Statistical Analysis Plan

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

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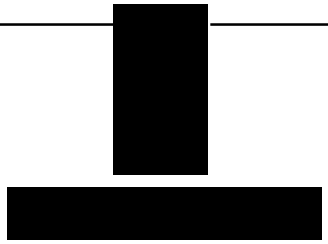
Appendix 16.1.9 Documentation of Statistical Methods



STATISTICAL ANALYSIS PLAN

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Date

Date

Dale

Date

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GLOSSARY OF TERMS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AK	Actinic Keratosis
ATC	Anatomical Therapeutic Classification
BSA	Body Surface Area
CRF	Case Report Form
CSR	Clinical Study Report
EOS	End of Study
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
pp	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOC	System Organ Class
[redacted]	[redacted]
UPT	Urine Pregnancy Test
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol 094-3153-301, "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."

This SAP was created using Clinical Protocol 094-3153-301 Version 1.0 dated 30 July 2013 and the Case Report Forms for Protocol 094-3153-301 Version 1.0 dated 04 October 2013.

2 PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol 094-3153-301. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3 STUDY OBJECTIVES

The objective is to evaluate the safety and therapeutic equivalence[1] 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, randomized, double-blind, vehicle-controlled, parallel group comparison study of a generic imiquimod cream, 2.5% and Zyclara™ (imiquimod) cream, 2.5% in subjects with AK on the full face or balding scalp. Approximately 435 subjects with at least 5 but no more than 20 clinically typical, visible or palpable AK lesions at least 4 mm in diameter on either the face (excluding the ears) or the balding scalp who fulfill the eligibility criteria as defined in the protocol (including inclusion/exclusion criteria) will be enrolled at approximately 25 US 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)

Subjects who are eligible for enrollment into the study will be randomized by assigning the lowest subject kit number available at the site. 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,

[1] "Therapeutic equivalence" is synonymous with the term "bioequivalence with clinical endpoint" as used in Draft Guidance on Imiquimod, Feb 2011.

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.

5 STUDY SCHEDULE AND PROCEDURES

5.1 Study Schedule

Visit	Visit 1	Visit 2 (Call)	Visit 3	Visit 4	Visit 5 (Call)	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 I-Visit 1 to Visit 3 Treatment Cycle 2-Visit 4 to Visit 6**						
Informed Consent2	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 (LSR) Assessment	X		X	X		X	X
Confirm Next Visit Appointment, Review Dosing Instructions and Query About AEs.		X			X		
Pregnancy Testing[3] for WOCBP [4]	X						X
Issue Subject Diary	X			X			
Review/ Collect Subject Diary for Compliance			X			X	
Adverse Events	X	X	X	X	X	X	X
Dispense/Return Test Article (Perform Drug Accountability)	X		X	X		X	

5.2 Procedures at Study Assessment Time Points

The study consists of five protocol-specified visits and two follow-up phone contacts as follows:

[2] Informed consent may be obtained within 30 days prior to the Baseline Visit.
[3] Urine pregnancy tests must have a minimum sensitivity of 25 mIU 13-hCG/mL of urine and must be performed within 24 hours prior to the start of test article at baseline.
[4] See Protocol Section 14.4 for definition of woman of childbearing potential (WOCBP).

- Visit 1 /Screening/ Baseline/ Day -30 to 1
  Study subjects may be consented up to 30 days before Visit 1. If no washout from prohibited medications or treatments is required, the Screening and Baseline Visits may occur the same day. Procedures to be performed include:

Informed consent	Identify Treatment Area
Inclusion/exclusion criteria review	%BSA of the Treatment Area
UPT for WOCBP	AK lesion count
Medical history	Diameter of each AK lesion
Demographics	LSR assessment
Prior and/or concomitant therapies	Randomize the subject
Brief dermatologic exam	Dispense test article
Vital signs assessment	Issue subject diary

- Visit 2 - Phone Call (Week 1/Day 8 ± 2)
  The subject will be queried regarding changes in health status or any adverse events since the last visit. The application instructions will be reviewed and the next visit confirmed.

- Visit 3 (Week 2 / Day 15 + 3)
  Procedures to be performed include:

LSR assessment	Collect used and unused test article pumps
Collect and review subject diary	Adverse events
	Concomitant therapies

- Visit 4 (Week 4 / Day 29 ± 2)
  Procedures to be performed include:

LSR assessment	Adverse events
Issue subject diary	Concomitant therapies
Dispense test article pumps	

- Visit 5 - Phone Call (Week 5/Day 36 ± 2)
  The subject will be queried regarding changes in health status or any adverse events since the last visit. The application instructions will be reviewed and the next visit confirmed.

