CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA:	50-782
Applicant:	Target Research Associates
Name of Drug:	Clindagel (Clindamycin Phosphate [redacted] gel), 1%
Indication:	Topical treatment of acne vulgaris
Documents Reviewed:	Volumes 1.1 and 1.26-1.31 dated January 27, 2000, and data sets provided by the sponsor
Medical reviewer:	Phyllis Huene, M.D. (HFD-540)
Statistical reviewer:	Valeria Freidlin, Ph.D. (HFD-725)

INTRODUCTION AND BACKGROUND

The sponsor submitted a report of a single, adequate and well-controlled Study CGEL-003 to support the claim that Clindagel gel administered once daily (QD) for 12 weeks is safe and effective in the treatment of acne vulgaris.

Clindamycin phosphate in gel formulation is currently marketed under the trade name Cleocin T® (NDA 50-615, Pharmacia and Upjohn, 1987). It is indicated for twice daily (BID) topical application in the treatment of acne vulgaris. Clindagel™ has been developed by the sponsor for once daily application. The sponsor states that once daily administration regimen of Clindagel is effective in the treatment of patients with acne and ensures a better compliance and safety compared with Cleocin T administered twice daily.

At the End-of-Phase-2 meeting, January 19, 1999, the FDA stated that Clindagel is a candidate for a 505(b)(2) submission. In this submission, demonstration of non-inferiority of Clindagel QD to Cleocin T gel BID is no longer required for approval because once daily regimen has a potential of better compliance and safety. The FDA stated that for the 505(b)(2) application, it is sufficient to submit a single adequate and well-controlled trial with the following five treatment arms: Clindagel (QD), Clindagel Vehicle (QD), Clindagel (BID), Clindagel Vehicle (BID), and Cleocin T gel (BID). For approval, Clindagel QD would need to be superior to its vehicle. The labeling would reflect the results of comparisons of Cleocin T (BID) versus Clindagel (QD). The inclusion of the Clindagel BID and Clindagel vehicle BID arms was recommended by the FDA in order to obtain dosing information regarding the Clindagel product.

STUDY DESIGN

This was a multicenter, randomized, evaluator-blind, vehicle-controlled, parallel comparison study in patients with acne vulgaris. Patients were randomized in a 2:1:2:1:2 ratio to one of the five treatment groups: Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, or Cleocin T gel BID.

A total of 667 patients were randomized to one of the five treatment groups (168 patients were randomized to Clindagel QD, 84 to Vehicle QD, 166 to Clindagel BID, 84 to Vehicle BID, and 165 to Cleocin T gel BID). A total of 16 independent centers randomized approximately 24 to 64 patients each (with the exception of Site 11, which only enrolled six patients).

Patients received the study gel for a period of 12 weeks. Each patient's disease was evaluated by inflammatory, non-inflammatory, and total lesion counts. If a patient was assigned to the Cleocin T gel group, both the patient and the Drug Administrator were unblinded. If a patient was not assigned to the Cleocin T gel group, then both the patient and the Drug Administrator were blinded. However, both the patient and the Drug Administrator knew if the patient was using the study gel either QD or BID. The investigator was blinded to all of the study gels, and the investigator did not know whether a patient was using the study gel QD or BID.

Patients returned to the study center for lesion counts and localized irritation assessments at Weeks 2, 4, 8, and 12/Final Visit. The Physician's Global Severity Assessment was performed at baseline and after 12 weeks of treatment. Adverse events were monitored throughout the study.

Inclusion Criteria

To be eligible to participate in this study, a patient must be a male or female at least 12 years of age, diagnosed with acne vulgaris. Patients must have a minimum of 25, but no more than 100, inflammatory facial lesions (papules, pustules) and a minimum of 20, but no more than 100, non-inflammatory lesions (open and/or closed comedones).

Randomization

Prior to the start of the study, a randomization list was generated assigning patients to one of the five treatment groups in a 2:1:2:1:2 ratio (Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, or Cleocin T gel BID, respectively). Patients were randomized in blocks of eight. Upon randomization, each patient was assigned a unique number in sequential order within the center. This patient number also corresponded to the number indicated on the test material label.

Blinding

Clindagel and the vehicle were masked so that the patient and the Physician did not know whether the patient received Clindagel or the vehicle gel. However, a double-blind, double-dummy technique was not used to mask the treatment groups from each other; hence, patients knew whether they had

been randomized to the QD or BID treatment group. Therefore, an evaluator-blind design was employed to reduce the possibility of bias.

Efficacy Variables

The efficacy measurements and the assessment of localized irritation were assessed by the same evaluator for the same patient at each visit. The area of assessment was defined as the face from the jaw line to the hairline, excluding the nose.

