CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

STATISTICAL REVIEW(S)

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CLINICAL/STATISTICAL REVIEW AND EVALUATION
(Addendum)

NDA/DRUG CLASS: 50-756/4S

NAME OF DRUG: ——— (clindamycin 1% & Benzoyl Peroxide 5%) Topical Gel

APPLICANT: Dermik Laboratories, Inc.

INDICATION(S): Topical Treatment of Acne Vulgaris

TYPE OF REVIEW: Clinical/Statistical

DOCUMENTS REVIEWED: Two Controlled Studies: DL-6021-9103 & DL-6021-9623, Dated April 1998

MEDICAL REVIEWER: Phyllis Huene, M.D./ HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./ HFD-725

INTRODUCTION

At the request of the reviewing medical officer, the conclusions of the statistical review of this NDA are summarized in more detail in this addendum for the primary endpoint variables which are the "Percent Lesion Reduction from Baseline to Week-10" in Inflammatory Lesion Counts, Non-Inflammatory Lesions Counts, Total Lesion Counts and the Investigator's Global Assessment.

CONCLUSIONS:

STUDY DL-6021-9103

Comparisons between ——— vs. **Clindamycin** and ——— vs. **Vehicle**:

- Highly statistically significant results were shown in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts in the "Percent Lesion Reduction from baseline to Week-10" ($p \leq 0.003$), as well as the Investigators' Global Assessment at Week-10 ($p=0.001$).

Comparison between ——— vs. **Benzoyl Peroxide**:

- Statistically significant results were observed in the "Percent Lesion Reduction from baseline to Week-10" in regards to Inflammatory Lesions and Total Lesions ($p \leq 0.01$), as well as the Investigators' Global Assessment at Week-10 ($p=0.009$).

- No statistically significant results were observed in regards to Non-Inflammatory Lesions ($p=0.96$).

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STUDY DL-6021-9623

Comparisons between ——— vs. **Clindamycin** and ——— vs. **Vehicle**:

- Statistically significant results were observed in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts in the "Percent Lesion Reduction from baseline to Week-10" ($p \leq 0.008$), as well as the Investigators' Global Assessment at Week-10, ($p \leq 0.02$).

Comparison between ——— vs. **Benzoyl Peroxide**:

- Statistically significant results were achieved in the "Percent Lesion Reduction from baseline to Week-10" in regards to Inflammatory Lesions and Total Lesions ($p \leq 0.03$).
- No statistically significant results were observed in regards to Non-Inflammatory Lesions ($p=0.2$).
- No statistical significance was observed in the "Physicians' Global Assessment" at Week-10 ($p=0.5$).

[/S/ 2/17/99]

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CLINICAL/STATISTICAL REVIEW AND EVALUATION

NDA/DRUG CLASS:	50-756/4S
NAME OF DRUG:	——— (clindamycin 1% & Benzoyl Peroxide 5%) Topical Gel
APPLICANT:	Dermik Laboratories, Inc.
INDICATION(S):	Topical Treatment of Acne Vulgaris
TYPE OF REVIEW:	Clinical/Statistical
DOCUMENTS REVIEWED:	Two Controlled Studies: DL-6021-9103 & DL-6021-9623, Dated April 1998
MEDICAL REVIEWER:	Phyllis Huene, M.D./ HFD-540
STATISTICAL REVIEWER:	Shahla S. Farr, M.S./ HFD-725

I. INTRODUCTION

Clindamycin and Benzoyl Peroxide have individually been used in the treatment of acne vulgaris for over 25 years. The sponsor believes it would, therefore, be logical that a combination of benzoyl peroxide and Clindamycin (because of their combined antibacterial, oxidative, and other yet unidentified activity) has the potential for being of greater benefit than either of the individual agents alone in treating acne.

