[redacted]

# STATISTICAL ANALYSIS PLAN

**Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of GDC 695 and Diclofenac Sodium Gel, 3% in Subjects with Actinic Keratoses

**Protocol Number:** GDC-695-001

**Sponsor:** Gage Development Company, LLC

[redacted]

**Date:** 14MAR2017

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[redacted]

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## GLOSSARY OF TERMS

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

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol GDC-695-001, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of GDC 695 and Diclofenac Sodium Gel, 3% in Subjects with Actinic Keratoses."

This SAP was created using Clinical Protocol GDC-695-001 Version 2.0 dated 26JAN2017, and the Electronic Case Report Forms (eCRF) Version 1.0 dated 14Oct2016.

# 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 GDC-695-001. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

# 3 STUDY OBJECTIVES AND ENDPOINTS

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

The primary efficacy endpoint is the proportion of subjects in the PP population with treatment success ("Complete Clearance") at Day 90 (30 days after completion of 60 days of treatment). Complete Clearance is defined as 100% clearance of all AK lesions (having a count of zero AKs) in the 25 $cm^2$ treatment area (face or bald scalp) at the Day 90 visit.

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

# 4 STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group comparison study of GDC 695 and Diclofenac Sodium Gel, 3% (Fougera) in subjects with AKs on the face or bald scalp. Approximately 600 subjects with at least five but no more than 10 clinically typical, visible or palpable, discrete, nonhyperkeratotic, nonhypertrophic, AK lesions, each at least 4 mm in diameter, contained within a continuous 25 $cm^2$ treatment area located on the face (excluding the ears) or the bald scalp who fulfill the inclusion/exclusion criteria will be enrolled at approximately 28 sites.

Subjects will be randomized to one of three treatment groups on a 1:1:1 basis as follows:

- GDC 695 (Gage) (diclofenac sodium gel, 3%)
- Diclofenac Sodium Gel, 3% (Fougera) (Reference Product)
- Vehicle gel (Gage)

All subjects will be instructed to apply the assigned test article to the entire 25 $cm^2$ treatment area (face [excluding ears] or bald scalp) identified by the investigator at Visit 1. The assigned test article will be applied twice daily, once in the morning and once in the evening, for 60 days to the entire 25 $cm^2$ treatment area. The study will consist of a Screening/Baseline Visit, telephone calls at Day 15 and at Day 45, and follow-up visits at Day 30, Day 60, and Day 90 (30 days after completion of 60 days of treatment).

# 5 STUDY SCHEDULE OF EVENTS

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

[1] Subjects who terminate early shall complete all final visit activities designated at Day 90.
[2] Subjects may have consent signed and if required wash-out from prohibited medications or treatments within 30 days prior to the Baseline Visit.
[3] A Treatment Area Identification Manual will be provided to the sites with instructions on how to perform photography of the treatment area and on how to create the "subject specific" template.
[4] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.

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

[5] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women 50 years of age or older). Even women who are using oral, implanted, injectable, intravaginal contraceptive hormones, an IUD, barrier methods (diaphragm/cervical cap and spermicidal, condom and spermicidal) to prevent pregnancy, practicing abstinence, or where the partner is sterile and the subject states she is in a monogamous relationship should be considered to be of childbearing potential. Surgical means of sterilization (e.g., vasectomy, tubal ligation) must be a minimum of six months post-procedure to be considered effective birth control.

# 6 DEFINITIONS

- End of Treatment (EOT): Visit 5/Day 60
- End of Study (EOS): Visit 6/Day 90 or Early Termination Visit
- Study Day: The study day is the day of study relative to the date of randomization (Baseline visit/Day 1).
  Study Day = follow-up visit date – randomization date + 1
- Baseline: The baseline assessment is defined as the last non-missing measurement collected at Baseline visit prior to the test article application.

# 7 CLINICAL EVALUATIONS

## 7.1 Efficacy Measurements

### 7.1.1 *AK Lesion Evaluation and Counting*

AK lesion counts will be performed at Baseline, Day 60/EOT, and Day 90/EOS. At the Baseline Visit (Visit 1) all AK lesions in the 25 $cm^2$ Treatment Area, independent of size, will be identified, counted, recorded on the transparency, and measured for size (i.e., diameter). The number and location of AK lesions to be treated that are ≥4 mm in diameter will also be documented at the Baseline Visit. At Day 60/EOT and Day 90/EOS, the number of total AK lesions, independent of size, in the 25 $cm^2$ Treatment Area will be counted including Baseline AKs and new AKs; a new AK is defined as a lesion that was not present at Baseline.

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

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

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

## 7.2 Safety and Baseline Measurements

### 7.2.1 *Adverse Events*

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

Serious adverse events (SAE) are defined as an AE or suspected adverse reaction that in the opinion 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, or important medical events defined in the protocol.

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

### 7.2.2 *Local Skin Reactions Assessments*

At Baseline, Day 30 follow-up, Day 60/EOT, Day 90/EOS, and Unscheduled Visits (if applicable), LSRs will be assessed in the 25 $cm^2$ Treatment Area using a four-point ordinal scale of 0 = absent, 1= mild (slight, barely perceptible), 2=moderate (distinct presence) and 3 = severe (marked, intense) for the following:

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

These LSRs will be collected independently of AEs. LSRs that require medical intervention (e.g. prescription medication) or extend beyond the 5 cm surrounding skin will be documented as AEs.

