketed Zyclara (imiquimod) cream, 2.5% and b) both imiquimod 2.5% creams are superior in comparison to the vehicle cream.

4.1 Estimated Duration of Study

The duration of the study as a whole will vary based upon the relative rates of recruitment and completion of subjects at all sites within the study. It is anticipated that each subject will participate for approximately 14 weeks or longer if the subject requires a medication washout period.

5. STUDY POPULATION

Approximately 435 adult male and female subjects with 5 (five) to 20 AKs that are at least 4 mm in diameter on the full face or balding scalp who meet the entry criteria will be enrolled into the treatment phase of the study.

5.1 Subject Eligibility

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

5.1.1 Inclusion Criteria

To enter the study, a subject must meet the following criteria:

1. Subject is a male or female, 18 years of age or older.
2. Subject has provided written informed consent.
3. Subject is willing and able to apply the test article as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
4. Subject has a clinical diagnosis of actinic keratoses (AK) with at least five (5) and no more than twenty (20) clinically typical, visible or palpable AK lesions, each at least 4 mm in diameter, in an area greater than 25 cm^2 on the face (excluding ears) or balding scalp, but not both.
5. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of AK lesions or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.
6. Females must be post-menopausal[1], surgically sterile[2] or use an effective method of birth control[3,4] with a negative urine pregnancy test (UPT)[5] at the Baseline Visit.

5.1.2 Exclusion Criteria

A subject is ineligible to enter the study if he/she meets one or more of the following criteria:

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has hyperkeratotic, hypertrophic or atypical AKs (e.g., AK > 1 cm^2 in size) in the treatment area.
3. Subject is currently enrolled in an investigational drug or device study.

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[1] Defined as amenorrhea greater than 12 consecutive months.

[2] Hysterectomy, bilateral tubal ligation (at least 6 months prior to the Baseline Visit) or bilateral oophorectomy.

[3] Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal], intrauterine device (IUD), condom and spermicidal or diaphragm and spermicidal). IUD must be in place for at least one week prior to the Baseline Visit. 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., vasectomy performed at least 6 months prior to the Baseline Visit). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.

[4] Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment for at least 12 weeks prior to the Baseline Visit and must not change their dosing regimen during the study.

[5] Urine pregnancy tests must have a minimum sensitivity of 25mIU ß-hCG/mL.

4. Subject plans to be exposed to artificial tanning devices or excessive sunlight during the trial.
5. Subject is immunosuppressed (e.g., HIV, systemic malignancy, graft vs. host disease, etc.).
6. Subject has experienced an unsuccessful outcome from previous imiquimod therapy (an unsuccessful outcome is defined as after a reasonable therapeutic trial with no compliance issues and the topical drug did not work).
7. Subject has used an investigational drug or investigational device within 30 days prior to the Baseline Visit.
8. Subject has had dermatologic procedures or surgeries such as: laser resurfacing, PUVA (Psoralen + Ultraviolet A) therapy, UVB therapy, chemical peels or dermabrasion on the face or balding scalp within six (6) months prior to the Baseline Visit.
9. Subject has had cryodestruction or chemodestruction, curettage, photodynamic therapy, surgical excision or other treatments for actinic keratosis on the designated treatment area (face or scalp) within one month prior to the Baseline Visit.
10. Subject has used oral corticosteroid therapy, interferons, cytotoxic drugs, immunomodulators, immunosuppressive therapies or retinoids within one month prior to the Baseline Visit.
11. Subject has used topical medications; corticosteroids, alpha hydroxy acids (e.g., glycolic acid, lactic acid etc. >5%), beta hydroxy acid (salicylic acid >2%), urea >5%, 5-fluorouracil, diclofenac, imiquimod, ingenol mebutate or prescription retinoids (e.g., tazarotene, adapalene, tretinoin) to the face or balding scalp within one month prior to the Baseline Visit.
12. Subject has used topical creams, lotions or gels of any kind to the selected treatment area within one day prior to the Baseline Visit.
13. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the selected treatment area (face or scalp).
14. Subject has a history of sensitivity to any of the ingredients in the test articles (see **Section 6.1**).
15. Subject has any skin pathology or condition (e.g., facial/scalp psoriasis, atopic dermatitis, acne, rosacea, etc.) that, in the investigator's opinion, could interfere with the evaluation of the test article, worsen due to the treatment or requires the use of interfering topical, systemic or surgical therapy.
16. Subject has any condition which, in the investigator's opinion, would make it unsafe or precludes the subject's ability to fully participate in this research study.
17. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

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

6. TEST ARTICLES AND REGIMEN

6.1 Description

Reference product name:	Zyclara (imiquimod) cream, 2.5%
Active ingredient:	Imiquimod
Other ingredients:	isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.
Test article name:	Generic imiquimod cream, 2.5%
Active ingredient:	Imiquimod
Other ingredients:	[redacted]
Placebo name:	Vehicle cream
Active ingredient:	None
Other ingredients:	[redacted]