The sponsor has submitted three U.S. Phase III, randomized, multicenter, double-blind, controlled studies which consist of the combination of 1% Clindamycin (as phosphate) and 5% benzoyl peroxide in a gel vehicle used topically twice daily to treat patients with Grade II and Grade III acne vulgaris:

1) DL-6021-9103, comparing:
- Clindamycin -Benzoyl Peroxide bid, CB
- Clindamycin bid, C
- Benzoyl Peroxide bid, B
- Vehicle bid, V

2) DL-6021-9301 comparing:
- Clindamycin -Benzoyl Peroxide bid, CB
- Benzoyl Peroxide bid, B
- Benzamycin bid, BZ

3) DL-6021-9623 comparing:

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- Clindamycin -Benzoyl Peroxide bid, CB
- Clindamycin bid, C
- Benzoyl Peroxide bid, B
- Vehicle bid, V

Of these, the two four arm, vehicle controlled trials (DL-6021-9103 & DL-6021-9623) are the focus of this review. Table I lists these pivotal studies:

Table I
Summary of the Pivotal Study

Study # (# of Centers)	Study Design, Duration	Treatment Arm (n)	N	Endpoint
DL-6021-9103 (4)	Controlled, Double-Blind & Multicenter (10 Weeks)	1) Clindamycin-Benzoyl Peroxide CB, (120) 2) Benzoyl Peroxide B, (120) 3) Clindamycin C, (120) 4) Vehicle V, (120)	480	1) Percent Decrease in: - Inflammatory - Total Lesion Count 2) Investigators' Global
DL-6021-9623	Controlled, Double-Blind & Multicenter (10 Weeks)	1) Clindamycin-Benzoyl Peroxide CB, (95) 2) Benzoyl Peroxide B, (95) 3) Clindamycin C, (49) 4) Vehicle V, (48)	287	1) Percent Decrease in: - Inflammatory - Total Lesion Count 2) Investigators' Global

II. REVIEW

Objective & Design:

The two studies were similar in their study objective and the study design. The objective of this submission was to determine the safety and superiority of the combination of benzoyl peroxide and Clindamycin to its individual components alone and vehicle in the treatment of acne vulgaris.

These were controlled, randomized, multicenter, double-blind, parallel comparative studies of the effectiveness of benzoyl peroxide-Clindamycin combination CB, benzoyl peroxide B, Clindamycin C, and vehicle V in the treatment of patients with acne for 10 weeks. Patients were evaluated at Weeks 0, 2, 4, 6, 8 and 10.

Patient Population, Primary Endpoint Variables, Sample Size & Statistical Methods:

Some discrepancies were observed in regards to the patient population (entry criteria), primary endpoint variables and the sample size calculations of the studies.

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The entry criteria for both studies include males and females between 13 to 30 years of age with moderate or moderately severe acne (Grade II or III acne, by Pillsbury classification). Both studies were to enroll subjects with a minimum of 10 and maximum of 100 comedones. However, the range for the number of inflammatory lesions were different in the two studies. In study DL-6021-9103, patients with a minimum of 10 and maximum of **50** inflammatory lesions were allowed into the study. But, in study DL-6021-9623, subjects with a minimum of 10 and maximum of **80** inflammatory lesions were enrolled.

The requirements by the Division of Dermatological and Dental Products for the range of the inflammatory and noninflammatory lesion entry criteria has changed since these trials were conducted. The ranges now are: 20 to 100 for comedones and 20 to 65 for inflammatory lesions (papules or pustules) and no more than 5 nodules.

The primary efficacy measures in study DL-6021-9103 were: Change from baseline in the number of inflammatory lesions and in the total number of lesions (total number of lesions are the sum of the inflammatory and comedones) and the physician and patient overall improvement ratings. But, in study DL-6021-9623, the primary measures of treatment efficacy were inflammatory lesions (reduction from baseline) and endpoint physician global evaluations. The comedones and total lesion reductions from baseline were considered as the secondary efficacy variables.

In this review, the primary endpoint variables under consideration are the Mean Percent Change from Baseline in:
1) Total Inflammatory Lesion Count
2) Total Non-Inflammatory Lesion Count
3) Total Lesion Count (sum of the inflammatory and noninflammatory lesions), and
4) Investigators' Global Assessment

Statistically significant difference in two of three lesion count parameters (Inflammatory, Non-Inflammatory and total lesion count) is acceptable by the agency.

The sample sizes were different in the two studies. Four hundred and eighty subjects participated in study DL-6021-9103, however, only 287 patients were enrolled in study DL-6021-9623.

The method of sample size calculation was not mentioned in this submission. It is not clear to this reviewer the basis and requirements for the samples size calculations that were considered by the sponsor.

