CLINDAMYCIN 1% GEL

PROTOCOL: CLMG 1711

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Clindamycin 1% Gel to Clindamycin 1% Gel (Greenstone LLC) and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

CLINICAL STUDY REPORT

1 TITLE PAGE

Indication studied	Acne Vulgaris
Developmental phase of study	Bioequivalence [BE] Study with Clinical Endpoints
Study initiation date	26 April 2018
Study completion date	23 October 2018
Sponsor	Akorn Pharmaceuticals
Principal investigators	Sites 1, 2, 3: Julian Melamed, MD Site 4: Hector Wiltz, MD, CPI Site 5: Francisco Flores, MD Site 6: Ines Mendez-Moguel, MD Site 7: Julitta Bradley, MD Sites 8, 9: Reginald Williams, MD Site 10: Shahram Jacobs, MD Site 11: Tooraj Raoof, MD Site 12: Zoe Diana Draelos, MD
Sponsor signatory	Rob Adamczyk, PharmD, RPh Director, Clinical Development Akorn Pharmaceuticals
Release date of report	23 Dec 2018

This study was conducted in compliance with International Council for Harmonisation (ICH) harmonized tripartite guideline E6 (R2): Good Clinical Practice (GCP), including the archiving of essential documents.

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2 SYNOPSIS

Name of the Sponsor: **Akorn Pharmaceuticals**	Individual Study Table Referring to part of the dossier Volume Page	*(For national Authority use only)*
Name of the Finished Product: **Clindamycin 1% Gel**		
Name of Active Ingredient: **Clindamycin 1%**		

Title of Study

A Multi-Center, Double-Blind, Randomized, Vehicle- Controlled, Parallel-Group Study Comparing Clindamycin 1% Gel to Clindamycin 1% Gel (Greenstone LLC) and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

Investigators and Study Centers

The study was conducted at 12 study sites in the United States and Belize. The list of sites and investigators is as follows:

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Publications

None

Study Period	**Phase of Development**
Start Date (first subject enrolment): 26 April 2018 End Date (last study visit): 23 October 2018	Bioequivalence [BE] Study with Clinical Endpoints

Objectives

- To evaluate the therapeutic equivalence and safety of Clindamycin Phosphate Topical Gel, 1% (Akorn Pharmaceuticals) and Clindamycin Phosphate Topical Gel, 1% (Greenstone LLC) in the treatment of acne vulgaris.
- To demonstrate the superiority of the efficacy of the Test and Reference products over that of the Placebo control in the treatment of acne vulgaris.

Methodology

Clindamycin Phosphate Topical Gel, 1% (CleocinT®, Greenstone, LLC) for topical use was approved by the FDA in 1987 as a prescription product for the safe and effective topical therapy for acne vulgaris. Greenstone, LLC is the authorized generic manufacturer of CleocinT®. Akorn Pharmaceuticals has developed a new generic formulation of Clindamycin Phosphate Topical Gel, 1%. The current study was designed to evaluate the safety and efficacy of this new generic formulation.

Subjects in this multi-center, double-blind, placebo-controlled, parallel group study, were randomly assigned in a 2:2:1 ratio to treatment with the Test product, Clindamycin Phosphate Topical Gel, 1% (Akorn Pharmaceuticals), the Reference product, Clindamycin Phosphate Topical Gel, 1% (Greenstone LLC) or Placebo (Vehicle gel of the Test product).

The study treatment consisted of a topical self-application of the investigational product (IP) to the affected areas of the face twice daily, in the morning and evening, for 84 consecutive days (12 weeks). A thin layer of the IP, approximately a pea-sized amount was applied around the same time every day, after the subject's face had been washed with a non-medicated cleanser and warm water. For the purposes of this study, the face was considered to start at the hairline and end at the jaw line and excluded the eyes, lips, and all mucous membranes. Subjects were required to use diaries to document the date of study treatments, any missed treatments, and the occurrence of all adverse events (AEs).

Scheduled study visits included:

- Visit 1: Screening / Baseline Visit (Day 0);
- Visit 2: First Interim Visit (Week 4 / Day 28 ± 4 days);
- Visit 3: Second Interim Visit (Week 8 / Day 56 ± 4 days); and
- Visit 4: End of Treatment Visit (Week 12 / Day 84 ± 4 days).