6.2 Instructions for Use and Application

Subjects will be instructed to apply test article once daily approximately 1 to 2 hours before bedtime to the skin of the treatment area (either full face (excluding the ears) or balding scalp) for two, 2-week treatment cycles separated by a 2-week no-treatment period. Subjects will apply test article for 14 consecutive days for each treatment cycle, regardless of the visit window. However, if a subject did not apply for 14 consecutive days due to a dose held or missed, and 14 consecutive days has elapsed from baseline, then no additional test article will be applied to make up for missed or held doses. Test article should be applied as a thin film to the entire treatment area and rubbed until the cream is no longer visible. Up to two (2) full actuations of the pump may be dispensed and applied to the treatment area at each application. Subjects will be cautioned to avoid applying the cream to the lips, nostrils and periocular areas. The test article should be left on the skin for approximately eight (8) hours, after which time the test article should be removed by washing the area with mild soap and water. 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 pump and application technique using the pumps containing the vehicle cream provided for subject training. See **Appendix 1** for the complete Subject Instructions.

6.3 Investigator Prescribed Rest Periods

Rest periods of several days may be prescribed by the investigator or designee to manage intense local skin reactions (LSRs). Treatment should resume as soon as possible after the skin reaction has subsided as determined by the investigator or designee. Neither 2-week treatment cycle should be extended beyond the 14 consecutive days due to rest periods or missed doses.

6.4 Warnings, Precautions and Contraindications

Intense local skin reactions including skin weeping or erosion can occur after a few applications of imiquimod cream, 2.5% and may require an interruption of dosing (see **Section 6.3**). Imiquimod cream, 2.5% has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Administration of imiquimod cream, 2.5% is not recommended until the skin is healed from any previous drug or surgical treatment.

Concomitant use of any other imiquimod creams is not allowed in this study. The use of any other imiquimod cream in the same treatment area may increase the risk for and severity of local skin reactions.

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, and chills. An interruption of dosing and an assessment of the patient should be considered. See **Section 6.3** (Investigator Prescribed Rest Periods).

Lymphadenopathy occurred in 2% of subjects treated with imiquimod cream, 2.5%. This resolved in all subjects by four (4) weeks after completion of treatment.

The safety of concomitant use of imiquimod cream, 2.5% and any other imiquimod creams has not been established and should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of systemic reactions.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of imiquimod cream, 2.5% because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g., a hat) when using imiquimod cream, 2.5%. Patients with sunburn should be advised not to use imiquimod cream, 2.5% until fully recovered. Patients who may have considerable sun exposure (e.g., due to their

occupation, and those patients with inherent sensitivity to sunlight) should exercise caution when using imiquimod cream, 2.5%.

In an animal photo-carcinogenicity study, imiquimod cream shortened the time to skin tumor formation. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

Other Considerations

The 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.

The test articles should not be applied to open wounds, infections or exfoliative dermatitis.

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. Women of childbearing potential 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 [redacted] [Imiquimod cream, 2.5% (Actavis), Zyclara (imiquimod) cream, 2.5% (Medicis), Vehicle cream (Actavis), 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 (using the generic name, if known) with the dose and corresponding indication. The medications to be recorded include prescription and over-the-counter (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.

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. Any changes in concomitant medications during the study must be recorded on the case report forms. The reason for any change in concomitant therapies should be evaluated and, if appropriate, reported as, or in conjunction with, an adverse event.

8.1 Prohibited Medications or Therapies

Prohibited medications or therapies during the study include:

- Topical corticosteroids on the head. [NOTE: If treatment with topical steroids in the head area is deemed to be a material medical necessity for the subject by the investigator, this will be reviewed on a case by case basis with the Medical Monitor, requiring his approval.]
- Subjects should not apply moisturizers, sunscreen, make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area.
- Subjects should not use any type of bandage or occlusive dressing on the treatment area or apply the assigned cream to any skin diseases (e.g., open skin wounds, infections or inflammatory skin diseases).
- Systemic use of immunomodulators or immunosuppressive therapies, interferon, corticosteroid therapy, chemotherapeutic agents, photodynamic therapy, cytotoxic drugs or retinoids.
- Topical application of 5-FU, imiquimod, ingenol mebutate, diclofenac sodium, bichloroacetic acid, trichloroacetic acid, photodynamic therapy, prescription topical retinoids (e.g. tazarotene, adapalene, tretinoin), alpha-hydroxyacids [e.g. glycolic acid, lactic acid, etc. greater than 5%], beta-hydroxyacid [salicylic acid greater than 0.5%], or [urea greater than 5%] or other treatments for AK or photodamage at any body site. See **Section 8.2** for the limited treatment of AKs deemed to be a medical necessity at a body site exclusive of the head.
- Any AK therapy on the head including but not limited to topicals (e.g. 5-FU, imiquimod, diclofenac sodium, etc.), laser ablation or resurfacing, electrocautery, photodynamic therapy, chemical peels, dermabrasion, cryotherapy, chemodestruction, surgical excision, curettage.
- Sunlamps, tanning beds or booths, non-prescription UV light sources, and excessive sunlight.