Inflammatory Lesion Count

The inflammatory lesion count, performed at Visits 1 to 5/Final Visit, included the individual count of papules and pustules that were defined as follows:

papule: a type of inflammatory lesion: a small, solid elevation ≤1 cm in diameter; most of the lesion was above the surface of the skin

pustule: a type of inflammatory lesion: a small, circumscribed elevation of the skin that contained yellow-white exudate

Non-inflammatory Lesion Count

The non-inflammatory lesion count, performed at Visits 1 to Final Visit, included the individual count of open and closed comedones that were defined as follows:

open comedone: a mass of sebaceous material that was impacted behind an open follicular orifice (blackhead)

closed comedone: a mass of sebaceous material that was impacted behind a closed follicular orifice (whitehead)

Global Severity Assessment

At Visit 1 and Final Visit, the evaluator assessed the Global Severity of the patient's acne. The following 9-step scale, based upon the Cook Scale, was used:

0. facial skin need not have been perfectly clear; a few scattered comedones or papules may have been present, but these should have been visible only on close examination.
1. comedones and small papules were present and noticeable from a distance of 1 to 3 feet away.
2. about one fourth of facial area was involved, with small papules (about 6 to 12) and comedones (a few pustules or large prominent papules may have been present).
3. approximately 30% (26 to 49%) of facial area was involved with small papules (13 to 20) and small comedones (a few pustules or large prominent papules may have been present).

4. about half of facial area was involved, with small papules and large or small comedones; a few pustules or large prominent papules were usually present (if lesions were generally large, the patient may have had "grade 4" severity, although less than half of the facial area was involved).
5. more than half (51 to 74%) of the facial area was involved with large and small papules and comedones (lesser facial area of involvement was permissible if the inflammatory lesions were large); a moderate number of pustules was usually present, some of which may have been large.
6. about three fourths of the facial area was involved, with papules and/or large open comedones (lesser facial area of involvement was permissible if the inflammatory lesions were large); numerous pustules were usually present, some of which may have been large.
7. greater than 75%, but less than 85%, of the facial area was involved with lesions with the majority being papules and large open comedones; pustules may have been large and prominent.
8. practically all of the facial area was involved with lesions: large prominent pustules were usually visible; lesions were usually highly inflammatory; other types of acne may be present.

Primary Efficacy Variables in the Sponsor Analysis

The primary efficacy variables, specified in the Protocol:

- Mean percent change from baseline in inflammatory lesion counts
- Mean percent change from baseline in non-inflammatory lesion counts
- Mean percent change from baseline in total lesion counts
- Percent of patients with a two category improvement from baseline in the Physician's Global Assessment of Severity.

Statistical Methods specified in the Protocol

Populations:

Intent-to-treat (ITT) population

This population consisted of all patients who were dispensed any of the study gels (all of the patients who were dispensed study gel also applied the gel at their initial visit). The primary efficacy analysis for superiority comparisons was based on the ITT population. The primary efficacy analysis for superiority comparisons was performed at "Endpoint" defined as last observed visit.

Per-Protocol (PP) population

The Per Protocol population was a primary efficacy population for the non-inferiority comparisons. This population was a subset of the ITT population. Patients or individual visits may have been excluded from the Per Protocol population because of major deviations from the protocol. Major deviations from the protocol included:

- visits occurring outside a ±7-day window around the planned visit date (as measured from baseline)
- patients missing more than 5 consecutive days of dosing
- patients missing two or more consecutive visits before the Week 12 visit
- patients enrolled who did not meet the inclusion/exclusion criteria
- patients receiving concomitant therapies liable to interfere with the results of the study

Comparison of Treatment Groups at Baseline

The five treatment groups were compared at baseline with respect to demographic and baseline characteristics. Categorical variables (gender, race, and baseline values of the Global Severity Assessment) were summarized with frequencies and percentages. The CMH test, adjusted for center, was used to compare treatment groups with respect to these variables. Continuous variables (age and baseline lesion counts) were summarized using descriptive statistics. The distributions of these variables at baseline were compared among the five treatment groups using a two-way ANOVA model, with terms for treatment and center.

Primary Efficacy Analysis

The analysis of percent change from baseline in each type of lesion count was performed using an ANOVA model with terms for treatment, center, and treatment-by-center interaction. The significance level for interactions was 0.1. The Global Severity Assessment was a nine-point scale. The Sponsor's Dichotomized Global Severity Assessment was defined as:

- good to excellent improvement from baseline (change from baseline less than or equal to -2).
- worsening to no change or fair improvement (change from baseline greater than -2).

Secondary Efficacy Variables

The percent change from baseline to Week 12 in each of the three lesion counts was compared between the Clindagel BID and Vehicle BID treatment groups, and between each of the active Clindagel treatment groups and the Cleocin T gel treatment group. The methods used for these comparisons were the same as those described above for the primary efficacy analysis. Comparisons between the Clindagel treatment groups and the Cleocin T gel treatment groups were intended to demonstrate non-inferiority of Clindagel as compared with Cleocin T gel.

The actual change in lesion count from baseline to each visit and to endpoint was analyzed for each type of lesion count (inflammatory, non-inflammatory, and total). The analysis was done using an ANCOVA model with terms for treatment and center, and with baseline lesion counts as a covariate. Each active Clindagel treatment group was compared with its Vehicle and with the Cleocin T gel treatment group.

According to the protocol, non-inferiority of Clindagel QD vs. Cleocin T gel BID and Clindagel BID vs. Cleocin T gel BID was evaluated for lesion counts (inflammatory, non-inflammatory, and total) and the percent of patients with two-category improvement in the Global Severity Assessment on the Per-Protocol population at Week 12. According to the protocol, the 95% confidence intervals were constructed for each variable using the **ratio** of Clindagel to Cleocin T gel. According to the protocol, the non-inferiority of Clindagel QD or Clindagel BID was claimed if the lower bound of the observed 95% confidence interval of the **ratio** was greater than 0.90.