- Visit 6 (14-17 Days after Visit 4)
  Procedures to be performed include:

AK lesion count	Collect used and unused test article pumps
LSR assessment	Adverse events
Collect and review subject diary	Concomitant therapies

- Visit 7 (Week 14 / Day 99 ± 4)
  Procedures to be performed include:
  AK lesion count
  LSR assessment
  Collect and review subject diary
  UPT for WOCBP
  Adverse events
  Concomitant therapies
  End of Study Form

- Unscheduled Visits
  Unscheduled visits occur at the investigator's discretion with the following procedures to be performed:
  LSR assessment
  Review subject diary
  Adverse events
  Concomitant therapies

6 EFFICACY AND SAFETY MEASUREMENTS

6.1 Efficacy Measurements

6.1.1 AK Lesion Counts

AK lesion counts within the Treatment Area (full face or balding scalp) will be performed at Visits 1, 6 and 7 by the investigator or qualified designee. All AK lesions (baseline AKs and new AKs), independent of size, in the Treatment Area will be identified, counted, and recorded. The number of AK lesions in the Treatment Area that are 4 mm in diameter and the diameter of each AK lesion in the treatment area will be documented at the Baseline Visit. The Treatment Area at Baseline must include 5 to 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 AK count cannot be performed due to a LSR this will be documented on the CRF.

The AK clearance rate for a subject will be calculated as follows:
{1 - [(#AKs at follow-up)/ (#AKs at Baseline)]}* 100.

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

6.2 Safety Measurements

6.2.1 Laboratory

UPTs must be performed on all WOCBP at Baseline prior to randomization and at the EOS visit.

6.2.2 Local Skin Reactions (LSR) Assessments

The Treatment Area will be assessed for the following LSRs at Visits 1, 3, 4, 6, 7, and Unscheduled Visits: erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudate, flaking/scaling/dryness, pain (within the last 24 hours) and pruritus (within the last 24 hours). Each LSR will be rated according to the following 4-point scale: 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe.

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 of skin surrounding the Treatment Area will be documented as an adverse event.

6.2.3 Adverse Events

An adverse event (AE) is defined as 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.

Any AE caused by a drug is an adverse drug reaction (ADR). ADRs are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. Any AE for which there is a reasonable possibility that the drug caused the event is a suspected adverse reaction (SAR). Serious adverse events (SAE) are defined as any untoward medical occurrence that at any dose in the view of either the Investigator or Sponsor results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/birth defect.

The 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. Throughout the clinical trial the subject will be questioned in a non-directive way as to the occurrence of adverse events. All adverse events which were not present at Screening will be recorded. Adverse events will be followed 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.

The severity of an AE will be recorded as mild, moderate or severe. The relationship between an AE and the test article will be classified as certain, probable, possible or not related. The AE outcome will be specified as not recovered/resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, fatal, or unknown.

6.2.4 Concomitant Medications and Concurrent Therapies/Procedures

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

7 DATA SETS ANALYZED

The Safety population will include all randomized subjects who received the test article. Subjects who were randomized and applied at least one dose oftest article and returned for at least one post-Baseline evaluation will be included in the intent-to-treat (ITT) population. 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.

The per-protocol (PP) population is a subset of the ITT population. [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.

8 STATISTICAL METHODS

8.1 General Considerations

All statistical processing will be performed using SAS Version 9.4, unless otherwise noted. Continuous data will have the following summary statistics reported: number of subjects, mean, standard deviation, minimum and maximum. For categorical data, the number and percentage of subjects within each category will be reported.

All data will be listed in subject data listings sorted by treatment group, site and subject number unless otherwise noted. Data tabulations will be prepared as described in the sections below.

8.2 Efficacy Endpoints

8.2.1 Primary Endpoint

Complete clearance rate (treatment success) is defined as the proportion of subjects in a treatment group with a 100% clearance of all AK lesions within the Treatment Area. The primary endpoint is the proportion of subjects in the PP population with treatment success at Visit 7 (Week 14/ End of Study). All AKs (Baseline and new lesions), independent of size, within the Treatment Area will be included in the AK lesion count for each visit.

8.3 Safety Endpoints

8.3.1 Dosing Compliance

Measures of test article compliance will include the total number of days of test article applications recorded in the case report forms 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.

8.3.2 Adverse Events and LSRs

The severity and frequency of adverse events and local skin reactions (LSRs) will be assessed in the three treatment groups.

8.4 Subject Disposition

All subjects enrolled into the study that are issued a subject number will be accounted for in Subject Disposition. 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. Data will be tabulated by treatment group and the number and percentages of subjects in each treatment group who are enrolled, randomized and treated, who comprise the ITT population, who comprise the PP population, and who complete the study or withdraw prematurely along with the reason for discontinuation will be presented. The number of subjects who were seen at each assessment time point will also be tabulated.