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 actinic keratosis may be used unless specifically excluded or prohibited by this protocol (see Prohibited Medications 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 electrodessication. Use of any other treatment methods are prohibited (see **Section 8.1**) as are the treatment of any AKs on the HEAD using any method.
- Intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders or other conditions.
- 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 [AHA]) 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 8 hours of test article application.

9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

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

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 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 therapies.

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

- Perform a limited physical exam including a brief dermatologic exam and vital sign assessment. Consistent with Exclusion Criterion #13, 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 treatment area; either the full face or balding scalp.
- Estimate %BSA of the treatment area.
- Perform the AK lesion count (≥ 4 mm in diameter as well as any smaller lesions) and estimate the surface area of the entire treatment area (full face or balding scalp) to be treated as described in **Section 10.1**. (Note: A minimum of 5 to a maximum of 20 AKs ≥ 4 mm in diameter in the 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 two test article pumps from the kit. NOTE: The pumps will be weighed prior to being dispensed.
- Review and dispense a Subject Instruction Sheet to the subject (see **Appendix 1**). Instruct the subjects to apply test article for 14 consecutive days and demonstrate proper use of the pump and test article application using vehicle cream pumps provided for subject training.
- Issue the subject diary.
- Confirm the next visit.

9.2 Visit 2 - Phone Call (Week 1/ Day 8 ± 2)

The investigator or designee will contact the subject by phone and document the following:

- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Review the application instructions (see **Appendix 1**).

- Instruct the subject to continue to apply up to two (2) pump actuations of test article once daily in the evening and to stop after the Day 14 application, even if Visit 3 is scheduled on Day 16 through 18.
- Confirm the next visit.

If necessary, an unscheduled visit may occur at the discretion of the investigator, see **Section 9.8**.

9.3 Visit 3 (Week 2/ Day 15 + 3)

At this visit, the investigator or designee will:

- Perform the LSR assessment as described in **Section 10.2**.
- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Review subject study compliance requirements, emphasizing to the subject they will not apply test article and other prohibited medications for the next two-week period until Visit 4.
- Collect and review the subject diary. Pay particular attention to proper test article use and application per protocol, providing the subject feedback as required.
- Collect used and unused test article pumps and document the number returned on the Accountability Log as described in **Appendix 2**. **Do not re-dispense test article.** [redacted]
- Record any changes in the subject's concomitant therapies.
- Confirm the next visit.

9.4 Visit 4 (Week 4/ Day 29 ± 2)

At this visit, the investigator or designee will:

- Perform the LSR assessment as described in **Section 10.2**.
- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Review the application instructions (see **Appendix 1**).
- Issue a new subject diary.
- Dispense two test article pumps from the kit number assigned to the subject and complete the Test Article Accountability Log as described in **Appendix 2**. [redacted]
- [redacted]
- Record any changes in the subject's concomitant therapies.

- Confirm the next visit. NOTE: Visit 6 should be scheduled 14 to 17 days after Visit 4.

9.5 Visit 5 - Phone Call (Week 5/ Day 36 ± 2)

The investigator or designee will contact the subject by phone and document the following:

- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Review the application instructions (see **Appendix 1**).
- [redacted]
- Confirm the next visit.

If necessary, an unscheduled visit may occur at the discretion of the investigator, see **Section 9.8**.

9.6 Visit 6 (Week 6/14-17 Days after Visit 4)

At this visit, the investigator or designee will:

- Perform the AK lesion count as described in **Section 10.1**. NOTE: New AK lesions need to be identified, counted and recorded. A new AK lesion is one that was not present at the Baseline Visit.
- Perform the LSR assessment as described in **Section 10.2**.
- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Collect and review the subject diary.
- Review subject study compliance requirements, emphasizing to the subject they will remain off test article for the duration of the study.
- Collect used and unused test article pumps and document on the Test Article Accountability Log as described in **Appendix 2**. **Do not re-dispense test article.** [redacted]
- Record any changes in the subject's concomitant therapies.
- Confirm the next visit.