Reviewer's Comments:

1. *At the End-of-Phase-2 meeting, January 19, 1999, the Division stated that Clindagel QD is a candidate for a 505(b)(2) submission. As Clindagel QD is supposed to have better safety and compliance than Cleocin T gel BID, demonstration of equivalence between Clindagel QD and Cleocin T gel BID is no longer required for approval. The Division stated that for a 505(b) (2) application, a single adequate and well-controlled trial with the following five treatment arms would be sufficient for marketing approval: Clindagel (QD), Clindagel Vehicle (QD), Clindagel (BID), Clindagel Vehicle (BID), and Cleocin T gel (BID). For approval, Clindagel QD would need to be superior to its vehicle. The labeling would reflect the results of [redacted] The inclusion of the Clindagel BID and Clindagel vehicle BID arms were recommended by the Division in order to obtain dose finding information regarding the Clindagel product.*

   Although the study has two Clindagel regimens (QD and BID), no p-value adjustment for two multiple comparisons was applied in this review, because the sponsor does not have a choice of picking up either of the two regimens. The protocol pre-specified indication for once a day treatment of acne only.

2. *In agreement with the Medical Division, this reviewer did not use the Sponsor's Dichotomized Global Severity Assessment (defined as a two-category improvement from baseline). Instead, this reviewer used the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint. The CMH test adjusted for center was used for the analysis relative to this efficacy variable.*

3. *In accordance with the current policy requirements for acne products, this reviewer used the following primary efficacy variables: the percent change from baseline to endpoint in two of the three categories of lesion counts (inflammatory, non-inflammatory, and total) and the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment. The primary efficacy comparison in this review is the comparison of the Clindagel QD and the*

Vehicle QD treatment groups for each of the primary efficacy variables. The primary efficacy analysis is based on the ITT-LOCF population.

4. *No p-value adjustment for multiple endpoints was applied in this review because the effectiveness of Clindagel QD is established if:*

   - *there is a statistically significant difference in favor of Clindagel QD between the Clindagel QD and Vehicle QD treatment groups relative to the percent change from baseline to endpoint in two of the three categories of lesion counts and*

   - *there is a statistically significant difference in favor of Clindagel QD between the treatment groups relative to the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint.*

5. *In addition to the evidence that Clindagel QD is statistically significantly better than Vehicle QD relative to the percent change in lesion counts, the Medical Division also wants the evidence that the actual change from baseline is clinically meaningful. For this reason the actual changes from baseline to endpoint in lesion counts are the secondary efficacy variables.*

6. *In the sponsor's report, reduction from baseline in lesion counts is presented as a negative quantity (e.g., endpoint value-baseline value). In this review, for simplicity, reduction from baseline in lesion count is presented as a positive quantity (baseline value-endpoint value).*

7. *Another secondary efficacy variable in this review is the proportion of patients with grade 2 or less in the Physician's Global Severity Assessment at endpoint.*

8. *For the labeling purposes, the efficacy analysis includes comparisons of Clindagel vs. Cleocin T gel treatment groups relative to the percent change from baseline to Week 12 in lesion counts (inflammatory, non-inflammatory, and total) and the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment. These comparisons are intended to demonstrate non-inferiority of Clindagel to Cleocin T gel.*

   To demonstrate non-inferiority, the sponsor used the following procedure. A one-sided 95% confidence interval (CI) was constructed for each variable using the ratio of Clindagel to Cleocin T gel. Non-inferiority of Clindagel QD or Clindagel BID was claimed if the lower bound of the observed CI for the ratio was greater than 0.90. The sponsor's procedure does not follow the FDA policy on the assessment of therapeutic non-inferiority.

   In compliance with the FDA policy on therapeutic non-inferiority, this reviewer used the following approach. A one-sided 97.5% confidence interval was constructed for the difference between Clindagel and Cleocin T gel relative to the percent reduction from baseline in lesion count. Non-inferiority of Clindagel QD or Clindagel BID was established if the lower bound of the observed CI for the difference was greater than minus 10%.

RESULTS

Disposition of Patients

Table 1 presents the number and percentage of patients included in each population for each of the five treatment groups. A total of 667 patients were randomized in the study, and 651 (98%) patients were included in the ITT population. There was no statistically significant difference between treatment groups relative to the number of patients included in the ITT population (p=0.47). A total of 553 patients (82.9%) were evaluable for efficacy at Week 12 (Per-Protocol population). There was no statistically significant difference between treatment groups relative to the number of patients included in the Per Protocol population (p=0.64).

Table 1
Patient Populations

Population	Number (%) of Patients: Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID	Total	P-value
Randomized	168	84	166	84	165	667	
Intent-to-treat	162 (96.4)	82 (97.6)	161 (97.0)	84 (100)	162 (98.2)	651 (97.6)	0.47
Per-Protocol	139 (82.7)	69 (82.1)	140 (84.3)	65 (77.4)	140 (84.8)	553 (82.9)	0.64

Table 2 presents completion and withdrawal information for patients enrolled into the study. Of the 667 randomized patients, 580 (87.0%) completed the study, and 87 (13.0%) discontinued prior to Week 12. The treatment groups were similar with respect to the number of patients who discontinued the study (p= 0.9).