Analysis of variance and analysis of covariance were used to analyze the data in both of the studies. In this review, baseline categorical demographic variables (race and sex) are analyzed using Cochran-Mantel-Haenszel (CMH) test, controlling for center. Continuous demographic

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variables (age, weight) are analyzed using two-way analysis of variance (ANOVA), with center interaction. An analysis of variance is also performed on the mean percent change from baseline on the lesion counts and the Week-10 Physicians' Global Assessment, with and with center interaction. In addition, the dichotomized version of the Global Assessment is analyzed using CMH test.

Since these are superiority trials, the results of this review are based on the Intent-to-Treat (ITT) population, where ITT includes all subjects who were randomized to the study and were given the study medication, regardless of their use of the dispensed drug. For subjects with no week 10 data available, their baseline observation data was carried forward.

In order to demonstrate efficacy, the sponsor should show statistical superiority of Clindamycin-Benzoyl Peroxide gel to its vehicle and to each of the individual components in the objective primary endpoint variables (percent reduction of lesion counts), in addition to the investigators' global assessment at a two-sided alpha=0.05.

Study DL-6021-9103:

Demographics:

A total of 480 subjects from four centers were randomized to participate in this study, 120 subjects in each arm. A total of 43 subjects did not finish the study. Of these, 8 were in CB arm, 11 in B, 14 in C and 10 in the Vehicle group.

It was observed that a total of thirteen subjects were entered into the study with non-inflammatory lesions of less than 10 (outside the range for the entry criteria). All these subjects were from investigator Ellis and five had been randomized to CB treatment arm. In addition, eight subjects were allowed in the study with inflammatory lesions of more than 50. Of these subjects 3 were from investigator Ellis, four were from investigator Dunlap and one from center Burger. Five of these subjects were randomized to CB treatment group.

Table II summarizes the demographics of these subjects.

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Table II
Demographics of All Randomized Subjects
Study DL-6021-9103

	Whole Population (N=480)	CB (n=120)	B (n=120)	C (n=120)	Vehicle (n=120	P-Value
Gender (n):						0.8
Female	258 (54%)	68 (57%)	62 (52%)	56 (47%)	72 (60%)	
Male	222 (46%)	52 (43%)	58 (48%)	64 (53%)	48 (40%)	
Race (n):						0.1
White	438 (91%)	112 (93%)	110 (92%)	111 (93.5%)	105 (85.5%)	
Black	42 (9%)	8 (7%)	10 (8%)	9 (7.5%)	15 (12.5%)	
Age (Mean ± Std):	19 ± 4.3	19 ± 4.1	19 ± 4.3	19 ± 4.1	19 ± 4.5	0.5
Weight (Mean ± Std):	145 ± 31.7	147 ± 34.3	146 ± 31.9	146 ± 30.9	140 ± 29.5	0.3
Investigator (n):						1.00
Burger=11	30 (25%)	30 (25%)	30 (25%)	30 (25%)	30 (25%)	
Dunlap=30	30 (25%)	30 (25%)	30 (25%)	30 (25%)	30 (25%)	
Ellis=8	30 (25%)	30 (25%)	30 (25%)	30 (25%)	30 (25%)	
Leyden=16	30 (25%)	30 (25%)	30 (25%)	30 (25%)	30 (25%)	

-Clindamycin-Benzoyl Peroxide CB -Clindamycin C -Benzoyl Peroxide B -Vehicle V

As it is shown in Table II, no statistical differences were found among the four treatment groups in regards to the demographics of the subjects ($p>0.05$).

Clinical Efficacy Analysis & Results:

Table III illustrate the baseline and Week-10 values, as well as the change from baseline at Week-10 and the percent change from baseline at Week-10 for the primary endpoint variables for each treatment arm with center interaction.

At the last visit, both the physician and patient rated the patients's change from baseline on a 5 point scale: (0=Worse to 4=Excellent).

In addition to the analysis of the mean in the Physicians' Global Assessment at the end of treatment, this parameter was examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, if a subject's signs and symptoms are "Excellent", they are considered "Cured" (Success) and the rest are classified as "Not Cured" (Failure).

