CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

MEDICAL REVIEW(S)

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 50-756

SPONSOR: Dermik Laboratories

NOV 19 2000

DRUG: BenzaClin

CLINICAL INDICATION: Acne vulgaris

REASON FOR ADDENDUM: Labeling for pediatric use

It is felt that the pediatric labeling is adequate for pediatric patients aged 12 and older. Appropriate information has been submitted in this application and has been adequately summarized in the labeling to permit satisfactory labeling in these pediatric groups. No further information is required.

APPEARS THIS WAY ON ORIGINAL

/S/

Phyllis A. Huene, M.D.

Cc: Orig NDA 50-756
HFD-540 Division files
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/White
HFD-540/Farr

11/15/00

/S/ 11/15/00

/S/ 11/19/00

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last in DFS 11/15/00

Not in DFS 11/19/00

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HFD Trac No: 006164
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Correspondence date: 7/7/00
CDER Stamp date: 7/7/00

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 50-756
ORIGINAL SUBMISSION

October 16, 2000

SPONSOR: Dermik Laboratories

DRUG: ——— Topical Gel

INDICATION: Acne

OCT 26 2000

DATE OF ORIGINAL SUBMISSION: April 9, 1998

DATE OF AMENDMENT: July 7, 2000

REASON FOR AMENDMENT: Safety Update

This submission provides a Safety Update Report on BenzaClin Topical Gel, covering the period from 10/20/98 to the present. Three Phase 1 studies have been performed during this time, which are summarized as follows.

1. Study DL 6021-9902: This was an open label, single center study of BenzaClin vs Cleocin T formulations in the reduction of *P. acnes* in 80 subjects. Applications were made BID for 2 weeks. There were no drug-related adverse events.

2. Study DL-6021-9904: This was a primary irritation study on 27 subjects, which utilized repeat insult patch tests with BenzaClin for 10 consecutive days. Minor irritation was found in the majority of subjects, but no other adverse reactions were reported.

2. Study DL-6021-9903: This was a primary irritation study on 27 subjects, which utilized the same design as the preceding study. Minor irritation was found in the majority of subjects, but no other adverse reactions were reported.

Reviewer's evaluation: This Safety Update reports no adverse events with BenzaClin Gel that would alter the safety profile previously provided.

/S/

Phyllis A. Huene, M.D.

10/16/00

Cc: Orig NDA 50-765
Division Files
HFD-540/Wilkin
HFD-540/Huene
HFD-540/Walker
HFD-540/White
HFD-540/DeCamp
HFD-540/Jacobs

/S/ 10/19/00

/S/ 10/24/00

n50756.su

In DFS 10/16/00

No DFS on 10/27/00

MAR 16 1999

HFD-540 Trac No: 980789

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 50-756

March 1, 1999

SPONSOR: Dermik Laboratories
Collegeville, PA

DRUG: BenzaClin Topical Gel

INDICATION: Acne

REASON FOR ADDENDUM: Revision of the labeling review

In accordance with the provision of additional data by the sponsor, and with the discussion at the labeling meeting of 3/1/99 for NDA 50-756, the following changes are recommended in the labeling for BenzaClin.

1. The tabulation of the results of the clinical studies in the CLINICAL STUDIES section should be as follows.

Mean percent reduction in inflammatory lesion counts				
	BenzaClin	Benzoyl peroxide	Clindamycin	Vehicle
Study 1	-46%	-32%	-16%	+ 3%
Study 2	-63%	-53%	-45%	-42%
Mean percent reduction in non-inflammatory lesion counts				
Study 1	-22%	-22%	-9%	+1%
Study 2	-54%	-50%	-39%	-36%
Mean percent reduction in total lesion counts				
Study 1	-36%	-28%	-15%	-0.2%
Study 2	-58%	-52%	-42%	-39%

Shahla Farr concurs with the tabulation of the results of the clinical studies.

2. The tabulation of the adverse events in the ADVERSE EVENTS section should be as follows:

Local Adverse Events - all causalities in >/= 1% of patients n = 420		
	BenzaClin	Vehicle
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

It is recommended that in the fourth sentence under ADVERSE EVENTS the word 'local' be added, to read "The table below lists local adverse events ______ .... ".

/S/

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Phyllis A. Huene, M.D. 3/1/99

/S/ 3/1/99

Concurrence: Shahla Farr

See attached TL Review

/S/ 3/15/99

Recommend that label not show (-) sign.

Cc: Orig NDA 50-756
HFD-540 Division files
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/White
HFD-540/Farr
n50756.add

As above and TL Team Leader review.

/S/ 3/16/99

NDA 50-756 Team Leader Addendum to Clinical Review March 5, 1999

SPONSOR: Dermik Laboratories, Collegeville, PA

DRUG: BenzaClin Topical Gel

INDICATION: Acne Vulgaris

REASON FOR ADDENDUM: Revision of labeling review

The tabulation of local adverse events includes nine patients on the active drug who are coded as experiencing

The sponsor was asked to send Case Report Forms and a clinical summary for each case. On March 3, 1999 the sponsor submitted a facsimile which describes all patients in the trial who were coded as experiencing . Three patients used clindamycin, one patient used erythromycin-benzoyl peroxide, and 9 patients used the test product clindamycin-benzoyl peroxide. Although all these patients were coded with the COSTART term , the adverse events were listed as mild to moderate and the descriptions included "facial skin peeling", "peeling", "scaling and erythema", and "scaling and dryness". The duration of the adverse events ranged from one day to eighty seven days, with the majority lasting less than 15 days. All patients except the erythromycin-benzoyl peroxide patient finished the study.

After review of the sponsor's information, it is apparent that these patients did not experience true It would be more appropriate to categorize these patients under the term "peeling".

/S/ 3/5/99

Susan J. Walker, M.D.
Medical Team Leader, Dermatology

Cc: Orig NDA 50-756
HFD-540 Division File
HFD-540/Wilkin/Walker/Huene
HFD-540/Cross

/S/ 3/12/99

HFD-540 Trac No: 980789

FEB 25 1999

MEDICAL OFFICER'S REVIEW OF NDA 50-756
ORIGINAL SUBMISSION

December 29, 1998

SPONSOR: Dermik Laboratories
Collegeville, PA

DRUG: ——— Topical Gel

ACTIVE INGREDIENTS: Clindamycin 1%/benzoyl peroxide 5%

FORMULATION: ——— Topical Gel will be distributed to pharmacies in a carton containing a jar of benzoyl peroxide gel labeled ——— Topical Gel, and a vial of clindamycin powder labeled ——— Prior to dispensing to patients, water will be added to the ——— vial by the pharmacist, and this will then be added to the jar. After mixing, the product will then be dispensed to the patient in the jar labeled ——— Topical Gel.

The formulation as dispensed to the patient is as follows.

	Mg/gm
Clindamycin (as clindamycin phosphate)	—
——— benzoyl peroxide —	—
Carbomer —	—
Sodium hydroxide	—
Dioctyl sodium sulfosuccinate	—
Purified water	—

INDICATION: Acne

Labeling indication: For the topical treatment of acne vulgaris.

DOSAGE AND ADMINISTRATION: Applications are to be made twice daily.

DATE OF SUBMISSION: April 9, 1998

RELATED SUBMISSIONS: IND ———

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

NDA 50-756
Topical Gel
Index to Medical Officer's review

Scientific rationale

The rationale for the use of this clindamycin/benzoyl peroxide combination product in acne is that both clindamycin and benzoyl peroxide are active against *P. acnes*, and benzoyl peroxide also has mild keratolytic and desquamative activity.