Table 2
Patient Disposition

Disposition		Number (%) of Patients: Clindagel QD (N=168)	Vehicle QD (N=84)	Clindagel BID (N=166)	Vehicle BID (N=84)	Cleocin T BID (N=165)	P-value
Completed Study	Yes	147 (87.5)	71 (84.5)	145 (87.3)	72 (85.7)	145 (87.9)	0.9
	No	21 (12.5)	13 (15.5)	21 (12.7)	12 (14.3)	20 (12.1)	

STUDY RESULTS

Data Sets Analyzed

Two patient populations were analyzed: ITT and Per-Protocol (PP). The primary efficacy analysis was based on the ITT population. Both ITT and PP populations were analyzed at baseline and Week 12 for each of the lesion counts (inflammatory, non-inflammatory, and total) and for the Physician's Global Severity Assessment. The ITT population analyses are presented at endpoint (LOCF) and Per-Protocol analyses are presented at Week 12.

Demographic and Other Baseline Characteristics

Table 3
Baseline Demographics and Disease Characteristics
(All Patients Enrolled into Study)

Characteristic	Treatment Group: Clindagel QD (N=168)	Vehicle QD (N=84)	Clindagel BID (N=166)	Vehicle BID (N=84)	Cleocin T BID (N=165)	P-Value
	Number (%) of Patients					
Gender						
Male	80 (47.6)	43 (51.2)	79 (47.6)	35 (41.7)	86 (52.1)	0.611
Female	88 (52.4)	41 (48.8)	87 (52.4)	49 (58.3)	79 (47.9)	
Race						
White	141 (83.9)	74 (88.1)	143 (86.1)	77 (91.7)	149 (90.3)	0.292
Black	19 (11.3)	6 (7.1)	22 (13.3)	7 (8.3)	13 (7.9)	
Other	8 (4.8)	4 (4.8)	1 (0.6)	0 (0.0)	3 (1.8)	
Age (years)						
Mean (SD)	19.6 (6.87)	20.0 (7.99)	18.8 (7.08)	19.2 (6.85)	18.9 (6.98)	0.672
Range	12, 42	13, 51	12, 48	12, 47	12, 48	
Duration of Acne (years)						
Mean (SD)	3.2 (4.18)	4.8 (7.10)	3.5 (4.63)	3.9 (5.20)	3.4 (4.34)	0.082
Range	1, 30	1, 30	1, 27	1, 30	1, 26	

There were no statistically significant differences in baseline or demographic characteristics among the five treatment groups. As shown in Table 3, a majority of patients were white (>83% in each group). Similar numbers of male (41.7% to 52.1%) and female (47.9% to 58.3%) patients were enrolled into each of the five groups (p=0.61). The patients in this study ranged in age from 12 to 51 years. The mean age across the groups was 19.6, 18.8, 20.0, 19.2, and 18.9 years for the Clindagel QD. Clindagel BID. Vehicle QD, Vehicle BID, and Cleocin T BID groups, respectively (p=0.67). At the time of screening, the mean length of time that patients had acne was 3.2 to 4.8

years (p=0.08). There was no statistically significant difference between the five treatment groups at baseline relative to the Physician's Global Assessment of severity at baseline (p=0.56). The difference between the Clindagel QD and Vehicle QD groups relative to the Physician's Global Assessment of severity at baseline was not statistically significant (p=0.98).

Efficacy Results

Inflammatory, Non-inflammatory, and Total Lesions

The primary efficacy comparison was between Clindagel QD and Vehicle QD for the ITT population. Results of the efficacy analysis relative to the lesion counts are shown in Table 4. The primary efficacy analysis relative to the percent change from baseline to endpoint in inflammatory lesions showed that the difference between Clindagel QD and Vehicle QD groups was statistically significant (p=0.015, 51.5% and 39.8%, respectively). Relative to the percent change in non-inflammatory lesion count at endpoint, there was also statistically significant difference (p=0.043) between the Clindagel QD group (25.3%) and the Vehicle QD groups (12.4%). Relative to the percent change in total lesion count, there was also statistically significant difference (p=0.010) between the Clindagel QD group (38.4%) and the Vehicle QD groups (26.8%). There was no significant treatment-by-center interaction (p>0.1).

Table 4
Mean Percent Change and Actual Change from Baseline to Endpoint in Inflammatory, Non-Inflammatory, and Total Lesion Counts. Clindagel QD versus Vehicle QD (ITT Population)

Lesion Count		Treatment Group: Clindagel QD	Treatment Group: Vehicle QD	P-value [b]
N		162	82	
Inflammatory:	**% change** [a]	**51.5 %**	**39.8 %**	**0.015**
	actual change	19.5	14.7	0.006
Non-Inflammatory:	**% change**	**25.3 %**	**12.4 %**	**0.043**
	actual change	13.1	7.7	0.128
Total :	**% change**	**38.4 %**	**26.8 %**	**0.010**
	Actual change	32.5	22.4	0.013

[a] Percent change=(baseline value-week 12 value)/baseline value.
[b] ANOVA with treatment and center as factors. Data from centers 11 and 12 were pooled.