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Table III
Mean ± SD &P-Values for
Baseline, Week-10, the Difference & Percent Difference
for the Primary Endpoint Variables
(With Center Adjustment)
Study DL-6021-9103

	CB (n=120)	B (n=120)	C (n=120)	Vehicle (n=120)	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
Inflammatory:								
Baseline	21 ± 12	19 ± 8	21 ± 9	19 ± 8	0.1			
Week-10	11 ± 7	14 ± 9	18 ± 12	20 ± 11	0.001	**0.051**	0.001	0.001
Difference	10 ± 9	6 ± 6	3 ± 10	-0.4 ± 8	0.001	0.001	0.001	0.001
Percent Difference	43% ± 30%	29% ± 28%	14% ± 42%	-3% ± 4%	0.001	0.002	0.001	0.001
Non-Inflammatory:								
Baseline	27 ± 20	30 ± 23	29 ± 21	28 ± 20	0.6			
Week-10	20 ± 16	23 ± 20	26 ± 22	26 ± 19	0.007	**0.17**	0.002	0.005
Difference	7 ± 13	7 ± 13	2 ± 10	2 ± 9	0.001	**0.8**	0.001	0.001
Percent Difference	20% ± 36%	20% ± 25%	8% ± 33%	0.9% ± 33%	0.001	**0.96**	0.003	0.001
Total Lesion Count:								
Baseline	48 ± 28	49 ± 27	50 ± 25	47 ± 23	0.6			
Week-10	31 ± 20	37 ± 25	45 ± 30	46 ± 23	0.001	**0.053**	0.001	0.005
Difference	17 ± 19	13 ± 16	5 ± 15	1 ± 13	0.001	0.03	0.001	0.001
Percent Difference	33% ± 22%	26% ± 21%	13% ± 28%	0.2% ± 27%	0.001	0.01	0.001	0.001
Physicians' Global:					0.001	0.009	0.001	0.001
Cured	30 (27%)	14 (13%)	4 (4%)	1 (1%)				
Not Cured	82 (73%)	95 (87%)	102 (96%)	109 (99%)				

-Clindamycin-Benzoyl Peroxide CB -Clindamycin C -Benzoyl Peroxide B -Vehicle V

As it is seen in Table III, no statistical difference was found among the four arms in regards to the baseline characteristics of the subjects ($p>0.05$).

Highly statistically significant results ($p<0.05$) were observed when ——— was compared to its comparators and the vehicle arms (overall) in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

Comparisons between CB vs. C and CB vs. V arms also showed highly statistically significant results ($p<0.01$) in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

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However, when CB was compared to B, no statistically significant results were observed in regards to Non-Inflammatory Lesions ($p>0.1$); and only borderline significant results were achieved for Week-10 Inflammatory ($p=0.051$) and Total Lesion count ($p=0.053$).

Table IV illustrates the results of the mean ± sd for physician global Assessment @ week-10, the proportions & p-values for the secondary endpoint variables for each treatment arm with the center interaction.

Table IV
Mean ± SD for Physician Global @ Week-10,
The Proportions & P-Values
for the Secondary Endpoint Variables
(With Center Adjustment)
Study DL-6021-9103

	CB	B	C	Vehicle	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
Investigators' Global @Week-10	2.83 ± 0.98	2.25 ± 1	1.75 ± 1	1.15 ± 1	0.001	0.001	0.001	0.001
ects' Global.:					0.001	0.001	0.004	0.001
orse	0 (0%)	2 (2%)	2 (2%)	17 (15%)				
No Change	9 (8%)	19 (17%)	17 (16%)	26 (24%)				
Slight Improve	38 (34%)	46 (42%)	43 (41%)	45 (41%)				
Moderate Imp.	42 (38%)	34 (31%)	30 (28%)	22 (20%)				
Excellent Imp.	23 (21%)	8 (7%)	14 (13%)	0 (0%)				
Grade of Acne					0.001	0.006	0.001	0.001
I	41 (34%)	28 (23%)	15 (12.5%)	9 (8%)				
II	74 (62%)	78 (65%)	87 (72.5%)	89 (74%)				
III	5 (4%)	14 (12%)	18 (15%)	22 (18%)				
Erythema:					0.9	0.3	0.6	0.7
None	77 (64%)	84 (70%)	77 (64%)	77 (64%)				
Mild	39 (33%)	31 (26%)	42 (35%)	42 (35%)				
Moderate	4 (3%)	5 (4%)	1 (1%)	0 (0%)				
Severe	0 (0%)	0 (0%)	0 (0%)	1 (1%)				
Oiliness:					0.6	0.3	0.2	0.4
None	85 (71%)	80 (67%)	80 (67%)	81 (68%)				
Mild	5 (4%)	11 (9%)	11 (9%)	10 (8%)				
Moderate	29 (24%)	26 (22%)	26 (22%)	28 (23%)				
Severe	1 (1%)	3 (3%)	3 (3%)	1 (1%)				
Peeling:					0.6	0.08	0.3	0.5
None	110 (92%)	116 (97%)	115 (96%)	112 (93%)				
Mild	9 (8%)	4 (3%)	4 (3%)	8 (7%)				
Moderate	1 (1%)	0 (0%)	1 (1%)	0 (0%)				