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After informed consent process and completion of all screening assessments, a baseline acne grade was assigned to the subject using the Investigator's Global Assessment (IGA) and a baseline lesion count was performed. Subjects were admitted into the study if they had a clinical diagnosis of acne vulgaris of severity Grades 2, 3, or 4 at baseline and if they met inclusion/exclusion criteria. The blinded IP was dispensed to those subjects who met all of the inclusion and exclusion criteria. The first application of IP was performed by the subject at home.

During each subsequent study visits, evaluations of efficacy (i.e., lesion counts and IGA) were conducted. Safety was assessed by monitoring AEs and documenting signs and/or symptoms of local irritation.

Number of Subjects (Planned and Analyzed)

Approximately, 1125 subjects were planned to be enrolled and randomly assigned in a 2:2:1 ratio (Test 450: Reference 450: Vehicle 225) to obtain approximately 1070 (428:428:214) subjects in the modified intent-to-treat (mITT) population and 855 (342:342:171) subjects in the Per-Protocol (PP) population.

In the study, 1125 subjects were enrolled and randomized; 450 subjects to Test drug group, 450 subjects to Reference drug group, and 225 subjects in the Vehicle group. Overall, all of the 1125 subjects qualified for the Safety population, 1095 (97.3%) subjects qualified for the mITT population, and 988 (87.8%) subjects for the PP population.

Diagnosis and Criteria for Inclusion

Subjects were eligible for the study only if they met all of the following criteria:

1. Healthy male or non-pregnant female aged ≥12 and ≤40 years with a clinical diagnosis of acne vulgaris.
2. 18 years or older (up to the age of 40) had to provide an institutional review board (IRB)-approved written informed consent. Subjects who were 12 to 17 years of age, inclusive had to provide IRB approved written assent; this written assent was to be accompanied by an IRB approved written informed consent from the subject's legally acceptable representative (i.e., parent or guardian). In addition, all subjects or their legally acceptable representatives (i.e., parent or guardian) had to sign a Health Insurance Portability and Accountability Act (HIPAA) authorization.
3. Had a minimum ≥25 non-inflammatory lesions (i.e., open and closed comedones) and ≥20 inflammatory lesions (i.e., papules and pustules) and ≤2 nodulocystic lesions (i.e., nodules and cysts), at baseline on the face. For the purposes of study treatment and evaluation, these lesions were limited to the facial treatment area. All lesions were counted, including those present on the nose. Subjects who had acne lesions on other areas of the body were excluded from the count, treatment, and the IGA evaluation (e.g., on the back, chest and arms).

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4. Had a definite clinical diagnosis of acne vulgaris severity Grade 2, 3, or 4 as per the IGA as follows:

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

*The electronic case report form (eCRF) for acne studies allowed for reporting of lesion worsening beyond Grade 4 with treatment. Investigators were recommended to not enroll acne vulgaris subjects with nodulocystic acne. Subjects who worsened beyond Grade 4 were described in the safety evaluation. Note: Nodulocystic lesions were not included in the inflammatory lesion count. Counts of nodules and cysts were reported separately and not included in the inflammatory or non-inflammatory lesion counts.

5. Refrained from using all other topical acne medications or antibiotics for acne vulgaris during the 12-week treatment period for acne vulgaris, other than the IP.
6. Female subjects of childbearing potential (excluding women who were premenarchal, surgically sterilized, or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, had to be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study, the following were considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g., condom and spermicide), intrauterine device, or abstinence with a second acceptable method of birth control if the subject became sexually active. Subjects on hormonal contraception had to be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. A sterile sexual partner was not considered an adequate form of birth control.
7. All male subjects had to agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 30 days after the last administration of study drug. Abstinence was an acceptable method of birth control. Female partners had to use an acceptable method of birth control as described above (# 6).
8. Were willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.

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9. Had to be in good health and free from any clinically significant disease, including but not limited to, conditions that could interfere with the evaluation of acne vulgaris. Such conditions included, but were not limited to the following: autoimmune disease; rosacea; seborrheic dermatitis; perioral dermatitis; corticosteroid-induced acne; carcinoid syndrome; mastocytosis; acneiform eruptions caused by make-up, medication, facial psoriasis and facial eczema.
10. Subjects who used make-up had to use the same brands/types of make-up for a minimum period of 14 days prior to study entry and had to agree to not change make-up brand/type or frequency of use throughout the study.