9.7 Visit 7 (Week 14/ Day 99 ± 4)

At this visit, the investigator or designee will:

- Perform the AK lesion count as described in **Section 10.1**. NOTE: New AK lesions need to be identified, counted and recorded. A new AK lesion is one that was not present at the Baseline Visit.
- Perform the LSR assessment as described in **Section 10.2**.
- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Collect any used or unused test article pumps and diaries not returned at the previous visit and document on the Test Article Accountability Log as described in **Appendix 2**.
- Record any changes in the subject's concomitant therapies.
- Perform a UPT, if applicable.
- Complete the End of Study Form.

9.8 Unscheduled Visits

The investigator may see the subject at an unscheduled visit to manage any AEs or LSRs. During this visit, the investigator or designee will:

- Query the subject about any changes in health status or any adverse events since the last visit. Document in the AE section of the CRF, as appropriate.
- Perform the LSR assessment as described in **Section 10.2**.
- Record any changes in the subject's concomitant therapies.
- Review subject diary and the requirements for test article application, if applicable.
- Confirm the next visit.

10. CLINICAL EVALUATIONS

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

10.1 AK Lesion Counts

AK lesion counts will be performed at Visit 1, 6 and 7. [redacted] he number and location of AK lesions to be treated that are ≥ 4 mm in diameter and the diameter of each AK lesion in the treatment area will also be documented at the Baseline Visit. The suggested procedure for AK counting and definition of full face and balding scalp will be detailed in a separate document. At the Baseline Visit, the treatment area must include at least 5 and no more than 20 clinically typical, visible or palpable AKs, each at least 4 mm in diameter, in an area greater than 25 cm^2 on either the face (excluding ears) or the balding scalp, but not both. At Visits 6

and 7, the number of total AK lesions in the 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.

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.

At the Baseline Visit, estimate the surface area of the entire treatment area (full face or balding scalp) to be treated with the test article as a percentage of the total body surface area (BSA). For this assessment, the subject's palmar surface of the hand (palm and fingers/thumb held together) is 1% BSA.

10.2 Local Skin Reactions (LSR) Assessment

At Visit 1, 3, 4, 6, 7 and Unscheduled Visits, if applicable (prior to test article application), the investigator or designee will assess the treatment area and rate on a scale of 0 = none, 1= mild, 2 =moderate and 3 = severe (through observation and subject query) the following LSRs:

- Erythema
- Edema
- Erosion/ulceration
- Scabbing/crusting
- Weeping/exudate
- Flaking/scaling/dryness
- Pain (within the last 24 hours)
- Pruritus (within the last 24 hours)

These LSRs will be collected independently of adverse events. Any LSR that occurs **within the treatment area (full face [excluding the ears] or balding scalp) and extends to adjacent surrounding skin (defined to be up to a 5 cm border around the 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 adverse event. LSRs may be of such intensity that the subject may require rest periods (see **Section 6.3** for details on rest periods).

11. PHOTOGRAPHY

Photography documentation is not required in this study. The investigator may elect to photograph the subject's treatment area to document the effects of treatment, adverse events or other findings during the trial. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment.

12. LABORATORY TESTS

12.1 Urine Pregnancy Tests

Urine pregnancy tests must be performed on all WOCBP at baseline prior to randomization and at the EOS visit. All WOCBP must have a negative pregnancy test at baseline to be eligible for study entry. The urine pregnancy testing will be performed at the study site if the site is registered and conforms to CLIA regulations for such testing or at an appropriately registered reference laboratory. The investigator will report the urine pregnancy test results on the case report forms, in the subject's medical records and in independent records maintained at the study site. The urine pregnancy test used must have a minimum sensitivity of 25mIU of β-HCG/mL of urine.

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 two, 2-week cycles of treatment and all of the Visit 7 follow-up evaluations at Week 14 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:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject

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 (Week 14) to perform all required visit activities and complete the EOS Case Report Forms. 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 adverse event, when possible, the subject should be followed until resolution of the adverse event. If a subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed (see **Section 14.4**).

13.3 Study Termination

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

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

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

14. ADVERSE EVENT REPORTING

14.1 Definitions

The following definitions will be utilized:

Adverse Event (AE) - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a test article, whether or not considered related to the test article.

Adverse Drug Reaction (ADR) - Any adverse event 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.

Suspected Adverse Reaction (SAR) – Any AE for which there is a reasonable possibility that the drug caused the event. A "reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the adverse reaction.

Serious Adverse Event (SAE) - Any untoward medical occurrence that at any dose in the view of either the investigator or the Sponsor:

- Results in death
- Is life-threatening (i.e., its occurrence places the patient or subject at immediate risk of death),

- Requires inpatient hospitalization or prolongation of existing hospitalization with the following exceptions:
  - Hospitalization for preplanned treatment for an existing condition
  - Hospitalization for social reasons (in countries which permit such hospitalization)
  - Hospitalization required for protocol-required-testing or efficacy measurement.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect
- Important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization, or the development of drug dependency or drug abuse.