Various formulations of topical clindamycin phosphate 1% have been approved for the treatment of acne for over ten years, and topical benzoyl peroxide in formulations of from 2.5% to 10% have been marketed for the treatment of acne for over 25 years.

The sponsor states that antimicrobial resistance to topical therapy is becoming an important factor in the treatment of acne, and clinically an association between the presence of antibiotic resistant organisms and therapeutic failure has been made. They further state that it has been documented that clinical use of topical clindamycin may result in clindamycin-resistant *P. acnes*. In addition, erythromycin-resistant *P. acnes* may develop cross-resistance to clindamycin. Studies with Benzamycin (3% erythromycin/5% benzoyl peroxide) are stated to demonstrate that increased antibacterial resistance can be avoided by the concomitant use of benzoyl peroxide with erythromycin. Although the antibiotic resistance patterns with the use of topical 1% clindamycin/5% benzoyl peroxide have not been studied, a correlation may be made with Benzamycin.

Foreign marketing history

[redacted] Topical Gel is not marketed in any country, [redacted]. Neither the product nor any applications for the product have been withdrawn in any country.

Sponsor - FDA meetings

A pre-NDA meeting was held on July 29, 1996, at which the sponsor summarized the results of four Phase I studies and two Phase III studies as follows.

Phase I studies			
Study #	Study design	Treatment groups	N
KGL 2465	Primary irritation	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide Vehicle	25 25 25
KGL 2466	Contact sensitization	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide Vehicle	26 26 26
KGL 2467	Phototoxicity	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide Vehicle	10 10 10
KGL 2468	Photoallergy	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide Vehicle	25 25 25

Phase III studies		
Study #	Study design	Treatment groups
9103	Double blind, multicenter	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide 1% clindamycin Vehicle
9301	Double blind, multicenter	1% clindamycin/5% benzoyl peroxide 5% benzoyl peroxide Benzamycin (1% erythromycin/5% BP)

The agreements reached regarding the clinical portion of the NDA were as follows:

- An additional repeat insult patch test study is not needed.
- An additional Phase III study is needed. The study should be a four arm design comparing the combination product to benzoyl peroxide, clindamycin, and the vehicle. This was to be submitted for FDA review prior to study initiation.

Dermal safety studies

All the dermal safety studies were performed by _____

1. Irritation potential (Study #2465). A 21 day cumulative irritancy study was performed on 25 subjects; this compared benzoyl peroxide 5% and clindamycin phosphate 1% gel, benzoyl peroxide 5% gel, and the vehicle. Applications of 0.1 ml of the test products were made under occlusive patches to the same skin sites of the upper back once daily from Monday through Friday, with the Friday patch left in place over the weekend, for three weeks. At each patch removal irritant reactions were graded on the following scale:

0	=	no visible erythema
1	=	mild erythema
2	=	moderate erythema
3	=	intense erythema with edema
4	=	intense erythema with edema and vesicular erosion

If a test site developed an irritant reaction of grade 3 or more, applications were discontinued, and a score of 3 was carried through the rest of the test period.

The individual daily scores for each test product were added to provide a cumulative irritancy score for each subject. The total cumulative irritancy scores and the mean cumulative irritancy scores are as follows.

Total and mean cumulative irritancy scores

	Benzoyl peroxide	Benzoyl peroxide and clindamycin	Vehicle
Total score	648	525	381
Mean score	25.9	21.0	15.2

The individual scores were not provided, but it is stated that the irritation scores were generally high, and often reached a score of 3 or 4, which necessitated discontinuation of applications.

The conclusion was that both the combination product and benzoyl

peroxide alone have a high irritancy potential, as was expected, and are not designed for occlusive applications. In a comparison of mean cumulative irritation scores, the combination was found to be numerically less irritating than 5% benzoyl peroxide alone.

2. Contact sensitization (Study #2466). This was a maximization test performed on 25 subjects; the test products were benzoyl peroxide 5%/ clindamycin phosphate 1% gel, benzoyl peroxide 5% gel, and the vehicle.

In the induction phase, occlusive patches with 0.1 ml of sodium lauryl sulfate (SLS) were applied to sites on the upper arm for 24 hours. After 24 hours the SLS patches were removed, and 0.1 ml of each test material was applied under occlusive patches to the pre-treated sites. These remained in place for 48 hours during the week and for 72 hours over the weekend. If no irritation was found on removal of the patch, the procedure was repeated to the same skin site. This sequence was repeated for a total of 5 exposures. If irritation developed during the induction phase, the SLS pre-treatment patch was eliminated, and after a 24 hour rest period only the test material was applied to that site.

A 10 day rest period followed the induction phase. The subjects were then challenged with a single application of each of the test materials to a new skin site. Pre-treatment with SLS was performed prior to the challenge applications, using an occlusive patch left in place for one hour. The test materials were then applied under occlusive patches to the pre-treated sites, and these were left in place for 48 hours. The sites were graded for reactions at 1 and 24 hours after patch removal, using the following scale:

0	=	not sensitized
1	=	mild sensitization (erythema and a little edema)
2	=	moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)
3	=	strong sensitization (large vesiculo-bullous reaction)

The system used to classify the allergenic potential of the test materials was as follows:

Classification of sensitization potential		
Sensitization rate	Grade	Classification
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

Results were that at 72 hours after application of the challenge patches, 8 subjects had reactions that were strongly suggestive of contact sensitization to both the 5% benzoyl peroxide and to the 5% benzoyl peroxide - 1% clindamycin phosphate combination. The reactions ranged from 1+ to 3+, and were associated with pruritus in all subjects. There were no reactions to the vehicle.

The conclusion was that the 5% benzoyl peroxide gel and the 5% benzoyl peroxide/1% clindamycin gel were found to have a similar and moderate potential to induce delayed contact hypersensitivity. The investigator stated that this finding was consistent with his experience with other benzoyl peroxide preparations.

3. Phototoxicity (Study 2467). This study was performed on 10 subjects; the test products were benzoyl peroxide 5%/clindamycin phosphate 1% gel, benzoyl peroxide 5% gel, and the vehicle gel. Applications of 50 uL of the test agents were made to duplicate skin sites of the lower back under occlusion for 6 hours. One set of patches was then removed, and the sites were exposed to 20 Joules/cm^2 of UVA light. The other set of patches served as unirradiated controls. Reactions were graded immediately and at 24 and 48 hours after irradiation, using the following scale.

0	=	normal skin
1	=	minimal visible erythema
2	=	moderate deeper erythema with clear distinct margins
3	=	intense erythema and edema
4	=	vesicular or blistering reaction

Results were that no abnormal reactions were seen at any observation time. The conclusion was that the test agents do not have a detectable phototoxic potential under these test conditions.

4. Photosensitization (Study 2468). This study was performed on 25 subjects; the test products were benzoyl peroxide 5%/clindamycin phosphate 1% gel, benzoyl peroxide 5% gel, and the vehicle gel.

In the induction phase, applications of 10 ul/cm^2 of each test agent were made to skin sites of the lower back under occlusion for 24 hours. The patches were then removed and the sites were exposed to 3 MEDs of ultraviolet light from a xenon arc solar simulator. The sites were left open for 24 hours, and the procedure was then repeated. This sequence was repeated twice weekly for three weeks.

Challenge applications were made at 10 to 14 days following the last induction exposure. The test agents were applied as in the induction phase in duplicate to new skin sites for 24 hours. One site was then irradiated with 4 Joules/cm^2 of UVA, while the other set of patches served as unirradiated controls. Reactions were graded at 48 and 72 hours after application on the following scale.

