CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64160

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
January 4, 2000

ANDA 64-160
Drug Product: Clindamycin Phosphate Gel USP 1%
Sponsor: Altana, Inc.

A statistical review was received and reviewed. The statistical analysis of the in vivo bioequivalence study indicates that both the test and reference products are more effective than placebo and they are bioequivalent to each other.

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Medical Officer Review
October 13, 1999

ANDA 64-160
Drug Product: Clindamycin Phosphate Gel USP, 1% (base)
Sponsor: Altana, Inc.
Reference Listed Drug: Cleocin T (clindamycin phosphate) Gel 1%, Pharmacia & Upjohn

Background

The protocol entitled "A Randomized, Double-Blind, 12-Week, Multicenter, Clinical Trial to Determine the Bioequivalence of 2 Formulations of Clindamycin Phosphate Gel USP, 1% (base) and Placebo in the Treatment of Moderately Severe Acne Vulgaris" was submitted to the Office of Generic Drugs. It was reviewed by the OGD Medical Officer and the Division of Dermatologic and Dental Drug Products and found to be acceptable. Correspondence dated 6/15/98 outlined the statistical comparisons necessary for bioequivalence of the two active components and to prove superiority of the actives over placebo.

Composition

Drug Component	Altana	Cleocin
Clindamycin (from clindamycin phosphate)	10 mg/g(1%)	10 mg/g(1%)
Carbomer 934P		
Propylene Glycol		
Propylene Glycol 400		
Methylparaben		
Sodium Hydroxide		
Purified Water USP	q.s.	q.s.

Study Title

A Randomized, Double-Blind, 12-Week, Multi-center Clinical Trial to Determine the Bioequivalence of Two Formulations of Clindamycin Phosphate Gel USP, 1% (base) and Placebo in the Treatment of Moderately Severe Acne Vulgaris

Protocol ID Number

ALT 02/97F

Data Entry and Management and Statistical Analysis

Patient Enrolment and Follow-up Period

December 4, 1997 – July 15, 1998

Objectives

1. To determine if clindamycin phosphate gel USP, 1% (base) (Altana, Inc.) is therapeutically equivalent to Cleocin T ® 1%, Topical Gel by comparing the percent reduction from baseline in the numbers of inflammatory, non-inflammatory, and total lesions, and categorical improvement in Physician's Global Assessments. The primary time-point for determination of effectiveness was the Day 84 (planned end of treatment) visit.
2. To determine if clindamycin phospate gel USP, 1% (base) (Altana, Inc.) and Cleocin T 1% Topical Gel are significantly different from the test product vehicle when comparing the percent reduction from baseline in the numbers of inflammatory, non-inflammatory, and total lesions, and categorical improvement in Physician's Global Assessments.
3. To compare the incidence of signs and symptoms in the 3 treatment arms.

Investigators

Study Design

This was a prospective, randomized, double-blind, vehicle-controlled, parallel group clinical study. Patients were enrolled after screening for inclusion/exclusion criteria. These are listed below:

Inclusion Criteria

1. Patients signed written informed consent documents; patients under the legal age of consent in the state of enrollment were also required to have the written consent of a parent or guardian.
2. Patients were between the ages of 12 to 30 years, inclusive and otherwise healthy except for the diagnosis of moderate to severe acne vulgaris.
3. Patients had at least 12, but not more than 70, inflammatory papules and no more than 6 nodulocystic lesions on the face, excluding the nose.
4. Females of childbearing potential, if sexually active, concurrently used medically acceptable methods of birth control (for a list of acceptable methods of birth control in this study, see p. 11, sec. 5.3 of the study protocol in Appendix A of this report). These patients were not enrolled until a negative urine pregnancy test result was obtained.
5. Patients had used the same brand of make-up (if applicable) for a minimum of two months prior to baseline and did not change make-up brands or types during the study.