### 7.2.3 *Dermatologic Exam*

A dermatologic examination will be performed at the Baseline Visit.

### 7.2.4 *Laboratory Tests*

Urine Pregnancy Tests (UPTs) will be performed on all WOCBP at the Baseline Visit prior to randomization and at the Day 60/EOS visit.

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

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

## 8 STATISTICAL METHODS

### 8.1 General Considerations

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

## 8.2 Analysis Populations

### 8.2.1 *Safety Population*

The Safety population will include all randomized subjects who received at least one dose of the test article.

### 8.2.2 *mITT Population*

The modified Intent-to-Treat (mITT) population will include all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of test article, and returned for at least one post-baseline evaluation clinic visit (Visits 3, 5 and 6). Randomized subjects who are lost to follow-up after Visit 1, who return for the EOT visit but have not applied any test article, or who are found not to have met the eligibility criteria will be excluded from the mITT population.

### 8.2.3 *PP Population*

The per-protocol (PP) population will include all randomized subjects who met all the following requirements:

- met inclusion/exclusion criteria,
- were compliant with the assigned test articles (applied at least 75% and no more than 125% of the expected (120) test article applications, did not miss more than 10 consecutive scheduled applications and have no other evidence of material dosing noncompliance),
- completed the primary endpoint evaluation at Day 90 visit within the designated visit window (± 4 days), and
- had no protocol violations that would affect treatment evaluation.

As exceptions to the above requirements, the following subjects will be included in the PP population as treatment failures if they met the mITT criteria:

- Subjects who are discontinued from the study due to worsening condition that requires alternate or supplemental therapy for the treatment of AK,
- Subjects who are discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment.

## 8.3 Methods for Handling Missing Data

If AK lesion counts are missing at post-baseline visits, depending on the reason for the early discontinuation, the following rules will be applied:

- For subjects who are discontinued prematurely due to worsening condition that requires alternate or supplemental therapy for the treatment of AK, or who are discontinued prematurely after completing at least four weeks of treatment due to lack of treatment effect, they will be included in the mITT and PP populations and considered as treatment failures.
- For subjects who are discontinued prematurely for any other reasons, Last Observation Carried Forward (LOCF) imputation will be used to impute the missing data. They will be included in the mITT population, but excluded from the PP population.

## 8.4 Subject Disposition

Subjects who complete the 60 days of treatment and all of the EOS visit evaluations at Day 90 will be considered to have completed the study.

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

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

Subjects who were screen failures with their reason for screen failure will be listed.

## 8.5 Screening and Baseline Assessments

### 8.5.1 *Demographic and Baseline Characteristics*

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

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

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

### 8.5.2 *Medical History*

Medical history at Screening/Baseline will be presented in a subject data listing for the Safety population.

### 8.5.3 *Prior Medications*

Listings will be provided for the prior medications that were taken and stopped prior to the randomization date.

## 8.6 Efficacy Analyses

### 8.6.1 *Primary Efficacy Analyses*

The primary efficacy endpoint is the proportion of subjects in the PP population with treatment success ("Complete Clearance") at Day 90 (30 days after completion of 60 days of treatment), where Complete Clearance is defined as 100% clearance of all AK lesions (having a count of zero AKs) in the 25 $cm^2$ treatment area (face or bald scalp) at the Day 90 visit.

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

Test for bioequivalence of test and reference treatments

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

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

, where $\pi_T$ is the proportion of subjects with treatment success in test treatment group (GDC 695 (diclofenac sodium gel, 3%)) and $\pi_R$ is the proportion of subjects with treatment success in reference treatment group (Diclofenac Sodium Gel, 3% (Fougera)).

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

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

Test for superiority of each active treatment over vehicle treatment

To establish that the study is sufficiently sensitive to detect the difference between treatments, two-sided, continuity-corrected chi-square tests with an alpha of 0.05 will be used to test the superiority of each active treatment group's treatment success rate over that of the Vehicle treatment in the mITT population. If any cells have an expected frequency of less than 5, then Fisher's exact tests will be used instead.

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

### 8.7 Dosing Compliance and Test Article Exposure

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

Descriptive statistics of the total number of applications, the number of missed applications, and the duration of treatment by treatment group will be presented for the Safety, mITT and PP populations.

## 8.8 Safety Analyses

### 8.8.1 *Adverse Events*

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

All adverse events will be listed.

### 8.8.2 *Local Skin Reactions*

The frequency of the individual LSRs (erythema, dryness/flaking/scaling, burning/stinging, erosion/ulceration, edema, pain, and pruritus) will be tabulated by severity and treatment group at Baseline, Day 30, Day 60 and Day 90/EOS.

### 8.8.3 *Urine Pregnancy Tests*

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

### 8.8.4 *Concomitant Medications and Concurrent Therapies/Procedures*

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

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

## 8.9 Sample Size

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

## 8.10 Protocol Deviations

Protocol deviations will be provided in a subject listing.

### 8.11 Interim Analysis

No interim analyses are planned.

### 8.12 Subgroup Analyses

No subgroup analyses are planned.

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