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

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

14.2 Reporting of Adverse Events

Throughout the clinical trial the clinical trial staff will question the subject in a non-directive way as to the occurrence of adverse events. All adverse events which were not present at screening must be recorded in the subjects' case report forms, whether observed by the investigator, the investigator's staff, or spontaneously reported by the subjects. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Follow-up of adverse events will continue through the last day of the study, until the investigator determines outcome, stabilization, and/or resolution of the event, or not-relatedness to study medication, or up to 30 days after the last dose of study drug. For SAEs this can occur before or after day

30. In the event of death, if an autopsy is performed, a copy of the report should be sent to [redacted]

The most common AEs reported with the use of imiquimod cream, 2.5% include LSRs listed by decreasing frequency: erythema, scabbing/crusting, flaking/scaling/dryness, edema, erosion/ulceration and weeping/exudate. Other application site reactions that have been reported include pruritus, irritation, pain, bleeding and swelling. LSRs may range in severity from mild to severe and may extend beyond the treatment area to the surrounding skin. LSRs occurring within the treatment area will be assessed at each visit and documented as detailed in **Section 10.2**. Any LSR that requires medical intervention (prescription medication) or extends beyond the 5 cm surrounding skin should be documented as an adverse event. Other reported AEs occurring in ≥ 2% of imiquimod cream, 2.5% treated subjects are listed in the Package Insert for Zyclara.

14.2.1 Adverse Event and SAE Reporting Period

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

Adverse events classified as "serious" require expeditious handling and reporting to TI to comply with regulatory requirements. All SAEs whether related or unrelated to test article must be immediately reported to TI by email, telephone or confirmed facsimile transmission to the Medical Monitor or Project Manager listed on the first page of the protocol. Follow-up of AEs and SAEs is to occur as described in **Section 14.2**.

14.2.2 Assessment of AEs

The investigator must assess all AEs using the following criteria:

14.2.2.1 Severity

The term severity is described as the intensity grade or level for a specific event, i.e., mild, moderate, severe. Importantly, severity is *not* the same as seriousness, which is based on participant/event *outcome or action* criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A). The following definitions should be used to assess the severity of adverse events:

- **Mild**: an AE that is easily tolerated
- **Moderate**: an AE sufficiently discomforting to interfere with daily activity
- **Severe:** an AE that prevents normal daily activities

14.2.2.2 Causal Relationship

The relationship between an adverse event and the test article will be determined by the investigator on the basis of his/her clinical judgment using the following definitions:

Certain - A clinical event that definitely:

- follows a reasonable time relationship to drug administration.
- follows a known or expected response pattern to the suspected medicine.
- cannot be explained by an alternate factor (e.g. concurrent disease, drug, chemicals).
- follows a clinically reasonable response on withdrawal of the suspected drug.
- reappears on re-challenge with the offending drug.

Probable - A clinical event where association of the event with the study drug seems likely and that:

- follows a reasonable time relationship to drug administration.
- follows a known or expected response pattern to the suspected medicine.
- is unlikely to be attributed to an alternate factor (e.g. concurrent disease, drug, chemicals).
- follows a clinically reasonable response on withdrawal of the suspected drug.

(Re-challenge information is not required to fulfill this definition).

Possible - A clinical event where a relationship between drug and event cannot be ruled out and that:

- follows a reasonable time relationship to drug administration.
- follows a known or expected response pattern to the suspected medicine.
- can be produced by a number of other factors (e.g. concurrent disease, drug, chemicals).

Not Related- A clinical event that is clearly not related to the use of the study drug and that:

- does not follow a reasonable time relationship to drug administration.
- does not follow a known or expected response pattern to the suspected medicine.

14.2.2.3 Outcome

An AE outcome is defined as follows:

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

14.2.2.4 Treatment Required

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

14.2.3 Procedure for Reporting of Serious Adverse Events

14.2.3.1 Notification by Investigator to [redacted]

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

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

Even if all the information is not known, an initial report should be made. The investigator is obliged to provide follow-up information within 3 days of the initial report on a Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event.

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

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

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

Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome, if possible (see **Section 14.2**). Any serious

adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported to the Medical Monitor within 24 hours.

14.2.4 IRB/IEC Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local requirements. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Clinical Investigator's Regulatory binder.

As required, [redacted] will notify investigators of all AEs that are serious, unexpected, and certainly, probably or possibly related to the test article. This notification will be in the form of a Safety Update to the Investigator Brochure (i.e., "15-day letter").

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

14.2.5 FDA Notification by Sponsor

The study Sponsor shall notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than seven (7) calendar days from the Sponsor's original receipt of the information followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

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

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

14.3 Laboratory Test Abnormalities

Although there are no specific labs required in this study, any laboratory test result that meets the criteria for a Serious Adverse Event (see **Section 14.2**) must also be reported as

a SAE so [redacted] can collect additional information about that abnormality, including information regarding relationship to test article or other causes, any action taken, and resolution.