0	=	not sensitized
1	=	mild sensitization (erythema and a little edema)
2	=	moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation
3	=	strong sensitization (large vesiculobullous reaction)

During the induction phase mild to moderate erythema, scaling and tanning were seen. There were no reactions suggestive of photosensitization in the challenge phase. The conclusion was that the test agents do not possess a detectable photosensitization potential.

Reviewer's evaluation: The dermal safety studies, consisting of cumulative irritation, contact sensitization, phototoxicity, and photosensitization studies, are felt to have been adequately designed and conducted. The results show that the combination product has a high irritancy potential in this assay, which was slightly less than that with benzoyl peroxide alone, a moderate potential for induction of contact sensitization, comparable to that with benzoyl peroxide alone, and no detectable potential for phototoxicity or photosensitization under these test conditions.

Pivotal clinical effectiveness studies

The pivotal and other clinical effectiveness studies are summarized in the following tabulation.

Pivotal clinical effectiveness studies				
Study #	Study design	Treatment regimen	Treatment groups	Total patients enrolled
DL-6021-9103	Double blind, multicenter, parallel group	BID x 10 weeks	5% Benzoyl peroxide-1% clindamycin	120
			5% benzoyl-peroxide	120
			1% clindamycin	120
			Vehicle	120
DL-6021-9623	Double blind, multicenter, parallel group	BID x 10 weeks	5% Benzoyl peroxide-1% clindamycin	95
			5% benzoyl peroxide	95
			1% clindamycin	49
			Vehicle	48
Other clinical studies				
DL-6021-9301	Double blind, multicenter, parallel group	BID x 10 weeks	5% Benzoyl peroxide-1% clindamycin	165
			5% benzoyl peroxide	164
			Benzamycin*	163
* Benzamycin - 5% benzoyl peroxide/3% erythromycin				

I Study DL-6021-9103

The investigators for this study were as follows.

Richard Berger, M.D. East Brunswick, NJ	Charles Ellis, M.D. Ann Arbor, Michigan
Frank Dunlap, M.D. Tucson, AZ	James Leyden, M.D. Broomall, PA

1) Study objective: This was to determine whether a combination of benzoyl peroxide and clindamycin is more effective than its individual components or vehicle in the treatment of acne.

2) Study design: This was a double blind, randomized, multicenter, parallel group comparison of benzoyl peroxide 5%-clindamycin 1% gel, benzoyl peroxide 5% gel, clindamycin 1% gel, and the vehicle gel, with a treatment duration of 10 weeks.

3) Selection criteria: Patients were enrolled into the study who were between 13 and 30 years of age, had moderate to moderately severe acne, of Grade II or III by the Pillsbury classification, and a minimum of 10 and a maximum of 50 inflammatory lesions, and a minimum of 10 and a maximum of 100 non-inflammatory lesions of the face.

4) Exclusion criteria: Patients were excluded from enrollment into the study for the following reasons.

   a. Sensitivity to any of the ingredients of the study medication.
   b. Fewer than 10 or more than 50 inflammatory lesions.
   c. Fewer than 10 or more than 100 comedones.
   d. Classification as Grade I or Grade IV acne.
   e. Treatment with systemic antibiotics within the four weeks prior to the study.
   f. Treatment with topical anti-acne medications within the two weeks prior to the study.
   g. Pregnancy or lactation.

5) Treatment regimen: Applications of the test products were made BID for 10 weeks.

The patients were instructed not to use any cleansers or washes on the affected areas except ——— soap. They were to wash the face and neck just prior to application of the medication. No concomitant acne medication or antibiotic was to be used during the study. If a moisturizer were required, ——————— lotion, supplied by the sponsor, was to be used.

6) Effectiveness parameters: Return visits were made every two weeks, at which times the following evaluations were performed.

a. Lesion counts for facial comedones, papules, and pustules.
b. Global evaluation of the change from baseline by the investigator and patient, graded on the following scale:

0 = worse
1 = no change
2 = slight improvement (not defined)
3 = moderate improvement (not defined)
4 = excellent improvement (not defined)

The sponsor considered the primary efficacy variables to be the mean change from baseline in the number of inflammatory lesions and total lesions, and the physician and patient rating of overall improvement. The scales for overall improvement were collapsed to a dichotomous variable by combining moderate and excellent improvement together as one outcome, and the other three categories as another outcome.

7) Safety evaluations: Any adverse experience which occurred during the study was to be reported to the investigator. In addition, the amount of oiliness, erythema, and peeling of the face was graded at each visit as none, mild, moderate, or severe.

Results were as follows.

1) Patient enrollment and demographic characteristics: 480 patients were enrolled into the study; of these, 120 patients were randomized to each of the four treatment groups. Nineteen patients did not return after the baseline visit.

The demographic and baseline disease characteristics of all patients enrolled were as follows.

Demographic and baseline disease characteristics				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Age (mean)	18.9	18.6	18.6	19.3
Gender				
Male	68 (57%)	62 (52%)	56 (47%)	72 (60%)
Female	52 (43%)	58 (49%)	64 (53%)	48 (40%)
Race				
Caucasian	112 (93%)	110 (92%)	111 (93%)	105 (88%)
NonCaucasian	8 (7%)	10 (8%)	9 (8%)	15 (13%)
Acne grade				
II	102 (85%)	100 (83%)	89 (74%)	104 (87%)
III	18 (15%)	20 (17%)	31 (26%)	16 (13%)
Lesion counts (mean)				
Inflammatory	21.1	19.4	21.2	19.2
Noninflammatory	27.4	29.9	28.9	27.6
Total	48.5	49.4	50.2	46.7

2) Patient disposition: The number of patients at each visit and the reasons for discontinuation were as follows.

# patients at each return visit				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	120	120	120	120
Week 2	113	116	116	116
Week 4	113	114	112	114
Week 6	113	112	111	112
Week 8	112	112	106	111
Week 10	112	109	106	110
Completion rate	93%	91%	88%	92%

Reasons for discontinuation				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Dropout	2	4	3	2
Concurrent medication	0	2	2	2
Missed 2 visits	3	2	6	2
Adverse reaction	1	2	1	1
Other	2	1	2	3
Total # patients	8	11	14	10

3) Effectiveness parameters.

Analyses were performed on the intent-to-treat population, defined as all study patients with a diagnosis of Grade II or III acne who received study medication. This included all 480 patients enrolled in the study.

a. Lesion counts.

The mean change from baseline, and the mean percent reduction from baseline in the non-inflammatory lesion counts, the inflammatory lesion counts, and the total lesion counts were as follows.