Exclusion Criteria

1. The presence of severe eczema, psoriasis, or seborrheic dermatitis anywhere on the body.
2. The presence of any skin disease that might interfere with the diagnosis or assessment of acne vulgaris (e.g., acne rosacea, severe scarring acne, acneform eruptions caused by medications, steroid acne or steroid folliculitis, chloracne, etc.).
3. The presence of perioral dermatitis.
4. The presence of clinically significant rosacea.
5. The presence of bacterial folliculitis (by clinical appearance and/or bacterial culture).
6. Clinical evidence of cosmetic-related acne in the investigator's judgement.
7. Concomitant treatments which might influence therapeutic response or assessment of safety (e.g., acne surgery, intralesional steroids, chronic use of cryotherapy, dermabrasion, x-ray or UV therapy, etc.).
8. The planned use of tanning booths, sunbathing, or excessive exposure to the sun during the study. These were reasons for early termination if discovered during the study.
9. Previous use of oral retinoids or therapeutic vitamin A supplements (excluding multivitamins), e.g., Accutane ®, within the 6 months prior to enrollment.
10. Use of any topical anti-acne therapy on the face (e.g., alpha-hydroxy glycolic acid, benzoyl peroxide, tretinoin, antibiotics) during the 14 days prior to baseline or during the study.
11. Use of any systemic antimicrobials within 1 month prior to baseline or during the study.
12. Use of medications and vitamins during the study which are reported to exacerbate acne (azothiaprine, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or topical mid- to high-potency corticosteroids, phenytoin, and phenobarbital).

13. Use of abradants, astringents, toners, sunscreens (except Neutrogena ® 15), facials, masks, washes, medicated soaps, medicated shampoos, or facial cleansers during the study.
14. Patients who routinely experience "stinging" or "burning" upon applying any facial treatment (e.g., make-up, soap, masks, washes, sunscreens, etc.) to the face.
15. Known hypersensitivity or previous allergic reaction to any of the active or inactive components of the study medications.
16. Use of an investigational medication or participation in an investigational study within 30 days prior to baseline.
17. A known hypersensitivity to lincomycin.
18. A history of antibiotic-associated colitis or frequent periodic diarrhea, regional enteritis, or ulcerative colitis.
19. Females with histories of hirsutism or menstrual irregularities.
20. Women who were pregnant or nursing at baseline or, if sexually active, were of child-bearing potential and not practicing a medically acceptable method of contraception.
21. Use of estrogens (e.g., Depogen, Depo-Testadiol, Gynogen, Valergen, etc.) for less than two months immediately prior to baseline; patients using such medications were not allowed to change the regimen during the study.
22. Previous randomization into this study.
23. A history of alcoholism, medication abuse, psychosis, antagonistic personality, poor motivation, or emotional or intellectual problems which would likely make the patient unreliable during the study.
24. Males with beards.

Study Visits

At the Screening Visit patients were evaluated for the inclusion and exclusion criteria. A medical history, physical examination, assessment of concurrent medications, lesion count, and signs and symptoms score were completed. Patients who were eligible were assigned to a treatment arm immediately before dispensing their medication according to the randomization list. Patients were assigned to one of the following three groups:

A. Clindamycin phosphate Gel USP, 1% (base) (Altana Inc.), Lot # A313
B. Cleocin T ® 1% Gel (Pharmacia & Upjohn), Lot # 04MBA
C. Inactive gel base (Placebo) (Altana Inc.), Lot # A312

Patients received medication for 12 weeks. They were dispensed medication, given instructions on study medication application, and issued a patient instruction sheet.

Day 21 +/- 4 days (Week 3) Visit

Day 42 +/- 4 days (Week 6) Visit

Day 63 +/- 4 days (Week 9) Visit

Day 84 +/- 4 days (Week 12) Visit

Lesion counts, signs/symptom scores, and Physician/Patient Global Assessment were completed. Patients were assessed for adverse events and changes in concurrent medications. New medication was dispensed and the patient instruction sheet was reviewed except for the Day 84 (Week 12), end of therapy visit. Patient compliance was monitored by visual inspection of the returned tube. If too much or too little medication was left in the tube, the application procedure was reviewed with the patient.