Analysis of the secondary efficacy variables, the actual change from baseline in inflammatory and total lesion counts, supports the results for the percent change and shows statistical significance (p≤0.013, Table 4). Relative to the actual change from baseline in non-inflammatory lesions, Clindagel QD was only numerically better than Vehicle QD (p=0.128). The difference between the two groups in actual change was equal to 5.4 lesions.

In the Per Protocol population, results of the analysis of the percent change from baseline in inflammatory, non-inflammatory, and total lesion counts for Clindagel QD versus Vehicle QD were similar ($p \leq 0.027$) to the results in the ITT population (not shown).

Physician Global Severity Assessment

Table 5 shows the results of the primary efficacy analysis relative to the percentage of patients with grades 0 or 1 in the Physician's Global Assessment at endpoint. The percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment in the Clindagel QD group was only numerically greater than in the Vehicle QD group (p=0.076). This may be explained by the fact that the study had only a power of 42% for this comparison.

Table 5

Number and Percentage of Patients with Grades 0 or 1

in the Physician's Global Severity Assessment at Endpoint

Clindagel QD versus Vehicle QD (ITT Population)

(Reviewer's Analysis)

	Number (%) of Patients		P-value [a]
	Treatment Groups		
	Clindagel QD	Vehicle QD	
Grade 0 or 1	32 (20.5%)	9 (11.5%)	0.076
Grade >1	124 (79.5%)	69 (88.5%)	

[a] CMH test stratified by center. Data from centers 11 and 12 were pooled.

In the secondary efficacy analysis relative to the percentage of patients with grades 0, 1, or 2 in the Physician's Global Severity Assessment at the endpoint (Table 5a), Clindagel QD was statistically significantly better than Vehicle QD (p=0.002). Clindagel QD was only numerically better than Vehicle QD both in the all-category analysis of the Physician's Global Severity Assessment at endpoint (p=0.092, Table 6) and in percentage of patients with grade 0 in the Physician's Global Severity Assessment at the endpoint (p=0.24).

Table 5a Number and Percentage of Patients with Grades 0, 1, or 2 In the Physician's Global Severity Assessment at Endpoint Clindagel QD versus Vehicle QD (ITT Patients) (Reviewer's Analysis)			
	Number (%) of Patients		
	Treatment Groups		
	Clindagel QD	Vehicle QD	P-value
Grade 0, 1, or 2	79 (50.6%)	23 (29.5%)	0.002
Grade >2	77 (49.4%)	55 (70.5%)	

Table 6 All-category analysis of the Physician's Global Severity Assessment at Endpoint Clindagel QD versus Vehicle QD (ITT Patients) (Reviewer's Analysis)			
	Number (%) of Patients		
	Treatment Group		
Severity grade at endpoint	Clindagel QD	Vehicle QD	P-value
0	12 (7.7%)	3 (3.8%)	
1	20 (12.8%)	6 (7.4%)	
2	47 (30.1%)	14 (17.9%)	0.092
3	41 (26.3%)	27 (34.6%)	
4	21 (13.5)	14 (17.9%)	
5	10 (6.4%)	10 (12.8%)	
6	5 (3.2%)	3 (3.8%)	
7	0.0.0%)	1 (1.3%)	

For completeness, this reviewer performed analysis comparing Cleocin T gel BID versus Vehicle BID relative to the Physician's Global Severity Assessment at Endpoint. There was no statistically significant difference between the two groups relative to the percentage of patients with Grade 0 (p=0.3), Grades 0 or 1 (p=0.3), Grades 0, 1, or 2 (p=0.16), and in all-category analysis (p=0.8).

Assessment of Non-Inferiority of Clindagel versus Cleocin T

For labeling purposes, comparisons were made between treatment groups in the Per-Protocol population to demonstrate non-inferiority of Clindagel to Cleocin T BID. The reviewer's results of the non-inferiority analysis relative to the percent change from baseline in the inflammatory, non-inflammatory, and total lesion counts at Week 12 are shown in Table 7.

Table 7
Reviewer's Analysis of Non-inferiority Relative to the Percent Change from Baseline in Inflammatory, Non-inflammatory and Total Lesion Counts at Week 12 (Per-Protocol Population)

Lesion Count	Least Square Mean Percent Change[a] Treatment Group: Clindagel QD (N=139)	Clindagel BID (N=140)	Cleocin T BID (N=140)	97.5% Confidence Interval for the difference. Lower Bound[b]: Clindagel QD -Cleocin T BID	Clindagel BID -Cleocin T BID
Week 12					
Inflammatory	54.47	55.76	53.21	**-6.12**	**-4.83**
Non-inflammatory	27.50	32.13	34.59	-16.60	-11.97
Total	40.76	43.26	43.14	**-9.14**	**-6.64**

[a] Percent change=(baseline value-week 12 value)/baseline value.
[b] One-sided 97.5% confidence intervals for the difference between least square means, Clindagel-Cleocin T. The lower bound for the confidence interval for the difference must be greater than -10% to establish non-inferiority. This analysis was based on ANOVA with treatment and center as factors. Data from centers 11 and 12 were pooled.