Mean change in non-inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	27.4	29.9	28.9	27.6
Week 2	- 2.91	- 2.93	- 0.09	0.50
Week 4	- 5.43	- 5.39	- 2.18	- 1.58
Week 6	- 6.49	- 4.73	- 0.65	- 0.53
Week 8	- 8.13	- 6.89	- 2.97	- 3.03
Week 10	- 8.00	- 7.76	- 2.79	- 1.72

P values Mean change in non-inflammatory lesion counts						
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
2	0.7067	0.0023	0.0005	0.0019	0.6520	0.0075
4	0.5000	0.0048	0.0008	0.0068	0.5765	0.0322
6	0.1798	0.0001	0.0000	0.0029	0.7557	0.0080
8	0.1811	0.0003	0.0002	0.0156	0.9035	0.0237
10	0.5604	0.0001	0.0000	0.0000	0.3989	0.0010

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

Mean percent reduction in non-inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Week 2	2.6	6.4	- 1.0	- 3.8
Week 4	14.0	15.4	5.1	1.7
Week 6	15.7	15.6	4.2	0.2
Week 8	21.5	20.5	8.5	5.8
Week 10	21.9	22.3	9.1	- 1.0

p values * Mean percent reduction in non-inflammatory lesion counts Endpoint		
CB vs B	CB vs C	CB vs V
0.96	0.003	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

Mean change in inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	21.0	19.4	21.2	19.2
Week 2	- 4.59	- 3.23	- 1.95	1.07
Week 4	- 6.75	- 4.74	- 2.43	1.38
Week 6	- 8.42	- 4.57	- 2.50	1.17
Week 8	- 10.31	- 5.99	- 2.99	- 0.26
Week 10	- 10.38	- 6.20	- 3.39	0.44

P values Mean change in inflammatory lesion counts						
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
2	0.1887	0.0003	0.0000	0.0000	0.0011	0.0226
4	0.0505	0.0000	0.0000	0.0000	0.0001	0.0032
6	0.0022	0.0000	0.0000	0.0000	0.0017	0.0183
8	0.0004	0.0000	0.0000	0.0000	0.0176	0.0006
10	0.0009	0.0000	0.0000	0.0000	0.0017	0.0016
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle						

Mean percent reduction in inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Week 2	16.8	15.6	7.5	- 5.4
Week 4	30.1	25.3	10.2	- 6.8
Week 6	37.0	24.1	10.3	- 4.6
Week 8	45.6	30.4	13.2	1.6
Week 10	46.2	32.1	15.8	- 3.1

p values* Mean percent reduction in inflammatory lesion counts Endpoint		
CB vs B	CB vs C	CB vs V
0.002	0.001	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

Mean change in total lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	48.5	49.4	50.2	46.7
Week 2	- 7.50	- 6.16	- 2.03	1.57
Week 4	- 12.18	- 10.13	- 4.61	- 0.19
Week 6	- 14.91	- 9.30	- 3.15	0.64
Week 8	- 18.45	- 12.88	- 5.96	- 3.29
Week 10	- 18.38	- 13.96	- 6.18	- 1.28

P values Mean change in total lesion counts						
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
2	0.2314	0.0000	0.0000	0.0000	0.0208	0.0009
4	0.1162	0.0000	0.0000	0.0000	0.0142	0.0021
6	0.0085	0.0000	0.0000	0.0000	0.0561	0.0020
8	0.0040	0.0000	0.0000	0.0000	0.1761	0.0010
10	0.0184	0.0000	0.0000	0.0000	0.0174	0.0001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

Mean percent reduction in total lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Week 2	11.2	12.4	4.3	- 3.2
Week 4	22.6	21.1	9.8	- 0.4
Week 6	27.9	21.2	8.5	- 0.6
Week 8	34.4	26.7	12.7	6.2
Week 10	35.7	28.2	14.7	- 0.2

p values* Mean percent reduction in total lesion counts Endpoint		
CB vs B	CB vs C	CB vs V
0.01	0.001	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

b. Physician Global Evaluation.

The frequency distribution of the investigator's global evaluation, and the p values for pairwise comparisons were as follows.

Investigator's global assessment				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Excellent improvement	30 (25%)	14 (12%)	4 (3%)	1 (1%)
Moderate improvement	47 (39%)	30 (25%)	27 (23%)	10 (8%)
Slight improvement	22 (18%)	41 (34%)	30 (25%)	23 (19%)
No change	12 (10%)	20 (17%)	29 (24%)	47 (39%)
Worse	1 (1%)	5 (4%)	16 (13%)	30 (25%)
Missing	8 (7%)	10 (8%)	14 (12%)	9 (8%)

p values Investigator's global assessment					
CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
0.0000	0.0000	0.0000	0.0000	0.0000	0.0002
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle					

The p values for pairwise comparisons of the percent of patients with moderate or excellent improvement in the physician's global assessment were as follows.

p values Investigator's global assessment % with moderate or excellent improvement					
CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
0.0042	0.0076	<0.0001	0.0020	<0.0001	0.8357
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle					

c. Patient's Global Evaluation.

The frequency distribution of the patient's global evaluation, and the p values for pairwise comparisons were as follows.

Patient's global assessment				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Excellent improvement	23 (19%)	8 (7%)	14 (12%)	0
Moderate improvement	42 (35%)	34 (28%)	30 (25%)	22 (18%)
Slight improvement	39 (33%)	47 (39%)	43 (36%)	45 (38%)
No change	9 (8%)	19 (16%)	19 (16%)	27 (23%)
Worse	0	2 (2%)	2 (2%)	17 (14%)
Missing	7 (6%)	10 (8%)	12 (10%)	9 (8%)

p values Patient's global assessment					
CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
0.0008	0.0031	0.0000	0.0000	0.0000	0.6868
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle					

The p values for pairwise comparisons of the percent of patients with moderate or excellent improvement in the patient's global assessment were as follows.

p values Patient's global assessment % with moderate or excellent improvement					
CB vs B	CB vs C	CB vs V	B vs V	C vs V	B vs C
<0.0001	<0.0001	<0.0001	<0.0001	0.0003	0.0728
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle					

4) Adverse events.

The local adverse events were as follows.

Local adverse events - all causalities				
	Combination (n=120)	Benzoyl peroxide (n=120)	Clindamycin (n=120)	Vehicle (n=120)
Acne	-	-	1 (0.8%)	-
Application site reaction	1 (0.8%)	1 (0.8%)	1 (0.8%)	-
Contact dermatitis	-	-	1 (0.8%)	-
Dry skin	11 (9.2%)	11 (9.2%)	6 (5.0%)	6 (5.0%)
Erythema	3 (2.5%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
Exfoliative dermatitis	-	-	1 (0.8%)	-
Herpes simplex	1 (0.8%)	1 (0.8%)	-	-
Pruritus	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
Rash	-	1 (0.8%)	-	-
Facial rash	-	1 (0.8%)	-	-
Burning	1 (0.8%)	2 (1.7%)	-	-
Sunburn	1 (0.8%)	1 (0.8%)	-	-
Vesiculobullous rash	-	-	1 (0.8%)	-

Five patients were discontinued from treatment due to adverse events. These are described further as follows.

1. Patient # 39: Clindamycin-benzoyl peroxide combination. This patient had mild edema, erythema, and dry skin of the face on day 2 of treatment; this was considered by the investigator to be definitely related to treatment.

2. Patient # 54: Benzoyl peroxide. This patient had mild facial edema on days 23 and 25 of treatment, this was considered by the investigator to be definitely related to treatment.

3. Patient # 273: Benzoyl peroxide. This patient had a moderate rash, burning, and pruritus of the face on day 12 this was considered to be probably related to treatment.

4. Patient # 288: Clindamycin. This patient had mild erythema and pruritus of the face on the first day of treatment. This was considered to be possibly related to treatment.

5. Patient # 300: Vehicle. This patient experienced moderate diarrhea and pain at day 31; this was considered to be probably related to treatment.

Pairwise comparisons showed no differences in erythema, oiliness, or peeling between the combination and the vehicle groups during the course of the study.

Reviewer's evaluation: The primary efficacy variables are considered by this reviewer to be the percent reduction in inflammatory and total lesion counts, and the investigator's global evaluation.

The results of this study showed that the combination product of clindamycin and benzoyl peroxide is significantly superior to its components clindamycin and benzoyl peroxide, and to its vehicle, in the mean percent reduction in inflammatory and total lesion counts. It was also significantly superior to its components and the vehicle in the investigator's global assessment of improvement, and in the percentage of patients with moderate or excellent improvement in the investigator's global assessment.