Criteria for Removal of Patients from Study Therapy or Assessments

Patients were discontinued from the study before the end of the planned 12 week treatment period for any of the following reasons:

1. Discovery of the presence of any baseline exclusion criterion which was not disclosed at entry.
2. Use of any prohibited concomitant medication or therapy.
3. Use of tanning booths or excessive exposure to the sun.
4. Becoming pregnant.
5. Failure to adhere to the protocol requirements regarding study drug application or assessment visit scheduling.
6. Failure to respond to the study treatment.
7. Intolerable adverse event.

If a patient was discontinued early, the Week 12 (Day 84) visit procedures were completed at the patient's final visit. Patients who discontinued because of an adverse event were followed to the extent possible until it resolved.

Efficacy Variables

Lesion Counts

The number and type (open and closed comedones, papules, pustules, and nodulocystic lesions) of acne lesions in each facial quadrant were recorded at each visit using a facial dermogram. Per cent changes from baseline in counts of inflammatory (papules, pustules,and nodules) and non-inflammatory (open and closed comedones) and total lesions were calculated for each patient at Day 21, 42, 63, and 84 visits.

Physician's Global Assessment

At each visit (Day 21, 42, 63, and 84), investigators made an assessment of the amount of overall improvement in disease severity that had occurred compared to baseline using the following 6-point scale:

0 = Unchanged or worsened, compared to baseline
1 = Poor response, 1 – 24 % improvement compared to baseline
2 = Fair response, 25 – 49 % improvement compared to baseline

3 = Good response, 50 – 74 % improvement compared to baseline
4 = Excellent response, 75 – 99% improvement compared to baseline
5 = Completely cleared (100 % improvement, defined as no papules, pustules, comedones, or nodulocystic lesions. Residual erythema and/or pigmentation were not counted as signs of active disease.)

Patient's Global Assessment

Each patient completed an independent assessment of the degree of improvement from baseline in disease severity, including changes in skin parameters and reduction in the numbers of lesions at Day 21, 42, 63, and 84 using the following 6-point scale:

0 = Definitely worse than baseline
1 = No change from baseline
2 = Minimal improvement from baseline
3 = Definite improvement from baseline
4 = Almost clear
5 = Clear

Safety Variables

Sign/symptoms of Local Irritation

Local Irritation detected at any study visit was assigned a severity score using the following scale:

0 = None
1 = Mild – barely perceptible
2 = Moderate – distinctive presence
3 = Severe – marked/intense

Adverse Events

Any undesirable clinical change that began or became worse after the first application of study medication was reported as an adverse event (AE). The severity, duration, relationship to study medication, and outcome of each AE and resulting medical action was recorded.

Statistical Issues

Sample Size Determination

Based on data from a similar study, the percent decrease in lesion counts with the active treatments would be approximately 60% with a standard deviation of 30%. Using an alpha of 0.5 and power of at least 80%, a sample of 150-160 in the treatment groups and

75-80 in the placebo group was deemed to be adequate to declare equivalence of the actives and superiority over placebo.

Statistical Analysis

The three populations assessed were as follows:

Safety population – all randomized patients

Modified Intent to Treat (MITT) population– patients who met all entry criteria. This group was used for the efficacy analysis and any missing data was replaced by the Last Observation Carried Forward (LOCF) method.

Per Protocol (PP) population – patients who completed all visits required by the protocol or were discontinued early due to adverse events or lack of efficacy. The primary efficacy parameters were analyzed at Day 84 for this group. The day 84 visit had a revised window of –4 to +5 days. The upper limit was extended by one day to include 31 patients whose visits were at day 89 but who otherwise were evaluable.

The primary efficacy parameters were the mean percent change from baseline in lesion counts and the Physician's Global Assessment. Inflammatory, non-inflammatory, and total lesion counts were considered separate parameters for the lesion counts. Groups were compared at the last completed visit in the MITT population and the Day 84 visit for the Per Protocol population. Secondary efficacy outcomes were mean percent change from baseline in lesion counts and Physician's Global Assessment at all other on-treatment visits as well as Patient Global scores at all post-baseline visits. The primary analysis population was the MITT with the PP secondary. Analysis was performed using an ANOVA model.