At Week 12, for Clindagel QD versus Cleocin T BID comparison, the lower bound of the one-sided 97.5% confidence interval for the difference of the least square means was greater than -10% for the inflammatory lesions (-6.12%) and for the total lesions (-9.14%).

At Week 12, for Clindagel BID versus Cleocin T BID comparison, the lower bound of the one-sided 97.5% confidence interval for the difference of the least square means was greater than -10% for the inflammatory lesions (-4.83%) and for the total lesions (-6.64%).

Therefore, both Clindagel-QD and Clindagel BID were non-inferior to Cleocin T BID in the treatment of inflammatory and total acne lesions.

Relative to non-inflammatory lesion counts, the lower bound of the one-sided 97.5% confidence interval for the difference of the least square means was less than -10% for both Clindagel QD-

Cleocin (-16.60%) and Clindagel BID-Cleocin (-11.97%). This may be explained by the fact that for both comparisons the study had only a power of 53%. Because of inadequate power, this study does not support or exclude non-inferiority of Clindagel QD (or Clindagel BID) to Cleocin T BID relative to the treatment of non-inflammatory lesions.

Table 8 provides results of non-inferiority testing for the percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment at Week 12. The lower bound of the one-sided 97.5% confidence interval for the difference of percentages of patients with grade 0 or 1 was less than -10% for both Clindagel QD - Cleocin T BID comparison (-13.4%) and for Clindagel BID - Cleocin T BID comparison (-10.2%). This may be explained by the fact that for these comparisons, the study had a power of less than 47%. Therefore, the study does not support or exclude non-inferiority of Clindagel QD (or Clindagel BID) to Cleocin T BID relative to the percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment at Week 12.

Table 8
Reviewer's Analysis of Non-inferiority Relative to the Percentage of Patients with Grades 0 or 1 in the Physician's Global Severity Assessment at Week 12 (Per-Protocol Population)

	Number (%) of Patients			97.5% Confidence Interval for the difference of percentages. Lower Bound[a]	
	Treatment Group				
Grades	Clindagel QD (N=139)	Clindagel BID (N=140)	Cleocin T BID (N=140)	Clindagel QD -Cleocin T BID	Clindagel BID -Cleocin T BID
Grade 0 or 1	31 (22.3)	36 (25.7)	36 (25.7)	-13.4	-10.2
Grade > 1	108 (77.7)	104 (74.3)	104 (74.3)		

[a] One-sided confidence intervals for the difference of percentages of patients with grade 0 or 1, Clindagel – Cleocin T. The lower bound for the confidence interval for the difference must be greater than –10% to establish non-inferiority.

Subgroup Analyses

Subgroup analyses were performed for race, gender, age, and baseline disease severity. Subgroup analyses were done on the white/ black, male/ female, < 18 years old/ ≥18 years old, and baseline Physician's Global Severity Assessment ≤4 / baseline Physician's Global Severity Assessment > 4 ITT populations. Clindagel-QD was compared with Vehicle QD for differences in the percent change from baseline in the inflammatory lesion count, non-inflammatory lesion count, and total lesion count using ANOVA.

Race

The number of white patients in the study was greater than the number of black patients (approximately 8:1); therefore, the subgroup analysis by race can not be clearly interpreted.

The inflammatory lesion count in whites decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-50.7% and -39.8%, respectively), and the difference between treatments was statistically significant (p=0.03). In blacks, the inflammatory lesion count also decreased to a greater extent at endpoint in the Clindagel QD group compared with the Vehicle QD group (-56.7% and -36.6%, respectively), but the difference between treatments was not statistically significant (p=0.3). This may be attributed to the small number of patients in this subgroup.

The mean decrease in the non-inflammatory lesion count among white patients at endpoint was greater in the Clindagel QD group compared with the Vehicle QD group (-24.9% and -12.7%), but the difference was not statistically significant (p=0.07). In blacks, the Clindagel QD group was only numerically better (p=0.143) than the Vehicle QD group relative to the mean increase in the non-inflammatory lesion count at endpoint. The difference between Clindagel QD and Vehicle QD for the total lesion count was statistically significant (p=0.02) for white patients, but not for blacks (p=0.2).

Gender

The inflammatory lesion count in males decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-49.8% and -37.8%, respectively), but the difference between treatments was not statistically significant (p=0.075).

In females, the inflammatory lesion count decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-52.9% and –42.0%, respectively), but the difference between treatments was not statistically significant (p=0.09). The mean decrease in the non-inflammatory lesion count in males was greater in the Clindagel QD group compared with Vehicle QD (-24.3% and -16.3%), but the difference was not statistically significant (p=0.3). In females, the improvement in the Clindagel QD group (-26.2%) was only numerically greater than in the Vehicle QD (-8.4%) group with p=0.06.

Age

In patients <18 years old, the inflammatory lesion count decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-49.8% and -38.0%, respectively), and the difference between treatments was marginally statistically significant (p=0.054). In patients greater than or equal to 18 years old, the decrease in inflammatory lesion count in the Clindagel QD group was only numerically greater than in the Vehicle QD group (-53.8% and –42.2%, respectively with p=0.1).