The most frequent local adverse event was dry skin, which occurred in 9% of patients on the combination product. Except for erythema in 2.5%, other local adverse events were reported in less than 2% of the patients on the combination product.

Study DL-6021-9623

The investigators for this study were as follows.

Terry Jones, M.D. Bryan, TX	Stephen Kraus, M.D. Atlanta, GA
H. Irving Katz, M.D. Fridley, MN	Eugene Monroe, M.D. Milwaukee, WI
Eduardo Tschen, M.D. Albuquerque, NM	

1) Study objective: This was to compare the safety and efficacy of ~~[redacted]~~ gel (1% clindamycin phosphate/5% benzoyl peroxide) with 5% benzoyl peroxide gel, 1% clindamycin gel, and vehicle gel in the treatment of acne vulgaris.

2) Study design: This was a double blind, randomized, multicenter, parallel group comparison of benzoyl peroxide 5%-clindamycin 1% combination gel, benzoyl peroxide 5% gel, clindamycin 1% gel, and the vehicle gel, with a treatment duration of 10 weeks.

3) Selection criteria: Patients were enrolled into the study who met the following criteria.

   a. Between 13 and 30 years of age.
   b. Moderate to moderately severe acne, designated as Grades II or III on the Pillsbury scale.
   c. At least 10 and no more than 80 inflammatory lesions, and at least 10 and no more than 100 comedones, with no more than 2 nodules/cysts on the facial skin, excluding the nose.
   d. If female, post-menopausal for at least one year, or had a hysterectomy or tubal ligation, or agrees to abstain from sexual intercourse, or if sexually active uses oral contraceptives or an intrauterine device or a double barrier method or Depo Provera or Norplant. If of childbearing potential, there must be a negative urine pregnancy test prior to enrollment.

4) Exclusion criteria: Patients were excluded from enrollment into the study for the following reasons.

a. Pregnancy or lactation.
b. Sensitivity to any of the ingredients of the study medications.
c. Treatment with systemic antibiotics within four weeks prior to the study.
d. Treatment with topical antibiotics and/or acne medications within two weeks prior to the study.
e. Treatment with systemic steroids within four weeks prior to the study, or topical steroids on the face within two weeks prior to the study.
f. Treatment with oral retinoids within the prior six months or topical retinoids within the prior two weeks.
g. Systemic or dermatologic diseases that might affect the acne condition or interfere with treatment evaluation.
h. Beards or long side burns.
i. Those whose activities involve excessive or prolonged exposure to sunlight (to minimize exposure to sunlight, a hat or other clothing should be worn.)
j. Prior history of bowel inflammation (regional enteritis, ulcerative colitis, or antibiotic-associated colitis).

5) Treatment regimen: Applications of the test products were made twice daily for 10 weeks.

The patient was instructed to wash the face with ——— soap, using only the hands. Fifteen minutes after the face was thoroughly dry, application of the test product was made to the entire face. Non-medicated makeup could be applied at one hour after the study application.

No concomitant topical or systemic acne medication, or topical or systemic antibiotic was to be used during the study. Patients were to avoid sun exposure. If a sunscreen were required, patients were to use ——— Facial Moisturizing lotion, SPF 25; this was to be recorded in the CRF as concomitant medication. ——— cream lotion could be used as a moisturizer. Other products specifically prohibited were alcoholic toners, astringents, medicated topical preparations, and abrasive cleansers or washes.

6) Effectiveness parameters: Return visits were made every two weeks, at which times the following evaluations were performed.

a. Lesion counts for inflammatory and non-inflammatory lesions, for facial lesions excluding the nose.

b. Physician's Global Improvement Score, graded for improvement from baseline on the following scale.

Global Improvement Score		
Score	Description	Definition
5	Clear	100% improvement of clinical signs and symptoms
4	Excellent	75-99% improvement of clinical signs and symptoms
3	Moderate	50-74% improvement of clinical signs and symptoms
2	Mild	25-49% improvement of clinical signs and symptoms
1	Slight	1-24% improvement of clinical signs and symptoms
0	No change	No detectable improvement from baseline
-1	Slightly worse	1-24% deterioration in clinical signs and symptoms
-2	Mildly worse	25-49% deterioration in clinical signs and symptoms
-3	Moderately worse	50-74% deterioration in clinical signs and symptoms
-4	Severely worse	75-99% deterioration in clinical signs and symptoms
-5	Exacerbation	100% or greater deterioration in clinical signs and symptoms

c. Patient's Global Improvement score: This was scored at the final visit on the following scale.

Patient's Global Improvement Score	
Score	Description
3	Much better
2	Better
1	Somewhat better
0	No change
-1	Somewhat worse
-2	Worse
-3	Much worse

The primary efficacy variables were considered by the sponsor to be the inflammatory lesion counts and the investigator's global improvement scores.

7) Safety evaluation. The patients were queried at each visit as to the occurrence of adverse events. Erythema and peeling were graded at each visit on the following scales.

Erythema

0 = none
1 = mild; slight pinkness
2 = moderate; definite redness; slightly less than that of the inflammatory lesions
3 = severe; erythema indistinguishable from the inflammatory lesions

Peeling

0 = none; no evidence of scaling
1 = mild; slight fine peeling or scaling; cracks easily evident; edges of scales lifting; may occur in isolated areas of face.
2 = moderate; marked cracks with large and lifting scales evident over most of the face.
3 = severe; large peeling sheets of epidermis present on face.

Oiliness was also graded as none, mild, moderate, or severe.

Results were as follows.

1) Patient enrollment and demographic characteristics: 287 patients were enrolled into the study, of which 278 patients had any followup evaluations. These 278 patients were analyzed as the intent-to-treat population.

The demographic and baseline disease characteristics of all patients enrolled were as follows.

Demographic and baseline disease characteristics				
	Combination (n=94)	Benzoyl peroxide (n=90)	Clindamycin (n=48)	Vehicle (n=46)
Age (mean)	18.5	19.1	19.0	19.3
Gender				
Male	50 (53%)	41 (46%)	24 (50%)	25 (54%)
Female	44 (47%)	49 (54%)	24 (50%)	21 (46%)
Race				
Caucasian	73 (78%)	67 (74%)	36 (75%)	33 (72%)
Black	9 (10%)	7 (8%)	3 (6%)	4 (8%)
Hispanic	10 (11%)	15 (17%)	8 (17%)	8 (17%)
Asian	1 (1%)	1 (1%)	0	0
Other	1 (1%)	1 (1%)	1 (2%)	0
Acne duration				
Mean (years)	5.1	5.4	4.7	5.6
Lesion counts (mean)				
Inflammatory	25.4	22.9	26.6	26.5
Noninflammatory	39.1	41.9	39.9	39.5
Total	64.5	64.8	66.5	66.0

2) Patient disposition: The number of patients at each visit and the reasons for discontinuation were as follows.

# patients at each return visit				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	94	90	48	46
Week 2	93	87	47	46
Week 4	86	83	47	44
Week 6	87	81	46	44
Week 8	82	79	43	44
Week 10	88	82	45	44
Completion rate	93%	86%	92%	92%

Reasons for discontinuation				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Dropout	2	4	2	1
Missed 2 visits	4	6	2	1
Missed applications	0	0	0	1
Proscribed medication	1	3	0	1
Total # patients	7	13	4	4

3) Effectiveness par meters.

The 'Endpoint' in the following tabulations, as defined by the sponsor, is the last available data from a patient. This is usually data from week 10, but may be earlier if the patient discontinued prior to week 10.

a. Lesion counts.