Test Product, Dose, Mode of Administration, Batch No.

Test Product: Clindamycin Phosphate Topical Gel, 1% (Akorn Pharmaceuticals)

Dose and Mode of Administration: A thin layer of the Test drug, approximately a pea-sized amount was self-applied to the face, twice a day (in the morning and evening, around the same time every day) for 84 consecutive days (12 weeks), after the subject's face had been washed with a non-medicated cleanser and warm water. For the purposes of this study, the face was considered to start at the hairline and end at the jaw line and excluded the eyes, the lips, and all mucous membranes.

Lot Number: 358539, Manufactured Date: 19 June 2017, Expiry: June 2019

Reference therapy, Dose, Mode of Administration, Batch No.

Reference Product: Clindamycin Phosphate Topical Gel, 1% (Greenstone LLC)

Dose and Mode of Administration: A thin layer of the Reference drug, approximately a pea-sized amount was self-applied to the face, twice a day (in the morning and evening, around the same time every day) for 84 consecutive days (12 weeks), after the subject's face had been washed with a non-medicated cleanser and warm water. For the purposes of this study, the face was considered to start at the hairline and end at the jaw line and excluded the eyes, the lips, and all mucous membranes.

Lot Number: T27338, Expiry: June 2019

Placebo (Vehicle) therapy, Dose, Mode of Administration, Batch No.

Placebo Control: Vehicle gel of the Test product (Akorn Pharmaceuticals)

Dose and Mode of Administration: A thin layer of the Vehicle, approximately a pea-sized amount was self-applied to the face, twice a day (in the morning and evening, around the same time every day) for 84 consecutive days (12 weeks), after the subject's face had been washed with a non-medicated cleanser and warm water. For the purposes of this study, the face was considered to start at the hairline and end at the jaw line and excluded the eyes, the lips, and all mucous membranes.

Lot Number: 358075P, Manufactured Date: May 2017, Expiry: May 2019

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Duration of Treatment

The study treatment period was of 84 days (12 weeks). A 9-day window (i.e., ± 4 days) was considered acceptable for each scheduled visit following the baseline visit. The study duration was expected at 6 months.

Criteria for Evaluation

Co-primary Efficacy Endpoints:

- The co-primary efficacy endpoints were percent change from baseline to Week 12 in the inflammatory (papules and pustules) and in the non-inflammatory (open and closed comedones) lesion counts.

Secondary Efficacy Endpoint:

- The secondary endpoint was the IGA score, expressed in terms of treatment success or failure. Success was defined as an IGA score at Week 12 that was at least 2 grades less than the baseline assessment. Failure was defined as an IGA score that was the same, higher or one grade lower than the baseline assessment.

Safety Evaluation*:*

- Adverse events throughout.
- Vital signs (blood pressure, pulse, respiratory rate, and body temperature) at Visit 1.
- Brief physical examination at Visit 1.
- Concomitant medications and non-drug therapies at baseline and at each subsequent study visit.
- Signs/symptoms of local irritation (application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain, and itching were recorded at each study visit to allow a comparison between treatment groups)

Statistical Methods

All statistical analyses were conducted using SAS Version 9.4 and all data were listed by treatment group, subject, and visit/time point where appropriate.

Continuous data were described using descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, and maximum). Categorical data were described using count and percentages. All statistical tests were two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated.

The analysis populations used in this study were:

- **Safety Population**: The Safety Population consisted of all subjects who were randomized into the study and received at least one dose of IP according to subject's diary. If it was unknown whether

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the subject received any IP, that subject was also included in the safety population. The Safety Population was the primary population for the safety analysis.

- **Modified Intent-to-Treat (mITT) Population**: The mITT set consisted of all Safety population subjects who met all inclusion/exclusion criteria and had at least one post-baseline efficacy evaluation. This population was considered as definitive for testing superiority and supportive for testing bioequivalence.
- **Per-protocol (PP) Population**: The PP population included all mITT subjects who applied 75% to 125% of the scheduled applications of the assigned product; did not miss applications for more than three consecutive days; returned for the Week 12 evaluation within the visit window or discontinued prematurely from the study due to lack of treatment effect after completing minimum four weeks of treatment or; and had no protocol deviations that affected proper administration of the treatment, or accurate evaluation of its effectiveness. This population was considered as definitive for testing of bioequivalence and supportive for testing superiority.