14.4 Pregnancy

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral ovariectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months and for women on hormone replacement therapy, only with a documented plasma follicle stimulating hormone level greater than 35 mIU/mL). In cases where a woman's partner is sterile (e.g., vasectomy), she is considered to be of childbearing potential. Even women who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm and spermicidal, condom and spermicidal) to prevent pregnancy, or practicing abstinence should be considered to be of childbearing potential. Post-menopausal women who have fertilized eggs implanted are considered to be of childbearing potential.

All WOCBP participating in the clinical trial must use appropriate method of birth control or continuous abstinence from heterosexual sexual contact during the course of the clinical trial until the *onset of the first menses after the last dose of trial medication*, in a manner such that risk of failure is minimized

Any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants, Depo-Provera®, double barrier methods (e.g., condom and spermicide) or IUD. Female subjects must have a negative urine pregnancy test at baseline.

Prior to clinical trial enrollment, all WOCBP must be advised of the importance of avoiding pregnancy during clinical trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form (ICF) 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). The test article must immediately be withheld if it can be done safely until the result of pregnancy testing having a minimum sensitivity of at least 25 mIU/mL for hCG is known. If pregnancy is confirmed, the test article must be permanently discontinued if this can be done safely and in an appropriate manner (e.g., dose tapering if necessary for subject safety) and the subject must be withdrawn from the clinical trial. Exceptions to clinical trial discontinuation may be considered for life-threatening conditions only after consultation with the Medical Monitor. The investigator must follow the subject to determine the outcome and follow up the neonate for 8 weeks post -delivery to know the outcome and health status of the neonate.

Protocol-required procedures for clinical trial discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g., x-ray studies). Appropriate pregnancy follow-up procedures should be considered if indicated.

14.4.1 Reporting Procedure

The investigator must report any pregnancy associated with exposure to test article within 24 hours of becoming aware of the pregnancy using the appropriate [redacted] pregnancy surveillance form(s) to the Medical Monitor or Project Manager listed on page 1 of the protocol. If pregnancy was associated with an AE, procedures for AE reporting should be followed. If pregnancy was associated with a SAE, procedures for SAE reporting must be followed. Spontaneous abortion is always considered a serious adverse event. The investigator must report information regarding the course of the pregnancy, including perinatal and neonatal outcome on the [redacted] pregnancy surveillance form(s). The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

15. BLINDING/UNBLINDING

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

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability etc. is included in **Appendix 2**.

16.2 Additional Supplies Provided by [redacted]

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

- Case report forms.
- Site Regulatory Binder or document filing system.
- Urine pregnancy test kits.

- Large plastic bags for subjects to transport study drugs, diary and instruction sheet.
- Miscellaneous supplies such as markers for AK counting.

16.3 Supplies Provided by Investigator

- Urine collection containers.

16.4 Supplies Provided by Actavis, LLC

- Pumps containing vehicle cream for demonstration to subjects of test article application.

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

[redacted] ioequivalence was concluded if the 90% continuity-corrected confidence interval on the difference in active treatment complete clearance rates was between -0.20 and +0.20 in the per protocol (PP) population, and each active treatment was found to be statistically superior to the vehicle by independent continuity-corrected Z-tests in the intent-to-treat (ITT) population. [redacted] total of 435 ITT subjects [redacted] for demonstrating superiority of each active treatment over the vehicle treatment. [redacted].

17.2 Endpoints

17.2.1 Efficacy Endpoint(s)

Complete clearance rate (treatment success), defined as the proportion of subjects in each treatment group at Visit 7 (Week 14/ End of Study) in the per-protocol (PP) population with a count of zero AK lesions in the treatment area. All AKs (baseline and new lesions) independent of size within the treatment area will be included in the efficacy lesion count for each visit.

17.2.2 Safety Endpoint(s)

17.2.2.1 Dosing Compliance

Measures of test article compliance will include the total number of applications as determined from the data recorded in the subject diaries.

17.2.2.2 Adverse Events

Safety endpoints will also include assessment of the severity and frequency of adverse events including local skin reactions (LSRs) 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 Intent-to-Treat (ITT) population will include all randomized subjects who applied at least one dose of test article and returned for at least one post-baseline evaluation visit.

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 test article applications and no other evidence of material dosing noncompliance), completed the evaluation at Week 14 within the designated visit window (± 4 days) with no protocol violations that would affect treatment evaluation. Subjects who are discontinued from the study due to lack of treatment effect or 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 (non-responders). Subjects discontinued prematurely for other reasons should be excluded from the PP population, but included in the ITT population using the Last Observation Carried Forward (LOCF) to impute missing values for efficacy variables.