-Clindamycin-Benzoyl Peroxide CB -Clindamycin C -Benzoyl Peroxide B -Vehicle V

As it is represented in Table IV, ——— gel showed superiority to its individual components and to its vehicle in regards to Physicians' Global, Subjects' Global Assessment and Grade of

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acne at Week-10 ($p<0.05$). No statistically significant results were observed at Week-10 among the treatment groups in regards to Erythema, Oiliness and Peeling ($p>0.05$).

Conclusions:

Based on the results of study DL-6021-9103, ——— demonstrated statistical superiority to its individual components and the vehicle arms (overall $p<0.01$) in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

In addition, comparisons between CB vs. C and CB vs. V arms showed highly statistically significant results ($p<0.01$) in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

However, when CB was compared to B, no statistically significant results were observed in regards to Non-Inflammatory Lesions; and only borderline significant results were achieved for Week-10 Inflammatory ($p=0.051$) and Total Lesion count ($p=0.053$).

Study DL-6021-9623:

Demographics:

A total of 287 subjects from five centers were randomized to participate in this study. Ninety five subjects were enrolled in CB and C arms each and 49 and 48 subjects were randomized into C and Vehicle arms respectively. A total of 19 subjects did not finish the study. Of these, 4 were in CB arm, 10 in B, 3 in C and 2 in the Vehicle group.

It was observed that one subject was enrolled into the study with non-inflammatory lesion count of less than 10 (outside the range for the entry criteria). No subject was entered into the study outside the range for inflammatory lesions for this study (10-80).

Table V summarizes the demographics of these subjects.

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Table V
Demographics of All Randomized Subjects
Study DL-6021-9623

	Whole Population (N=287)	CB (n=95)	B (n=95)	C (n=49)	Vehicle (n=48	P-Value
Gender (n):						0.9
Female	143 (50%)	44 (46%)	52 (55%)	25 (51%)	22 (46%)	
Male	144 (50%)	51 (54%)	43 (45%)	24 (49%)	26 (54%)	
Race (n):						0.2
White	216(75%)	74 (78%)	71 (75%)	37 (76%)	34 (71%)	
Black	24 (8%)	9 (9%)	8 (8%)	3 (6%)	4 (8%)	
Hispanic	42 (15%)	10 (11%)	15 (16%)	8 (16%)	9 (19%)	
Asian	2 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
Other	3 (1%)	1 (1%)	0 (0%)	1 (2%)	1 (2%)	
Age (Mean ± Std):	19 ± 4.5	19 ± 4.4	19 ± 4.7	19 ± 4.3	19 ± 4.6	0.6
Weight (Mean ± Std):	152 ± 32	156 ± 33	150 ± 31	147 ± 31	152 ± 34	0.4
Investigator (n):						1.0
Jones	60 (21%)	20 (21%)	20 (21%)	10 (20%)	10 (20%)	
Katz	60 (21%)	20 (21%)	20 (21%)	10 (20%)	10 (20%)	
Kraus	60 (21%)	20 (21%)	20 (21%)	10 (20%)	10 (20%)	
Monroe	52 (18%)	17 (18%)	17 (18%)	9 (18%)	9 (18%)	
Tschen	55 (19%)	18 (19%)	18 (19%)	10 (20%)	10 (20%)	

- Clindamycin -Benzoyl Peroxide CB - Clindamycin C - Benzoyl Peroxide B - Vehicle V

As it is shown in Table V, no statistical differences were found among the four treatment groups in regards to the demographics of the subjects ($p>0.05$).