Results

Four hundred ninety-four patients were enrolled into the study; 198 were in the generic Clindamycin group, 197 in the Cleocin T group, and 99 in the placebo arm. Enrollment was well balanced among the study centers ranging from 8.1% to 16.2%.

Protocol Deviations

Two patients were enrolled in violation of an entry criterion; #261 had only 10 papules at baseline (minimum was 12) and #367 had > 70 (maximum allowed) baseline papules. Patient #311 became pregnant during the study and was discontinued from the study after 28 days of treatment. Two patients, #54 and #100 unblinded their treatment. Their data are excluded from the Per Protocol analysis. Patient #388 used all the allotted gel prior to completion of 84 days of therapy. Other deviations were the use of prohibited treatments and failure to adhere to the visit schedule.

The three analysis populations and the reasons for patient exclusion are presented in the following table.

Population	Clindamycin	Cleocin T	Placebo	Total
SAFETY				
Included	198	197	99	494
MITT				
Included	190	195	98	483
Reason for Exclusion				
No post-baseline visit	6	2	1	9
Did not meet Inclusion Criteria	2	0	0	2
Total	8	2	1	11
PER PROTOCOL				
Included	169	170	84	423
Reason for Exclusion				
No post-baseline visit	6	2	1	9
Prohibited concomitant Medication	0	1	0	1
Out of window Day 84	21	24	14	59
Did not meet Inclusion Criteria	2	0	0	2
Total	29	27	15	71

Demographics

Patients in the Safety population had a mean age of 17.4 (12 – 33); 54% of the subjects were male; and 79% were Caucasian. The distribution by age and sex was similar in the MITT and Per Protocol groups. The Per Protocol group had a slightly different distribution by race with 78% Caucasian, 16% Hispanic, 6% Black, < 1% Asian, and <1% Other. The MITT population was similar racially to the Safety population.

The groups were equally distributed with respect to severity of disease at baseline. The mean number of lesions for the entire cohort (MITT and PP populations)are presented in the following tables.

MITT				
Total	**Inflammatory**		**Non-Inflammatory**	
69.4 (13 - 674)	25 (12 – 76)		44.4 (0 - 650)	
	Papules	21 (12 – 68)	Open Comedones	22.5 (0 – 602)
	Pustules	3.8 (0 – 37)	Closed Comedones	21.9 (0 - 144)
	Nodules	0.2 (0 – 6)		

PP				
Total	**Inflammatory**		**Non-Inflammatory**	
69.8 (13 – 674)	25.2 (12 – 76)		44.6 (0 - 650)	
	Papules	21.1 (12 – 68)	Open Comedones	22.4 (0 – 602)
	Pustules	3.9 (0 – 37)	Closed Comedones	22.2 (0 – 144)
	Nodules	0.3 (0 – 6)		

The baseline lesion counts in all three MITT groups were statistically similar. The Per Protocol group had a difference only in that the number of Non-Inflammatory lesions in the Cleocin group was lower than the counts in the Placebo group (p=0.041).

Efficacy

Primary Efficacy Variables

The mean change from baseline was calculated for all lesion types in each of the three treatment groups. The data for the MITT and PP groups are presented in the following table.

Variable (MITT)	**Clindamycin**	**Cleocin**	**Vehicle**		**P-Value**
Mean % change from baseline	N=187	N=194	N=97	*	
Inflammatory	- 37.8	- 40.5	- 25.3	Clin vs Cleo	0.7993
				Clin vs Pla	0.0024
				Cleo vs Pla	0.0045
Non-Inflammatory	- 2.7	11.2	3.4	Clin vs Cleo	0.5226
				Clin vs Pla	0.0408
				Cleo vs Pla	0.0099
Total	- 29.4	- 31.5	- 19.4	Clin vs Cleo	0.7613
				Clin vs Pla	0.0020
				Cleo vs Pla	0.0008
Mean Physician's Global Score	2.21	2.20	1.80	Clin vs Cleo	0.8197
				Clin vs Pla	0.0103
				Cleo vs Pla	0.0170

*Clin – Clindamycin, Cleo – Cleocin, Pla - Placebo

Results for the PP analysis were noted in the report to be similar to those of the MITT, although they were not given in the text. Their location in the appendices was cited in the report but the tables were not present in the cited location.