The mean decrease in the non-inflammatory lesion count in patients less than 18 years old was greater in the Clindagel QD group compared with Vehicle QD (-20.6% and -13.3%), but the

difference was not statistically significant (p=0.4). In patients 18 years of age or older, greater improvement was shown in the Clindagel QD group (-31.8%) compared with the Vehicle QD (-11.3%) group, and the difference between treatments was statistically significant (p=0.04).

Baseline Disease Severity

In patients with a baseline Severity Score ≤4, the inflammatory lesion count decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-53.63% and -40.73%, respectively), and the difference between treatments was statistically significant (p=0.030). In patients with a baseline Severity Score >4, the inflammatory lesion count decreased to a greater extent in the Clindagel QD group compared with the Vehicle QD group (-46.89% and -38.12%, respectively), but the difference between treatments was not statistically significant (p=0.3).

The mean decrease in the non-inflammatory lesion count for patients with a baseline Severity Score ≤4 at endpoint was greater in the Clindagel QD group compared with Vehicle QD (-21.2% and -9.9%), but the difference was not statistically significant (p=0.2). For patients with a baseline Severity Score >4, greater improvement was shown in the Clindagel QD group (-33.9%) compared with the Vehicle QD (-17.4%) with p=0.057.

SAFETY RESULTS

The total length of therapy specified in the protocol was 12 weeks (84 days). The average duration of treatment for patients in this study was 79, 79, 84, 77, and 79 days for the Clindagel QD, Vehicle QD, Clindagel BID. Vehicle BID, and Cleocin T BID groups. respectively (p=0.5). Table 9 summarizes analysis of the adverse events.

Table 9
Summary of Adverse Events
(All Patients)

	Number (%) of Patients				
	Treatment Group				
	Clindagel QD (N=168)	Vehicle QD (N=84)	Clindagel BID (N=166)	Vehicle BID (N=84)	Cleocin T BID (N=165)
Number of adverse events	50	34	68	32	57
Number (%) of patients with at least one adverse event	29 (17.3)	26 (31.0)	50 (30.1)	23 (27.4)	42 (25.5)
Number (%) of patients with skin and appendages disorders	2 (1.2)	5 (6.0)	8 (4.8)	6 (7.1)	8 (4.8)

Clindagel QD therapy had a lower percentage of patients reporting adverse events than the other treatment groups (17% versus 31%, 30%, 27%, and 26% for the Vehicle QD, Clindagel BID, Vehicle BID, and Cleocin T BID groups, respectively). The majority of adverse events were not considered to be treatment related by the physicians. There were no serious adverse events during the study. Four patients (one Clindagel QD, one Clindagel BID, one Vehicle BID, and one Cleocin T gel BID) discontinued from the study because of an adverse event. The percentage of patients having at least one adverse event was numerically smaller (p=0.07) in the Clindagel QD group than in the Cleocin T gel BID group (17.3% versus 25.5%). The Clindagel QD group had a statistically significantly smaller (p=0.04) incidence of skin and appendages disorders than the Cleocin T gel BID group (1.2% versus 4.8%).

REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor)

At the End-of-Phase-2 meeting on January 19, 1999, the FDA stated that Clindagel QD is a candidate for a 505(b)(2) submission. As Clindagel QD is supposed to have better safety and compliance than Cleocin T gel BID, demonstration of non-inferiority of Clindagel QD to Cleocin T gel BID is no longer required for approval. The FDA stated that for a 505(b) (2) application, a single adequate and well-controlled trial with the following five treatment arms would be sufficient for marketing approval: Clindagel (QD), Clindagel Vehicle (QD), Clindagel (BID), Clindagel Vehicle (BID), and Cleocin T gel (BID). For approval, Clindagel QD would need to be superior to its vehicle. The labeling would [redacted] The inclusion of the Clindagel BID and Clindagel vehicle BID arms were recommended by the Division in order to obtain dose finding information regarding the Clindagel product.

The sponsor submitted a Phase 3, multicenter, randomized, evaluator-blind, parallel comparison, 12-week Study CGEL-003 to compare the safety and efficacy of Clindagel, Clindagel vehicle, and Cleocin T gel in patients with acne vulgaris. A total of 667 patients were randomized at the 2:1:2:1:2 ratio to Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, or Cleocin T gel BID, respectively, which were applied topically for 12 weeks.

In agreement with the medical division, this reviewer did not use the Sponsor's Dichotomized Global Severity Assessment (defined as a two-category improvement from baseline). Instead, this reviewer used the percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint.

Complying with the current policy on acne products, this reviewer used the following primary efficacy variables: the percent change from baseline to endpoint in two of the three categories of lesion counts (inflammatory, non-inflammatory, and total) and proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment.

The primary efficacy comparison in this review is the comparison of the Clindagel QD and the Vehicle QD treatment groups for each of the primary efficacy variables. The primary efficacy analysis in this review is based on the ITT-LOCF population.

No p-value adjustment for multiple endpoints was applied in this review because the effectiveness of Clindagel QD is established if:

a) there is a statistically significant difference in favor of Clindagel QD between the Clindagel QD and Vehicle QD treatment groups relative to the percent change from baseline to endpoint in two of the three categories of lesion counts and

b) there is a statistically significant difference in favor of Clindagel QD between the treatment groups relative to the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint.