Clinical Efficacy Analysis & Results:

Table VI illustrates the baseline and Week-10 values, as well as the change from baseline at Week-10 and the percent change from baseline at Week-10 for the primary endpoint variables for each treatment arm with center interaction.

The Physician's Global Improvement Score, from baseline, ranging from -5 to 5 was recorded: (-5=Disease Exacerbation to 5=Clear).

In addition to the analysis of the mean at the end of treatment in the Physicians' Global Assessment, this parameter was examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, if a subject's signs and symptoms were rated as "Clear=100% Clearance" or "Excellent Improvement=75%-99% Improvement", they were considered "Cured" (Success) and the rest were classified as "Not Cured" (Failure).

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Baseline, Week-10, the Difference & Percent Difference for the Primary Endpoint Variables
(With Center Adjustment)
Study DL-6021-9623

	CB (n=95)	B (n=95)	C (n=49)	Vehicle (n=48)	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
Inflammatory:								
Baseline	25 ± 16	23 ± 12	26 ± 14	27 ± 14	0.2			
Week-10	9 ± 8	12 ± 10	13 ± 8	16 ± 14	0.001	0.048	0.02	0.001
Difference	16 ± 15	11 ± 10	13 ± 14	11 ± 12	0.003	0.001	**0.06**	0.004
Percent Difference	60% ± 30%	49% ± 35%	42% ± 42%	42% ± 36%	0.001	0.01	0.001	0.001
Non-Inflammatory:								
Baseline	39 ± 25	41 ± 25	40 ± 23	39 ± 22	0.9			
Week-10	18 ± 19	23 ± 23	27 ± 26	27 ± 20	0.045	**0.09**	0.02	0.02
Difference	21 ± 22	18 ± 19	13 ± 18	12 ± 13	0.005	**0.2**	0.005	0.002
Percent Difference	51% ± 35%	45% ± 37%	36% ± 38%	33% ± 28%	0.003	**0.2**	0.008	0.001
Total Lesion Count:								
Baseline	65 ± 35	64 ± 30	66 ± 30	66 ± 27	0.9			
Week-10	27 ± 25	35 ± 30	40 ± 30	43 ± 28	0.004	0.04	0.008	0.001
Difference	37 ± 32	29 ± 25	26 ± 30	23 ± 17	0.001	0.008	0.003	0.001
Percent Difference	55% ± 31%	47% ± 32%	39% ± 36%	37% ± 25%	0.001	0.03	0.001	0.001
Physicians' Global:					0.001	**0.5**	0.02	0.001
Cured	41 (45%)	34 (40%)	12 (26%)	7 (15%)				
Not Cured	50 (55%)	51 (60%)	34 (73%)	39 (85%)				

- Clindamycin -Benzoyl Peroxide CB - Clindamycin C - Benzoyl Peroxide B - Vehicle V

As it is seen in Table VI, no statistical difference was found among the four arms in regards to the baseline characteristics of the subjects ($p>0.05$).

Statistically significant results (overall $p<0.05$) were observed when ——— was compared to its comparators and the vehicle arms in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences form baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

Comparisons between CB vs. C and CB vs. V arms also showed statistically significant results in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline (comparison between CB vs. C showed only a borderline significance in the difference from baseline in regards to Inflammatory lesion count, $p=0.06$) and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10, ($p<0.05$). However, when CB was compared to B, no statistically significant results were observed in regards to Non-Inflammatory Lesions and the Investigators' Global Assessment ($p>0.05$).

Table VII illustrates the results of the mean ± sd for physician global assessment,

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However, when CB was compared to B, no statistically significant results were observed in regards to Non-Inflammatory Le.ions and the Investigators' Global Assessment ($p>0.05$).

Table VII illustrates the results of the mean ± sd for physician global assessment, the proportions & p-values for the secondary endpoint variables for each treatment arm with the center interaction.