Secondary Efficacy Variables

Secondary endpoints included reduction in lesions counts on Days 21, 42, and 63, Physician's Global Assessments at Days 42 and 63, and the Patient's Global Assessment. The mean change from baseline for total lesions is shown in the table below (MITT).

Total Lesions	Clindamycin	Cleocin	Placebo	Statistics
Baseline	65.7	69.7	76.1	Ns
Day 21 *	-13.9	-11.3	-2.1	Clinda vs pl
Day 42	-21.2	-19.6	-10.2	<0.05
Day 63	-26.2	-26.2	-18.0	Actives vs Pl,
Day 84	-29.4	-31.5	-19.4	p<0.021

- Mean change from baseline
- Clinda – clindamycin; Pl – placebo

Clindamycin was found to be significantly better than Placebo from the first on treatment evaluation at Day 21 while Cleocin became significantly better than Placebo by Day 63.

The mean change in inflammatory and non-inflammatory lesions for the MITT population is shown below. Throughout the study period, the active treatments were both better than Placebo in the reduction of inflammatory lesions. Non-inflammatory lesions did not show improvement over Placebo until the final evaluation at the end of treatment (Day 84).

Inflammatory Lesions	**Clindamycin**	**Cleocin**	**Placebo**	**Statistics**
Baseline	25.4	25	24.2	Ns
Day 21*	-27.5	-24.6	-10.2	Actives vs
Day 42	-37.0	-31.0	-22.3	Placebo,
Day 63	-39.6	-36.9	--30.7	P<0.05
Day 84	-37.8	-40.5	-25.3	
Non-Inflammatory Lesions				
Baseline	40.3	44.7	51.8	Ns
Day 21	16.6	30.1	25.5	Ns
Day 42	9.7	23.8	16.2	Ns
Day 63	3.3	22.7	17.1	Ns
Day 84	-2.7	11.2	3.4	A vs P, p<0.05

The Physician and Patient Global Assessments are presented in the following table. Both actives were significantly better than placebo using the Physician's Global Assessment. The Patient's Global Assessment only detected differences between Clindamycin and Placebo at Day 21 and between Cleocin and Placebo at Day 63. The did not present this data as the proportion of patients who achieved each score on the respective scales.

	Clindamycin	**Cleocin**	**Placebo**	**Statistics**
Physician's Global Assessment				
Day 21	1.52	1.34	1.05	A vs P, p<0.03
Day 42	1.89	1.80	1.45	A vs P, p<0.01
Day 63	2.08	2.16	1.74	A vs P, p<0.03
Day 84	2.21	2.20	1.80	A vs P, p<0.02

Patient's Global Assessment *				
Day 21	1.96	2.03	1.86	Cleo vs P=0.09
Day 42	2.18	2.18	2.07	Ns
Day 63	2.41	2.34	2.17	Cli vs P=0.042
Day 84	2.46	2.51	2.34	Ns

*Cleo – Cleocin, P – Placebo, Cli – Clindamycin

Dropouts

Twenty-eight subjects (5.7 %) were discontinued from the study early due to lack of efficacy, AE, or prohibited concomitant medications.

Reason for Withdrawal	Clindamycin	Cleocin	Placebo
Lack of Efficacy	5	2	2
Adverse Event	3	2	1
Prohibited Medication	5	5	3
Protocol Violation/ Failure to Return	15	7	6
Total	28 (14.1%)	16 (8.1%)	12 (12.1%)

The proportion of dropouts at each visit was similar in all three groups.