The mean change from baseline, and the mean percent reduction in the non-inflammatory lesion counts, the inflammatory lesion counts, and the total lesion counts were as follows.

Mean change in non-inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	39.1	41.9	39.9	39.5
Week 2	- 7.6	- 9.2	- 6.3	- 5.7
Week 4	- 15.0	- 14.4	- 8.5	- 10.1
Week 6	- 18.5	- 17.5	- 8.0	- 13.8
Week 8	- 19.6	- 19.8	- 14.5	- 10.8
Week 10	- 20.8	- 19.8	- 13.5	- 13.6
Endpoint	- 21.5	- 20.4	- 13.6	- 13.1

P values Mean change in non-inflammatory lesion counts					
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V
2	> 0.50	0.364	0.327	0.179	> 0.50
4	> 0.50	0.004	0.076	0.184	0.369
6	0.377	<0.001	0.038	0.190	0.076
8	> 0.50	0.009	< 0.001	0.001	0.377
10	0.424	0.001	0.003	0.021	> 0.50
Endpoint	0.225	0.001	0.001	0.026	> 0.50

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

Mean percent reduction in non-inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	39.1	41.9	39.9	39.5
Week 2	20.0	22.3	14.1	13.1
Week 4	40.0	38.7	22.3	24.8
Week 6	46.7	44.1	21.4	34.6
Week 8	52.0	52.7	38.2	30.3
Week 10	53.9	50.3	38.6	35.7

p values * Mean percent reduction in non-inflammatory lesion counts Week 10		
CB vs B	CB vs C	CB vs V
0.2	0.008	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

Mean change in inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	25.4	22.9	26.6	26.5
Week 2	- 9.1	- 6.8	- 8.2	- 5.8
Week 4	- 12.7	- 10.7	- 10.1	- 8.2
Week 6	- 13.7	- 11.3	- 12.1	- 9.5
Week 8	- 15.8	- 11.2	- 13.8	- 9.0
Week 10	- 16.7	- 12.5	- 14.4	- 11.3
Endpoint	- 16.8	- 12.1	- 14.1	- 11.7

P values Mean change in inflammatory lesion counts					
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V
2	0.238	0.263	0.022	0.190	0.286
4	> 0.50	0.020	0.001	0.004	0.330
6	0.359	0.135	0.001	0.012	0.090
8	0.033	0.034	< 0.001	0.011	0.038
10	0.006	0.005	< 0.001	0.022	0.107
Endpoint	0.005	0.005	< 0.001	0.052	0.185

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

Mean percent reduction in inflammatory lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	25.4	22.9	26.6	26.5
Week 2	34.0	28.3	24.6	22.0
Week 4	47.2	45.7	29.1	28.8
Week 6	52.7	47.5	39.9	35.0
Week 8	60.3	49.4	45.7	33.8
Week 10	62.9	53.2	45.2	41.9

p values * Mean percent reduction in inflammatory lesion counts Week 10		
CB vs B	CB vs C	CB vs V
0.01	0.001	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

Mean change in total lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	64.5	64.8	66.5	66.0
Week 2	- 16.7	- 16.0	- 14.5	- 11.5
Week 4	- 27.7	- 25.0	- 18.6	- 18.3
Week 6	- 32.2	- 28.7	- 20.2	- 23.3
Week 8	- 35.4	- 31.0	- 28.3	- 19.7
Week 10	- 37.5	- 32.3	- 27.9	- 24.9
Endpoint	- 38.2	- 31.6	- 27.5	- 24.5

P values Mean change in total lesion counts					
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V
2	>0.50	0.208	0.040	0.119	0.466
4	0.368	0.001	0.005	0.042	> 0.50
6	0.218	< 0.001	0.004	0.068	> 0.50
8	0.144	0.004	< 0.001	0.001	0.118
10	0.065	0.001	< 0.001	0.015	> 0.50
Endpoint	0.023	0.001	< 0.001	0.028	> 0.50

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

Mean percent reduction in total lesion counts				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Baseline	64.5	64.8	66.5	66.0
Week 2	26.1	27.1	20.8	18.4
Week 4	43.5	43.4	28.7	28.0
Week 6	49.9	46.7	31.5	36.1
Week 8	55.2	52.3	42.8	32.9
Week 10	58.0	51.5	41.7	39.3

p values * Mean percent reduction in total lesion counts Week 10		
CB vs B	CB vs C	CB vs V
0.03	0.001	0.001

CB = clindamycin/benzoyl peroxide
B = benzoyl peroxide
C = clindamycin
V = vehicle

* p values provided by Shahla Farr

b. Physician Global Evaluation.

The frequency distribution of the investigator's global evaluation at endpoint is as follows.

Investigator's global assessment				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Clear	2 (2.1%)	2 (2.2%)	1 (2.1%)	0
Excellent improvement	39 (41.5%)	32 (35.6%)	12 (25.0%)	7 (15.2%)
Moderate improvement	24 (25.5%)	23 (25.6%)	10 (20.8%)	12 (26.1%)
Mild improvement	13 (13.8%)	13 (14.4%)	9 (18.8%)	12 (26.1%)
Slight improvement	11 (11.7%)	12 (13.3%)	8 (16.7%)	11 (23.9%)
No change	4 (4.3%)	5 (5.6%)	4 (8.3%)	1 (2.1%)
Slightly worse	1 (1.1%)	3 (3.3%)	4 (8.3%)	3 (6.5%)

The percentages of patients that had 75% or greater improvement at each visit, designated as a 'cure', and the p values for between group comparisons were as follows.

Percentage of patients with 75% or greater improvement				
	Combination	Benzoyl peroxide	Clindamycin	Vehicle
Week 6	22 (25.6%)	21 (26.9%)	8 (17.4%)	2 (4.8%)
Week 8	31 (40.3%)	31 (41.3%)	11 (25.0%)	1 (2.4%)
Week 10	40 (48.2%)	30 (39.5%)	11 (25.6%)	6 (13.6%)
Endpoint	41 (43.6%)	34 (37.8%)	13 (27.1%)	7 (15.2%)

P-values Percentage of patients with 75% or greater improvement					
Week	CB vs B	CB vs C	CB vs V	B vs V	C vs V
6	> 0.50	0.265	0.001	0.001	0.048
8	> 0.50	0.047	< 0.001	< 0.001	0.002
10	0.275	0.006	< 0.001	0.001	0.167
Endpoint	0.390	0.031	< 0.001	0.003	0.168
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide C = clindamycin V = vehicle					

4) Adverse events.

The local adverse events were as follows.

Local adverse events - all causalities				
	Combination (n=95)	Benzoyl peroxide (n=95)	Clindamycin (n=49)	Vehicle (n=48)
Dry skin	20 (21.1%)	22 (23.2%)	2 (4.1%)	4 (8.3%)
Application site reaction	1 (1.1%)	2 (4.2%)	1 (2.0%	1 (2.1%)
Pruritus	-	2 (2.1%)	1 (2.0%)	-
Rash	-	2 (2.1%)	-	-
Exfoliative dermatitis	1 (1.1%)	-	-	-
Herpes simplex	-	1 (1.1%)	-	-
Urticaria	-	-	1 (2.0%)	-

No patients were discontinued from the study due to adverse events. One patient on benzoyl peroxide discontinued treatment for two days due to burning and stinging, and another patient on benzoyl peroxide decreased the frequency of application to once daily for five days due to burning and facial irritation.

Reviewer's evaluation: The primary efficacy variables are considered by this reviewer to be the percent reduction in inflammatory and total lesion counts, and the investigator's global evaluation.