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

All patients who drop out of the study will be listed. The listing will include, site number, subject number, reason for dropout, treatment group, last visit, and whether the subject was replaced.

8.5 Methods for Handling Missing Data

[redacted]

8.6 Screening and Baseline Assessments

8.6.1 Demographic and Baseline Characteristics

Gender, age (derived), race and ethnicity will be summarized by treatment group for the ITT and PP populations. The number in each of the following age groups will also be summarized by treatment group for the ITT and PP populations: 18-40, 41-64, 65-75, and >75. Age will be calculated as floor[(screening date - date ofbirth)/365.25].

The size of the Treatment Area (in centimeters) at Baseline will be determined from an estimate of the %BSA treated, the subject's height and weight using the Mosteller formula. Characteristics of the AK lesions in the Treatment Area at Baseline will be summarized including the total number of AK lesions and the number of AK lesions at least 4 mm in diameter.

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

8.6.2 Medical History and Dermatologic Exam

Medical history, including onset of actinic keratoses, will be presented in a subject data listing. Verbatim terms on the CRFs will be mapped into system organ class and preferred term using MedDRA Coding Dictionary version 16.0. Tabulations of the number of subjects reporting medical history events will be presented by System Organ Class (SOC), Preferred Term (PT), and treatment group. Abnormalities noted during the dermatologic exam, excluding AKs, will be provided in a listing.

8.6.3 Vital Signs

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

8.6.4 Prior Medications and Therapies/Procedures Identified in the Exclusion Criteria

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

8.6.5 Concomitant Medications and Concurrent Therapies/Procedures

Concomitant medications and concurrent therapies/procedures will be provided in separate subject listings. Concomitant medications will be coded using the WHO Drug dictionary (version effective 01 September 2012). The medications will be tabulated by treatment group, Drug Class (pharmacological level, ATC3) and Drug Name (chemical substance level, ATC5).

8.6.6 Dosing Compliance

Study medication dosing will be recorded daily during each of the two-week treatment cycles including the number of pump actuations applied per day with indications of whether or not the dose was missed or held. The number of applications, missed doses, held doses and percent of expected doses will be summarized by descriptive statistics for the ITT and PP populations. The percent of expected doses will be calculated using 28 (once daily dosing for two 14 day treatment cycles) as the expected number of doses. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the expected test article applications.

8.7 Efficacy Analyses

8.7.1 Primary Efficacy Analyses

The primary efficacy endpoint is the complete clearance rate (treatment success), defined as the proportion of subjects in the **PP** population at the EOS visit with 100% clearance of 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 (generic imiquimod minus Zyclara) in the proportions of subjects with complete lesion clearance 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 complete clearance rate over that of the Vehicle treatment.

If the 90% confidence interval on the difference between the Test and Reference lesion complete clearance rates at EOS in the **PP** population is contained within the interval -0.20 to +0.20, and each of these proportions in the ITT population is greater than, and statistically different ($p<0.05$) from, the Vehicle proportion in the ITT population at EOS, 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.

8.8 Safety Analyses

8.8.1 Adverse Events

Verbatim terms on the CRFs will be mapped into system organ class and preferred terms using MedDRA Coding Dictionary version 16.0. Tabulations of the number of subjects experiencing adverse events will be presented by System Organ Class (SOC) and Preferred Term (PT) and treatment group for (a) adverse events, (b) adverse events by maximum severity and (c) adverse events by closest relationship to study drug. Adverse events will be counted only once for a subject within each Preferred Term and System Organ Class; thus, since a subject may have more than one Preferred Term within an SOC, percentages of PT may not sum to the percentage in the SOC. If a subject reports a PT multiple times with differing severities, only the most severe is counted. If a subject reports a PT multiple times with differing relationships to study medication, only the one most related to study medication is counted based on the following order: certain, probable, possible, and not related.

Fisher's Exact tests will be performed on adverse events with a 2% or greater frequency to facilitate evaluation of potential safety differences among treatments.

Serious adverse events will be listed separately for systemic AEs, if applicable.

8.8.2 LSRs

LSRs within the Treatment Area 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.

8.8.3 Urine Pregnancy Tests

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

8.9 Sample Size

[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. The probability of study success was estimated as the percent of the simulated trials that met both these confidence interval and superiority criteria. A total of 435 ITT subjects [redacted] for demonstrating bioequivalence between the active treatments and showing that each active treatment is superior to vehicle treatment.

8.10 Protocol Deviations

All protocol deviations will be listed.

8.11 Interim Analysis

No interim analyses are planned.

8.12 Subgroup Analyses

No subgroup analyses are planned.