Efficacy summaries and analyses will be carried out in the ITT and PP populations. All summaries of safety will be carried out in the safety population.

Demographic and baseline characteristics will be summarized by treatment group for the ITT and PP populations. The size of the treatment area (in centimeters) at baseline will be determined from an estimate of the % BSA treated. BSA will be determined from the subject's height and weight using the Mosteller formula. Frequency counts and percentages will be reported for categorical data. Sample size, mean, standard deviation, and minimum and maximum will be reported for the continuous variables.

17.3.1 Efficacy Analyses

The primary efficacy endpoint is the complete clearance rate (treatment success), defined as the proportion of subjects at the EOS visit in the PP population with a count of zero AK lesions in the treatment area. All AKs (baseline and new lesions) independent of size within the treatment area will be included in the efficacy lesion count for each visit.

The 90% Wald's confidence interval with Yate's continuity correction will be constructed on the difference between the proportions of subjects with lesion clearance in the Test and Reference treatments to evaluate the therapeutic comparability of the two active treatments. Two-sided, continuity-corrected Z-tests will be used to evaluate the superiority of each active treatment's clearance proportion over that of the Vehicle treatment.

If the 90% confidence interval on the difference between the Test and Reference lesion clearance proportions is contained within the interval -0.20 to +0.20, and each of these proportions is greater than, and statistically different ($p<0.05$) from, the Vehicle proportion, then the Test and Reference products will be considered to be therapeutically equivalent.

The therapeutic comparability evaluations in the PP population will be considered primary while those in the ITT will be considered supportive. The superiority comparisons in the ITT 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 ITT and PP populations. Measures of test article compliance will include the total number of applications as determined from the subject diaries. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the test article applications and no other evidence of material dosing noncompliance.

17.3.2.2 Adverse Events

Adverse events will be coded using the 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 study drug, and treatment group. All

adverse events (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

LSRs will be summarized by treatment group by the most intense score for each LSR and by the sum score at each visit and over the course of the study. The frequency of the individual LSRs will be tabulated by severity and treatment group at each visit.

17.3.3 Other Analyses

17.3.3.1 Medical History

Medical history events will be coded using the MedDRA dictionary. The number and percent of unique subjects reporting each medical history will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group.

17.3.3.2 Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary and will be summarized by treatment group, drug class (pharmacological level) and drug name (chemical substance level).

17.4 Subgroup Analyses

No subgroup analyses are planned.

17.5 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) 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 Institutional Review Board (IRB) approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

18.2 Institutional Review Board (IRB) and Informed Consent

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

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

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

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

18.3 Protocol Compliance

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

18.4 Protocol Revisions

[redacted] 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 [redacted]

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 [redacted]. 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 the Food and Drug Administration and other government regulatory authorities may also evaluate the study records, source documents, investigator, study staff and facilities.

The investigator should immediately notify [redacted] of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports. [redacted] will notify the Sponsor of any audits of the study by any regulatory agency.

18.6 Case Report Form Requirements

The study will utilize validated 21CFR Part 11 compliant electronic data capture (EDC) software to collect CRF data. All requested information must be entered on the CRFs in the areas provided in a timely manner. When changes or corrections are made in the CRF, 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 listed on the Delegation of Responsibilities Log with responsibility for CRF completion may make entries on the CRFs. Usernames and passwords will be provided to each authorized user to allow access to the training module. Access to additional features and functions will not be enabled until the user has successfully completed the training.

The investigator or physician sub-investigator must electronically sign and date each subject's CRF. 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 (QA) 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.

18.9 Records Retention

According to Title 21 of the Code of Federal Regulation § 312.62, an investigator is required to maintain study records for a period of two (2) 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 (2) years after the investigation is discontinued and the FDA is notified.

In accordance with 21CFR § 320.38, each reserve sample (retain) shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least five (5) 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 (5) years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used.

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

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

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 or the subject's guardian, except as necessary for monitoring by [redacted] or the Sponsor, the FDA or other regulatory authority, or the IRB/IEC.

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

1. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010*;* 4:582-90.
2. Zyclara® (imiquimod) Cream, 2.5% Prescribing Information, Issued February 2012, Distributed by Medicis, The Dermatology Company.

APPENDIX 1 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 Visit 1.