The results of this study showed that the combination product of clindamycin and benzoyl peroxide is significantly superior to its components clindamycin and benzoyl peroxide, and to its vehicle, in the mean percent reduction in inflammatory and total lesion counts. In the percentage of patients with 75% or greater improvement in the investigator's global assessment, the combination product was significantly superior to clindamycin and to the vehicle, but it was not superior to benzoyl peroxide.

The most frequent local adverse event was dry skin, which occurred in 21% of patients on the combination product. Other local adverse events with the combination product were reported in less than 2% of the patients.

Other clinical studies

Study DL-6021-9301

The investigators for this study were as follows.

Michael Goldfarb, M.D. Clinton Township, NJ	Michael Jarrett, M.D. Austin, TX
Janet Hickman, M.D. Lynchburg, VA	James Leyden, M.D. Broomall, PA

1) Study objective: This was to assess the relative efficacy of benzoyl peroxide 5%-clindamycin 1% gel, 5% benzoyl peroxide gel, and Benzamycin (3% erythromycin and 5% benzoyl peroxide) Topical Gel in the treatment of acne.

2) Study design: This was a single blind (investigator blind), randomized, multicenter, parallel group comparison of benzoyl peroxide 5%-clindamycin 1% combination gel, benzoyl peroxide 5% gel, and Benzamycin gel, with a treatment duration of 10 weeks.

3) Selection criteria: Patients were enrolled into the study who were between 13 and 30 years of age, with moderate to moderately severe acne, of Grade II or III by the Pillsbury classification, with a minimum of 10 and a maximum of 80 inflammatory lesions, and a minimum of 10 and a maximum of 100 open or closed comedones on the face.

4) Exclusion criteria: Patients were excluded from enrollment into the study for the following reasons.

   a. Sensitivity to any of the ingredients of the study medication.
   b. Fewer than 10 or more than 80 inflammatory lesions.
   c. Fewer than 10 or more than 100 comedones.
   d. Classification as Grade I or Grade IV acne.
   e. Previous treatment with systemic antibiotics or systemic steroids within the four weeks prior to the study.
   f. Treatment with topical anti-acne medications within the two weeks prior to the study.
   g. Pregnancy or lactation.
   h. History of bowel inflammation (regional enteritis, ulcerative colitis, or antibiotic-associated colitis).

5) Treatment regimen: Applications of the test products were made BID for 10 weeks.

The patients were instucted to wash their faces with _____ soap prior to applications. They were not to use any cleansers, washes, alcoholic toners, astringents, or medicated solutions on the affected areas, and no concomitant acne medication or topical antibiotic during the course of the study. If a moisturizer were requested, the sponsor provided _____ lotion.

6) Effectiveness parameters: Return visits were made every two weeks, at which times the following evaluations were made.

a. Lesion counts for comedones, papules, and pustules.

b. The investigator's global evaluation of the change from baseline. This was graded on a visual analog scale which was marked with improvement from baseline in 5% increments. The ranges of improvement were categorized as follows.

Worse
No change
Slight improvement (1-24% improvement)
Mild improvement (25-49% improvement)
Moderate improvement (50-74% improvement)
Excellent improvement (75% or greater)

c. The patient's global evaluation of the change from baseline at the last visit, graded on the following scale.

0 = worse
1 = no change
2 = slight improvement
3 = moderate improvement
4 = excellent improvement

d. Rating of oiliness, erythema, and peeling at each return visit as none, mild, moderate, or severe.

The sponsor considered the primary efficacy variables to be the change from baseline in the number of inflammatory lesions, and the physician and patient rating of overall improvement. The scales for overall improvement were collapsed to a dichotomous variable by combining moderate and excellent improvement together as one outcome, and the other three categories as another outcome.

7) Safety evaluation: The patients were queried as to the occurrence of adverse events.

Results were as follows.

1) Patient enrollment and demographic characteristics: 492 patients were enrolled into the study; this comprised 165 patients in the clindamycin-benzoyl peroxide combination group, 164 in the benzoyl peroxide group, and 163 in the Benzamycin group. Of these, 444 patients (90%) completed the study.

The demographic and baseline disease characteristics of all patients enrolled were as follows.

Demographic and baseline disease characteristics			
	Combination	Benzoyl peroxide	Benzamycin
Age (mean)	18.7	18.1	18.7
Gender			
Male	58 (35%)	73 (45%)	72 (44%)
Female	107 (65%)	91 (55%)	91 (56%)
Race			
Caucasian	131 (79%)	139 (85%)	132 (81%)
NonCaucasian	34 (21%)	25 (15%)	31 (19%)
Lesion counts (mean)			
Inflammatory	18.7	19.1	19.6
Noninflammatory	32.9	33.7	34.3
Total	51.6	52.8	53.9

2) Patient disposition: The number of patients at each visit and the reasons for discontinuation were as follows.

# patients at each return visit			
	Combination	Benzoyl peroxide	Benzamycin
Baseline	165	164	163
Week 2	164	160	160
Week 4	157	156	156
Week 6	155	150	151
Week 8	153	147	150
Week 10	153	141	150

Reasons for discontinuation			
	Combination	Benzoyl peroxide	Benzamycin
Dropout	2	5	7
Concurrent medication	1	3	2
Missed 2 visits	3	3	0
Adverse reaction	1	5	0
Lost to followup	4	5	2
Pregnancy	0	0	2
Protocol violation	0	1	0
Noncompliant	1	0	0
Other	0	1	0
Total # patients	12	23	13

3) Effectiveness parameters.

a. Lesion counts.

The mean change from baseline and the mean percent reduction from baseline in the non-inflammatory lesion counts, inflammatory lesion counts, and total lesion counts were as follows.

Mean change in non-inflammatory lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Baseline	32.93	33.74	34.31
Week 2	- 3.96	- 4.05	- 2.83
Week 4	- 7.38	- 5.97	- 5.71
Week 6	- 8.90	- 7.33	- 7.62
Week 8	- 10.97	- 9.76	- 8.58
Week 10	- 10.50	- 8.66	- 8.48

P values Mean change in non-inflammatory lesion counts			
Week	CB vs B	CB vs BE	B vs BE
2	0.9562	0.2484	0.2713
4	0.2921	0.1620	0.7255
6	0.2200	0.2420	0.9548
8	0.3518	0.0531	0.3225
10	0.2153	0.1468	0.8445
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = benzamycin			

Mean percent reduction in non-inflammatory lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Week 2	13.9	13.5	6.5
Week 4	24.9	22.4	19.4
Week 6	27.8	26.1	22.4
Week 8	35.2	34.0	28.7
Week 10	33.7	30.5	27.9

Mean change in inflammatory lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Baseline	18.73	19.13	19.63
Week 2	- 6.94	- 6.18	- 6.72
Week 4	- 8.63	- 8.02	- 8.82
Week 6	- 9.58	- 8.22	- 9.40
Week 8	- 10.39	- 9.50	- 10.61
Week 10	- 10.44	- 9.20	- 11.09

P values Mean change in inflammatory lesion counts			
Week	CB vs B	CB vs BE	B vs BE
2	0.1277	0.2074	0.7882
4	0.2070	0.5848	0.4727
6	0.1019	0.3385	0.4974
8	0.2593	0.5892	0.5607
10	0.0531	0.8291	0.0876
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = benzamycin			

Mean percent reduction in inflammatory lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Week 2	38.1	30.6	34.8
Week 4	46.7	42.2	46.0
Week 6	51.3	43.2	48.2
Week 8	54.6	50.2	54.3
Week 10	54.9	47.8	54.9

Mean change in total lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Baseline	51.66	52.88	53.94
Week 2	- 10.90	- 10.23	- 9.56
Week 4	- 16.01	- 13.99	- 14.54
Week 6	- 18.48	- 15.54	- 17.03
Week 8	- 21.36	- 19.27	- 19.19
Week 10	- 20.95	- 17.86	- 19.57

P values Mean change in total lesion counts			
Week	CB vs B	CB vs BE	B vs BE
2	0.5160	0.1872	0.5033
4	0.1673	0.2000	0.9247
6	0.0861	0.2195	0.6256
8	0.2385	0.0994	0.6446
10	0.0768	0.2784	0.4881
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = benzamycin			

Mean percent reduction in total lesion counts			
	Combination	Benzoyl peroxide	Benzamycin
Week 2	22.3	19.7	17.8
Week 4	33.2	29.8	30.7
Week 6	37.4	32.5	33.9
Week 8	43.4	40.3	39.1
Week 10	43.2	36.9	38.7

b. Physician Global Evaluation.