The efficacy results were evaluated for treatment-by-center interactions as well as age, gender, and race differences. While there were some differences noted, there were no trends that suggested that the results noted in the total group were misleading.

Safety

The extent of exposure of subjects in the three groups was similar. The following table shows the mean duration, range, and median of medication use.

Treatment	Mean	Range	Median
Clindamycin	81.1 days	10 to 101 days	55.5 days
Cleocin	82.1 days	15 to 102 days	58.5 days
Placebo	80.6 days	18 to 92 days	55.0 days

The occurrence of AEs was balanced among the groups. The indicated that the summary listing was contained in Appendix C, however, this table was missing. The information below was derived from the text and scrutiny of the line listings.

	Clindamycin	Cleocin	Placebo
1 or more AEs	86/198 (43%)	76/197 (39%)	35/99 (35%)
Mild	56 (65.1%)	44 (57.9%)	24 (68.6%)
Moderate	26 (30.2%)	26 (34.2%)	7 (20%)
Severe	4 (4.7%)	6 (7.9%)	4 (1.4%)

	Clindamycin	Cleocin	Placebo
Body as a whole	47		
Flu syndrome	10	10	3
Headache	12	19	5
Unspecified infection	17	15	5
Respiratory System	30		
Pharyngitis	24	28	8
Skin System	19		
Rash	8	3	5

Twenty-one AEs were judged to be possibly or probably related to study medication. Of these, 10 occurred in the Clindamycin group, 7 in the Cleocin group, and 4 in the Placebo group. Most of these events were mild (15) or moderate (5). Most were classified in the Skin and Appendages category (19). The one severe related event occurred in a patient in the Clindamycin arm. This individual experienced localized irritation coded as a rash and completed the study.

Two serious AEs were reported during the study. One patient dislocated a shoulder (Cleocin) and another was hospitalized for diagnosis and treatment of a severe complex migraine (Vehicle). Neither was related to the study medication.

Local Irritation

Signs and symptoms of local irritation, including interlesional erythema, dryness, burning, and itching, were assessed at each study visit using a 4-point scale. The summary table cited in the text was also missing for this item. The scores were compared among the groups at each study visit. The following table lists the comparisons where differences were noted and the direction of those differences.

Visit Day	Sign/Symptom	Comparison	P-value
Day 21	Erythema	Cleocin > Placebo	0.0329
	Dryness	Placebo > Clindamycin	0.0256
Day 42	Dryness	Placebo > Clindamycin	0.0083
		Placebo > Clindamycin	0.0004
Day 63	Dryness	Placebo > Cleocin	0.0013
		Placebo > Cleocin	0.0063
	Burning	Placebo > Clindamycin	0.0280
		Placebo > Cleocin	0.0095
Day 84	Erythema	Cleocin > Placebo	0.0117
		Cleocin > Clindamycin	0.0005
	Dryness	Placebo > Clindamycin	0.0463
	Burning	Placebo > Clindamycin	0.0140
		Placebo > Cleocin	0.0136

The highest mean score for any sign or symptom was 0.35 with the maximum being 3.0. Generally scores decreased at later visits. Three patients had dose reductions due to local irritation. One subject in the Placebo group eventually withdrew from the study for this. Two subjects were in the Clindamycin group. One reduced the frequency of administration to once a day for the last 3 weeks of the study. Another had an unspecified period of dose reduction and was considered an AE dropout.

Conclusion

This study has shown that the two active treatments are better than placebo. The analysis for bioequivalence was reported only for the MITT population and the table purported to give the data for the Per Protocol population, which is used for the bioequivalence analysis, could not be located in the jacket provided. The safety profile of the two active drugs was similar.

The study should be consulted to the Statistician and the missing Tables in Appendix C should be requested from the company. These include Table 6c and 8, Signs and symptoms of local irritation, Table 10b, 11b, and others with the summary data and analysis on the Per Protocol population, and Table 13, summary of adverse events.

/S/

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