Determination of Sample Size

The sample size for this protocol was based on published data on clindamycin phosphate topical gel, 1% and Cleocin T® Summary Basis of Approval and Label (approved January 2016).

Approximately, 1125 subjects were to be enrolled and randomly assigned in a 2:2:1 ratio (Test 450: Reference 450: Vehicle 225) to obtain approximately 1070 (428:428:214) subjects in the mITT population and 855 (342:342:171) subjects in the PP population. This sample size was to provide at least a 90% probability of showing that the 90% confidence intervals (CIs) on the Test/Reference ratio of mean percent reduction from baseline, for both lesion types, were contained within the interval 0.800 to 1.250 in the PP population and at the same time demonstrating that the Test and Reference products were statistically superior ($p<0.05$) to the Vehicle in the mITT population.

Hypothesis of Bioequivalence (Co-primary Endpoints)

A two-sided, 90% CI on the Test/Reference ratio for mean percent change from baseline to Week 12 in lesion count was constructed using Fieller's method. The estimates of treatment means and standard errors were obtained from a two-way analysis of variance (ANOVA) of the Test and Reference results, using a statistical model containing terms for treatment and center. If the assumptions of normal error and homogeneity of variance were not satisfied, a ranked-based, nonparametric approach was to be used to obtain the CI.

Bioequivalence was established if the 90% CIs for the ratio of Test/Reference means, for both lesion types, were contained within the interval [0.80, 1.25] for the PP population.

Hypothesis of Bioequivalence (Secondary Endpoint)

A two-sided, continuity-corrected, 90% CI on the test-to-reference difference for the proportion of subjects with treatment success on the IGA was constructed. Bioequivalence was established if the 90% CI for the difference was contained within the interval [-0.20, +0.20] for the PP population.

Hypothesis of Superiority (Co-primary Endpoints)

The null hypothesis to be tested was that there was no difference in the mean percent change from baseline to Week 12, in each lesion type, between the active treatment and the Vehicle treatment. The hypothesis testing was performed separately for the Test treatment versus the Vehicle treatment and for the Reference treatment versus the Vehicle treatment using ANOVA under assumption of normal error and homogeneity of variance. If the assumptions of normal error and homogeneity of variance were not satisfied, a ranked-based, nonparametric method was to be used.

Superiority was established if the mean percent change from baseline for each active treatment, for each lesion type, was less than (i.e., more negative), and statistically different from ($p<0.05$), that for the Vehicle (placebo) using the mITT study population and last observation carried forward (LOCF).

Hypothesis of Superiority (Secondary Endpoint)

The null hypothesis to be tested was that there was no difference in the proportions of subjects with treatment success on the IGA. The evaluation of superiority was conducted separately for the Test treatment versus the Vehicle treatment and for the Reference treatment versus the Vehicle treatment. The analysis was conducted using two-sided, $\alpha = 0.05$, Cochran-Mantel-Haenszel (CMH) exact test stratified by study center. Superiority was established if the success proportion for each active treatment was greater than, and statistically different from ($p<0.05$), that of the Vehicle (placebo).

Safety Analyses

Incidence of all AEs reported during the study were summarized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1) by treatment group, body system, severity, and relationship to study drug. A summary of the frequencies (number and percentage) of subjects with treatment-emergent AEs (TEAEs), serious TEAEs, TEAEs leading to treatment discontinuation and for TEAEs leading to death were presented by system organ class and preferred term. Additionally, number and percentage of subjects with TEAE were summarized by preferred term only in the descending order of frequency. Proportion of subjects experiencing TEAEs that occurred in at least 1% of subjects in either Test or Reference groups was compared between these groups using Fisher's exact test.

Results of physical examination findings, vital signs, and signs/symptoms of local irritation were listed. Number and percentage of subjects with each severity were presented by visit and symptom of local irritation.

Date of the Report: 23 Dec 2018