Table VII
Mean ± SD for Physician Global Assessment,
The Proportions & P-Values
for the Secondary Endpoint Variables
(With Center Adjustment)
Study DL-6021-9623

	CB	B	C	Vehicle	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
Investigators' Global @Week-10	2.9 ± 1.3	2.8 ± 1.4	2 ± 1.6	2 ± 1.3	0.001	0.4	0.001	0.001
Subjects' Global.:					0.001	0.5	0.02	0.001
th Worse	0 (0%)	0 (0%)	1 (2%)	0 (0%)				
se	0 (0%)	1 (1%)	0 (0%)	0 (0%)				
Somewhat Worse	2 (2%)	3 (4%)	1 (2%)	6 (13%)				
No Change	6 (7%)	8 (9%)	7 (15%)	9 (20%)				
Somewhat Better	24 (26%)	14 (16%)	11 (24%)	12 (26%)				
Better	27 (30%)	36 (42%)	19 (41%)	15 (33%)				
Much Better	32 (35%)	23 (27%)	7 (15%)	4 (9%)				
Erythema:					0.3	0.9	0.7	0.3
None	44 (46%)	43 (45%)	23 (47%)	22 (46%)				
Mild	35 (37%)	39 (41%)	19 (39%)	17 (35%)				
Moderate	16 (17%)	11 (12%)	5 (10%)	7 (15%)				
Severe	0 (0%)	2 (2%)	2 (4%)	2 (4%)				
Oiliness:					0.4	1.0	0.7	0.5
None	45 (47%)	49 (52%)	25 (51%)	22 (46%)				
Mild	39 (41%)	32 (34%)	17 (35%)	18 (38%)				
Moderate	10 (11%)	14 (15%)	6 (12%)	8 (17%)				
Severe	1 (1%)	0 (0%)	1 (2%)	0 (0%)				
Peeling:					0.07	0.1	0.08	0.2
None	51 (54%)	54 (57%)	33 (67%)	29 (60%)				
Mild	39 (41%)	40 (42%)	15 (31%)	18 (38%)				
Moderate	4 (4%)	1 (1%)	1 (2%)	1 (2%)				
Severe	1 (1%)	0 (0%)	0 (0%)	0 (0%)				

- Clindamycin -Benzoyl Peroxide CB - Clindamycin C - Benzoyl Peroxide B - Vehicle V

As it is represented in Table VII, ——— gel showed superiority to C and to its vehicle ($p<0.05$), but no statistically significant difference between CB vs. B in regards to Physicians' Global and Subjects' Global Assessment at Week-10 ($p>0.05$) was observed. No statistically

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significant results were observed at Week-10 between the treatment groups in regards to Erythema, Oiliness and Peeling (p>0.05).

Conclusions:

Statistically significant results (p<0.05) were observed when ——— was compared to its comparators and the vehicle arms (overall) in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10.

Comparisons between CB vs. C and CB vs. V arms also showed statistically significant results in regards to the Inflammatory, Non-Inflammatory and Total Lesions counts at Week-10, their differences from baseline (comparison between CB vs. C showed only a borderline significance in the difference from baseline in regards to Inflammatory lesion count, p=0.06) and their percent decrease from baseline, as well as the Investigators' Global Assessment at Week-10, (p<0.05).

However, when CB was compared to B, no statistically significant results were observed in regards to Non-Inflammatory Lesions and the Investigators' Global Assessment (p>0.05).

Subset Analysis:

Since the entry criteria for both the studies include subjects between the ages of 13 and 30, no subset analysis based on age was reasonable. Table VIII shows the P-Values for the analysis of the primary endpoint variables for males and females separately.

Table VIII
Gender Subset Analysis
% Change from Baseline for all Lesions (LSMeans±Std. Err.),
Investigator's Global Assessment (Rates)
& P-Values
(Females)
Both Studies Combined

Primary Endpoint Variables	CB	B	C	V	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
% Change from Baseline in:								
Inflammatory Lesions	-0.55±0.03	-0.39±0.03	-0.26±0.04	-0.27±0.05	0.001	0.001	0.001	0.001
Non-Inflammatory Lesions	-0.42±0.03	-0.36±0.03	-0.18±0.04	-0.21±0.05	0.001	**0.2**	0.001	0.001
Total Lesions	-0.49±0.03	-0.39±0.03	-0.23±0.03	-0.25±0.035	0.001	0.004	0.001	0.001
Investigator's Global					0.001	**0.09**	0.001	0.001
Cured	35 (34%)	26 (26%)	8 (11%)	3 (4%)				
Not-Cured	69 (66%)	73 (74%)	63 (89%)	81 (96%)				

- Clindamycin -Benzoyl Peroxide CB - Clindamycin C - Benzoyl Peroxide B - Vehicle V

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As it can be seen in Table VIII, in the female population, when CB was compared to B, statistical significance was found in regards to the Inflammatory and Total Lesion counts ($p<0.05$). No statistically significant results were found in regards to the Non-Inflammatory Lesions and the Investigator's Global Assessment among females ($p>0.05$).