The results are presented as the mean percent improvement from baseline.

Investigator's global assessment Mean percent improvement			
	Combination	Benzoyl peroxide	Benzamycin
Week 2	21.6	21.2	20.3
Week 4	34.2	29.6	32.2
Week 6	40.1	34.4	36.7
Week 8	46.2	44.0	44.5
Week 10	49.5	43.0	44.8

p values Investigator's global assessment Week 10		
CB vs B	CB vs BE	B vs BE
0.0133	0.0947	0.4108
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = Benzamycin		

c. Patient's Global Evaluation.

The frequency distribution of the patient's global evaluation, and the p values for pairwise comparisons were as follows.

Patient's global assessment			
	Combination	Benzoyl peroxide	Benzamycin
Excellent improvement	47 (28%)	29 (18%)	28 (17%)
Moderate improvement	56 (34%)	52 (32%)	70 (43%)
Slight improvement	40 (24%)	43 (26%)	43 (26%)
No change	10 (6.1%)	20 (12%)	12 (7.4%)
Worse	3 (1.8%)	7 (4.3%)	3 (1.8%)
Unknown	9 (5.5%)	13 (7.9%)	7 (4.3%)

p values Patient's global assessment		
CB vs B	CB vs BE	B vs BE
0.0008	0.1195	0.0684
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = Benzamycin		

The p values for pairwise comparisons of the percent of patients with moderate or excellent improvement in the patient's global evaluation were as follows.

p values Patient's global assessment % with moderate or excellent improvement		
CB vs B	CB vs BE	B vs BE
0.0184	0.6836	0.0515
CB = clindamycin/benzoyl peroxide B = benzoyl peroxide BE = benzamycin		

4) Safety evaluation.

The following events were felt to be possibly or definitely related to treatment.

Adverse events			
	Combination (n=165)	Benzoyl peroxide (n=164)	Benzamycin (n=163)
Possible (total)	15 (9.1%)	12 (7.3%)	13 (8.0%)
Acne	0	1 (0.6%)	0
Application site reaction	2 (1.2%)	1 (0.6%)	2 (1.2%)
Dry skin	7 (4.2%)	11 (6.7%)	7 (4.3%)
Erythema	0	2 (1.2%)	0
Exfoliative dermatitis	2 (1.2%)	0	1 (0.6%)
Pruritus	4 (2.4%)	1 (0.6%)	0
Rash	1 (0.6%)	0	0
Facial rash	0	0	1 (0.6%)
Burning	0	0	1 (0.6%)
Skin tightness	0	2 (1.2%)	1 (0.6%)
Sunburn	2 (1.2%)	0	2 (1.2%)

Definite (total)	1 (0.6%)	2 (1.2%)	0
Dry skin	1 (0.6%)	1 (0.6%)	0
Erythema	0	1 (0.6%)	0
Pruritus	0	1 (0.6%)	0

All of the above events were mild to moderate in severity.

Six patients discontinued treatment due to adverse events. One of these was on the combination product, and five were on benzoyl peroxide gel.

a. Patient 502: Clindamycin-benzoyl peroxide. This patient developed mild itching and burning of the face and neck on day 17, which continued for five days. The symptoms resolved after discontinuation of treatment.

b. Patient 64: Benzoyl peroxide. This patient developed chicken pox on day 60 of the study, which resolved after two weeks.

c. Patient 137: Benzoyl peroxide.This patient had a reaction to poison ivy on day 60; this resolved after 10 days.

d. Patient 254: Benzoyl peroxide. This patient had a moderate breakout of acne at day 20. The episode resolved after 22 days following discontinuation.

e. Patient 270: Benzoyl peroxide. On day 2 this patient had dryness, redness, tightness, and discomfort of the face, which were moderately severe. The condition had improved at five days after discontinuation of treatment.

f. Patient 540: Benzoyl peroxide. On day 2 this patient developed mild erythema and itching. This resolved after 12 days following discontinuation.

The frequency and severity of erythema and peeling are not provided. The p values for changes in erythema and peeling are provided, which show no significant differences between treatment groups.

Labeling review: The labeling review is attached at the conclusion of this review.

Summary and evaluation

This application is for ——— topical gel, a combination product containing 1% clindamycin and 5% benzoyl peroxide, to be used for the topical treatment of acne, with applications twice daily.

The dermal safety studies which were performed consisted of cumulative irritation, contact sensitization, phototoxicity, and photosensitization studies. These are felt to have been adequately designed and conducted. The results show that the combination product has a high irritancy potential in this assay, which utilized occlusive patches; the irritancy potential was slightly less than that with benzoyl peroxide alone. There was a moderate potential for induction of contact sensitization, comparable to that with benzoyl peroxide alone, and no detectable potential for phototoxicity or photosensitization under these test conditions.

Two pivotal clinical studies were performed for a determination of safety and effectiveness. Both studies were double blind, multicenter, parallel group comparisons of ——— gel with its components clindamycin and benzoyl peroxide, and the vehicle, in patients with acne, with applications twice daily for ten weeks. Study 9103 enrolled 480 patients, and Study 9623 enrolled 287 patients. The primary efficacy variables were considered by this reviewer to be the mean percent reduction in inflammatory lesion counts and in total lesion counts, and the investigator's global assessment of improvement from baseline.

The results of study 9103 showed that ——— topical gel is significantly superior to its components clindamycin and benzoyl peroxide, and to its vehicle, in the mean percent reduction in inflammatory and total lesion counts, and in the investigator's global assessment of improvement.

The results of study 9623 showed that ——— topical gel is significantly superior to its components clindamycin and benzoyl peroxide, and to its vehicle, in the mean percent reduction in inflammatory and total lesion counts. In the investigator's global assessment of improvement, ——— topical gel was significantly superior to clindamycin and to the vehicle, but was not superior to benzoyl peroxide.

In accordance with Division policy, however, a trend has been shown towards a superiority of the combination over benzoyl peroxide, and this is considered to be an adequate demonstration of the effectiveness for the indication.

The most frequent adverse event in both studies was dry skin. Other adverse events with the combination product were infrequent.

Conclusions: It is felt that the application is approvable for the labeling indication.

Recommendations: It is recommended that this application be approved for the twice daily applications of ——— topical gel for the treatment of acne.

/S/

Phyllis A. Huene, M.D.

2/10/99

cc: Orig NDA 50-756
HFD-540/Division files
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/White
HFD-540/Vidra
HFD-540/Farr
HFD-540/Jacobs

/S/ 2/24/99

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/S/ 2/25/9