Sample Subject Instruction Sheet

[redacted]

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

Name:_____ Phone: _____

- [redacted]

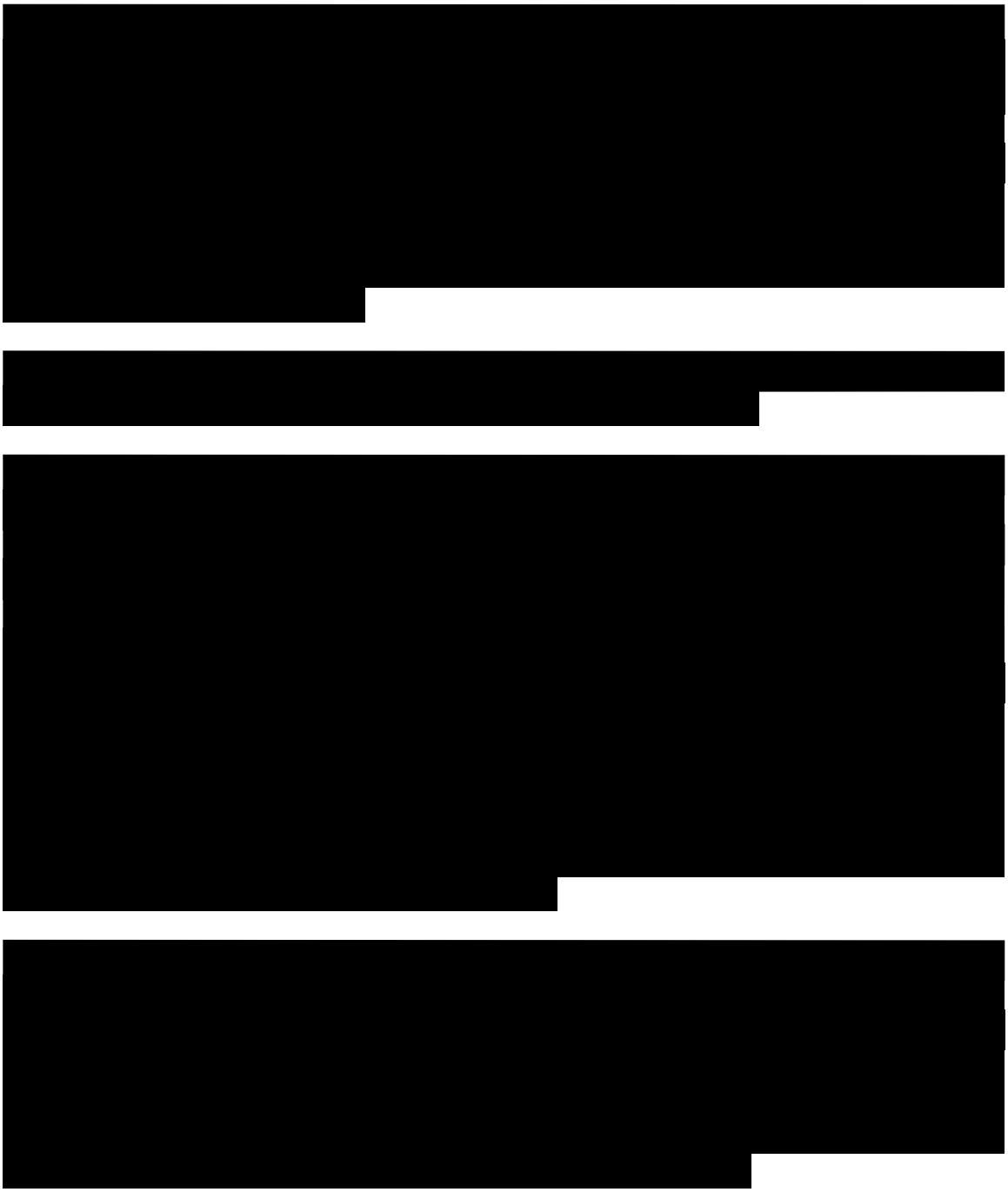
- [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			

SUBJECT INSTRUCTIONS FOR THE PREPARATION (PRIMING), DISPENSING AND APPLICATION OF CREAMS



A 2.1 Test Article Packaging and Labeling

Carton Label

Subject Kit Label

- [redacted]

[redacted]

Pump Label

[redacted]

A 2.2 Retains

[redacted]

A 2.3 Test Article Storage and Preparation

Test article should be stored at room temperature [25°C (77°F); excursions permitted from 15°C to 30°C (59°F 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 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.
- 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, if applicable.

A 2.6 Dose Interruptions

Temporary dosing interruptions (rest periods) may be instituted by the investigator as needed to manage LSRs or AEs. Treatment should be resumed upon adequate resolution as determined by the investigator. However, doses missed due to rest periods or for other reasons will not be made up and the duration of each dosing cycle must remain at 14 days. Dosing interruptions should be noted on the subject diary and documented in the subject's CRF (see **Section 6.3**).

A 2.7 Documentation of Test Article 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 pumps 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 article in the original containers by a traceable means (e.g., 2-day FedEx shipping) to:

[redacted]
Watson Laboratories, Inc.
[redacted]

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