Table IX
Gender Subset Analysis
% Change from Baseline for all Lesions (LSMeans±Std. Err.),
Investigator's Global Assessment (Rates)
& P-Values
(Males)
Both Studies Combined

Primary Endpoint Variables	CB	B	C	V	P-Value			
					Overall	CB vs. B	CB vs. C	CB vs. V
% Change from Baseline in:								
Inflammatory Lesions	-0.51±0.03	-0.42±0.036	-0.33±0.04	-0.17±0.04	0.001	**0.06**	0.001	0.001
Non-Inflammatory Lesions	-0.36±0.03	-0.33±0.03	-0.29±0.04	-0.17±0.04	0.002	**0.05**	**0.16**	0.001
Total Lesions	-0.44±0.03	-0.37±0.03	-0.31±0.04	-0.18±0.03	0.001	**0.07**	0.003	0.001
Investigator's Global					0.001	**0.14**	0.001	0.001
Cured	36 (36%)	22 (23%)	8 (10%)	5 (7%)				
Not-Cured	63 (64%)	73 (77%)	73 (90%)	67 (93%)				

- Clindamycin -Benzoyl Peroxide CB - Clindamycin C - Benzoyl Peroxide B - Vehicle V

No statistical significance was observed in any of the primary endpoint variables in the male population ($p \geq 0.05$) in the comparison of the CB arm to B.

III. CONCLUSION:

The results of the studies DL-6021-9103 and DL-6021-9623 indicate the superiority of ——— over the Clindamycin and vehicle in regards to percent change from baseline to Week-10 for Inflammatory, Non-Inflammatory and Total Lesion Counts ($p \leq 0.001$). Neither study supports the superiority of ——— to Benzoyl Peroxide in regards to Non-Inflammatory Lesions. Study DL-6021-9103 showed statistically significant difference in the Investigators' Global Assessment at Week-10. However, study DL-6021-9623 did not show a statistically significance difference in regards to this endpoint.

In regards to the secondary endpoint variables, in both studies, ——— gel showed superiority to Clindamycin and to its vehicle ($p<0.05$). In study DL-6021-9103, statistical significance was also observed in both Physician and Patients' Global Assessments when ——— gel was compared to Benzoyl Peroxide ($p<0.05$). But, no statistically significant difference between ——— gel vs. Benzoyl Peroxide in regards to Physicians' Global and Subjects' Global Assessment at Week-10 ($p>0.05$) was observed in study DL-6021-9623.

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Both studies showed no statistically significant results at Week-10 between the treatment groups in regards to Erythema, Oiliness and Peeling ($p>0.05$).

The analysis of subgroups revealed that in general, females showed better results than the male population in the analysis of the primary endpoint parameters. When ——— gel was compared to Benzoyl Peroxide, statistical significance was found in regards to the Inflammatory and Total Lesion counts ($p<0.05$). No statistically significant results were found in regards to the Non-Inflammatory Lesions and the Investigator's Global Assessment among females ($p>0.05$). No statistical significance was observed in any of the primary endpoint variables in the male population ($p\geq 0.05$) in the comparison of the ——— gel arm to Benzoyl Peroxide.

According to the reviewing medical officer, the data presented by the sponsor did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Based on results presented in this review:
1) ——— demonstrated statistical superiority over the Clindamycin and vehicle in regards to percent change from baseline at Week-10 for Inflammatory, Non-Inflammatory and Total Lesion Counts ($p\leq 0.001$).

2) Neither study supports the statistical superiority of ——— to Benzoyl Peroxide in regards to Non-Inflammatory Lesions. Study DL-6021-9103 showed statistically significant difference in the Investigators' Global Assessment at Week-10. However, study DL-6021-9623 did not show a statistically significance difference in regards to this endpoint.

/S/ 11/17/98

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