Although the study has two Clindagel regimens (QD and BID), no p-value adjustment for two multiple comparisons was applied in this review because the sponsor does not have a choice of picking up either of the two regimens. The protocol pre-specified that this is an indication for once a day treatment of acne only.

In addition to the evidence that Clindagel QD is statistically significantly better than Vehicle QD relative to the percent change in lesion counts, the Medical Division also wants the evidence that the actual change from baseline is clinically meaningful. For this reason, in this review, the actual changes from baseline to endpoint in lesion counts are the secondary efficacy variables.

In the sponsor's report, reduction from baseline in lesion counts is presented as a negative quantity (endpoint value - baseline value). For simplicity, this review presents reduction from baseline in lesion counts as a positive quantity (baseline value - endpoint value).

For the labeling purposes, the efficacy analysis includes comparisons of Clindagel vs. Cleocin T gel treatment groups relative to the percent change from baseline to Week 12 in lesion counts and the percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment at Week 12. These comparisons are intended to demonstrate non-inferiority of Clindagel to Cleocin T gel. The non-inferiority comparisons are based on the Per Protocol population.

To demonstrate non-inferiority, the sponsor used the following approach. A one-sided 95% confidence interval (CI) was constructed for each variable using the ratio of Clindagel to Cleocin T gel. Non-inferiority of Clindagel QD or Clindagel BID was claimed if the lower bound of the observed CI for the ratio was greater than 0.90. The sponsor's approach does not follow the FDA policy on the assessment of therapeutic non-inferiority.

In compliance with the FDA policy on therapeutic non-inferiority, this reviewer used the following approach. A one-sided 97.5% confidence interval was constructed for the difference between Clindagel and Cleocin T gel. Non-inferiority of Clindagel QD or Clindagel BID was established if the lower bound of the observed CI for the difference was greater than -10%.

Study Results

LESION COUNTS

The primary efficacy analysis showed that Clindagel QD was statistically significantly superior to Vehicle QD relative to the percent change of inflammatory (p=0.015), non-inflammatory (p=0.043), and total lesion counts (p=0.010) in patients with acne vulgaris.

Secondary analysis of the actual change from baseline in inflammatory and total lesion counts supported the results for the percent change: the difference between the two treatment groups relative to the actual change from baseline in inflammatory and total lesion counts was also statistically significant ($p \leq 0.013$). Relative to the actual change from baseline in non-inflammatory lesions, Clindagel QD was only numerically better than Vehicle QD (p=0.13). The difference between the two groups in actual change was equal to 5.4 lesions.

PHYSICIAN'S GLOBAL ASSESSMENT

The primary efficacy analysis showed that Clindagel QD was only numerically better than Vehicle QD relative to the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint (20.5% versus 11.5%, respectively, p=0.076). This may be explained by the fact that, for this comparison, the study had only a power of 42%.

Secondary analysis relative to the proportion of patients with grades 0, 1, or 2 in the Physician's Global Severity Assessment at endpoint showed that Clindagel QD was statistically significantly better than Vehicle QD (p=0.002). In the all-category analysis of the Physician's Global Assessment at endpoint, Clindagel QD was only numerically better than Vehicle QD (p=0.092)

For completeness, this reviewer performed analysis comparing Cleocin T gel BID versus Vehicle BID relative to the Physician's Global Severity Assessment at endpoint. There was no statistically significant difference between the two groups relative to the proportion of patients with Grade 0 (p=0.33), Grades 0 or 1 (p=0.31), Grades 0, 1, or 2 (p=0.16), and in all-category analysis (p=0.82).

NON-INFERIORITY TO CLEOCIN T GEL

The results of the reviewer's analysis showed that both Clindagel QD and Clindagel BID are non-inferior to Cleocin T BID relative to the percent change from baseline in inflammatory and total lesions.

The study does not support or exclude non-inferiority of Clindagel QD (or Clindagel BID) to Cleocin T BID relative to the percent change from baseline in non-inflammatory lesions and relative to the percentage of patients with grades 0 or 1 in the Physician's Global Severity Assessment at Week 12. For non-inferiority assessments relative to either of these two primary efficacy variables, the study had a power of less than 5[illegible]%.

SAFETY

Safety analysis showed that the percentage of patients having at least one adverse event was numerically smaller (p=0.07) in the Clindagel QD group than in the Cleocin T gel BID group (17.3% versus 25.5%). The Clindagel QD group had a statistically significantly smaller (p=0.04) incidence of skin and appendages disorders than the Cleocin T gel BID group (1.2% versus 4.8%).

Overall Conclusions:

Primary efficacy analysis showed that Clindagel QD was statistically significantly superior to Vehicle QD relative to the percent change of inflammatory (p=0.015), non-inflammatory (p=0.043), and total lesion counts (p=0.010) in patients with acne vulgaris. Clindagel QD was only numerically better than Vehicle QD relative to the proportion of patients with grades 0 or 1 in the Physician's Global Severity Assessment at endpoint (20.5% versus 11.5%, respectively, p=0.076). The Clindagel QD group had a statistically significantly smaller (p=0.04) incidence of skin and appendages disorders than the Cleocin T gel BID group (1.2% versus 4.8%). This is a matter of the clinical judgement of the reviewing medical division to decide whether Clindagel QD should be approved based on the efficacy and safety results described above.

[/S/] 8.28.2000

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