

## 8.1.1.3.3 STATISTICAL CONSIDERATIONS

Data analyses for efficacy were performed on two populations of patients: valid patients which consisted of all patients that completed 11 weeks of treatment without significant protocol violations (preferred data set) and all patients regardless of whether the protocol was followed (intent to treat data set).

Safety analyses were performed on the ITT data set. Each local tolerance score at each time was collapsed to a dichotomous classification (worsening versus same or improved) and statistical tests were performed to evaluate the equality of the distribution of the overall tolerance scores (see Biostatistics review). The sample size of 30 patients per group was based upon the assumption that this number would provide an adequate base for estimating the proportion of patients with good to excellent global improvement and for estimating the mean and variance of the reduction in lesion counts for each group.

## 8.1.1.4 RESULTS

## 8.1.1.4.1 POPULATIONS ENROLLED/ANALYZED

A total of 120 patients entered this study with 30 assigned to each arm in a random fashion: Successful study completion was achieved by 108 patients distributed among the arms as follows: Clindoxyl™ Gel (28), clindamycin phosphate gel (29), benzoyl peroxide gel (24), and vehicle gel (27). The subject numbers of the 12 patients who did not complete the study at 11 weeks and the reasons for dropping out are summarized below. These were all appropriate reasons for withdrawal from the intent to treat population.

	Site 150 Patients entered at Week 0	Site 150 Patients who completed week 11	Dropouts	
	N	N	Lost to follow-up	Concomitant violation med
BZPO	30	24	025, 084, 092, 114	93,103
Clindamycin	30	29	077	0
Vehicle	30	27	019, 099	089
Clindoxyl	30	28	004, 057	0
	120	108	9 + 3 = 12	



Characteristics and Baseline Features of All Patients Entered in Study 150 <sup>a</sup>					
	Clindoxyl™	Clindamycin	Benzoyl Peroxide	Vehicle	ALL
Distribution by Sex					
male	10 (33.3%)	11 (36.7%)	14 (46.7%)	11 (36.7%)	46 (38.3%)
female	20 (66.7%)	19 (63.3%)	16 (53.3%)	19 (63.3%)	74 (61.7%)
Distribution by Race					
Caucasian	25 (83.3%)	21 (70.0%)	24 (80.0%)	22 (73.3%)	92 (76.7%)
Black	5 (16.7%)	9 (30.0%)	6 (20.0%)	8 (26.7%)	28 (23.3%)
Age (in years) <sup>b</sup>	19.2±1.0	17.2±0.8	19.0±1.0	18.4±1.0	18.4 ± 0.5
Age Range (years)	13 - 30	13 - 29	13 - 30	13 - 30	13 - 30
Inflammatory Lesion Count <sup>b</sup>	26.5±2.6	30.5±2.7	34.0±3.6	34.7±3.5	31.4 ± 1.6
Noninflammatory Lesion Count <sup>b</sup>	58.7±8.2	69.2±7.7	88.3±10.6	85.4±11.3	75.4 ± 4.9
Erythema Baseline Score <sup>c</sup>	8 (26.7%)*	11 (36.7%)	10 (33.3%)*	8 (26.7%)	37 (30.9%)
Peeling Baseline Score <sup>c</sup>	5 (16.7%)	4 (13.3%)	1 (3.3%)*	2 (6.7%)	12 (10.0%)
Burning Baseline Score <sup>c</sup>	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	5 (4.2%)
<sup>a</sup> There were no significant differences between groups ( $p > 0.05$ ).					
<sup>b</sup> Data expressed as mean ± s.e.					
<sup>c</sup> Number (%) of patients with mild score (none were severe). * One patient was moderate.					

#### 8.1.1.4.2 EFFICACY ENDPOINT OUTCOMES

##### Noninflammatory Lesions

Baseline lesion counts are similar across treatment arms, but have a wide range with mean lesions of 38.1 in the Clindoxyl™ gel group, 70.7 in the clindamycin phosphate gel group, 89.3 in the benzoyl peroxide gel group, and 90.2 in the vehicle gel group.

Effect of Time and Treatment on Non-Inflammatory Lesion Counts for the Preferred Data Set in Study 150					
Week	Statistic <sup>1</sup>	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl™
0	Mean Count	89.3	70.7	90.2	58.1
11	Mean Reduction	14.7 <sup>v</sup>	-0.6	-4.3	12.0 <sup>v</sup>
	Mean % Reduction	14.2 <sup>v</sup>	-5.2	-12.6	26.5 <sup>v,c</sup>
<sup>1</sup> Reduction = baseline count - count at a later week					
<sup>v,c,b</sup> Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), $p < 0.05$					

At week 11 the Clindoxyl™ Gel group shows a significant statistical and clinical mean percent reduction and mean reduction compared to both the vehicle ( $p = 0.001/0.040$ ). Clindamycin phosphate demonstrates a 32% reduction in lesion counts ( $p = 0.007$ ) but this represents a mean count of only 12 lesions ( $p = 0.105$ ). This comparison is SUPPORTIVE of the superiority of Clindoxyl™ Gel compared to clindamycin phosphate gel. Clindoxyl™ Gel does not demonstrate superiority to benzoyl peroxide gel. Treatment with Clindoxyl™ Gel appears to be no better than treatment with benzoyl peroxide gel.

Results of Statistical Analyses of Non-Inflammatory Lesion Counts in the Preferred Data Set of Study 150( -% Reduction at Week 11)						
Treatment Comparison			Least Mean	Square		
First	Second	Statistic <sup>b</sup>	First	Second	Difference	p-Value
Clindoxyl	Vehicle	Reduction at Week 11	12.0	-4.3	16.3	0.040
		% reduction at week 11	26.5	-12.6	39.1	0.001
Clindoxyl	Benzoyl	Reduction at Week 11	12.0	14.7	-2.7	0.738
		% Reduction at Week 11	26.5	14.2	12.3	0.309
Clindoxyl	Clindamycin	Reduction at Week 11	12.0	-0.6	12.6	0.105
		% Reduction at Week 11	26.5	-5.2	31.7	0.007

<sup>b</sup> Reduction = baseline count - count at a later week

Benzoyl peroxide gel is superior to the vehicle gel in the treatment of noninflammatory lesions (p=0.030) as would be expected, but the clindamycin phosphate gel does not reach statistical significance (p=0.527).

*Reviewer Comment: Study 150 demonstrates that Clindoxyl™ Gel has superior clinical efficacy than the vehicle gel in the treatment of noninflammatory lesions. It is supportive of the superior efficacy of Clindoxyl™ Gel compared with clindamycin phosphate gel, but does not demonstrate superior efficacy than benzoyl peroxide gel.*

#### Inflammatory Lesions

Baseline lesion counts ranged from 26.8 to 35.6. The mean reduction in lesion counts ranges from a low of 8.1 for vehicle, to a high of 17.0 for Clindoxyl™ Gel. It should be noted that the number of inflammatory lesions at baseline is markedly less than the number of noninflammatory lesions.

Effect of Time and Treatment on Inflammatory Lesion Counts for the Preferred Data Set of Study 150					
Week	Statistic <sup>1</sup>	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl™
0	Mean Count	33.0	31.1	35.6	26.8
11	Mean Reduction	14.1	13.0	8.1	17.0 <sup>v</sup>
	Mean % Reduction	39.5	34.5	19.2	66.5 <sup>v,c,b</sup>

<sup>1</sup> Reduction = baseline count - count at a later week  
<sup>v,c,b</sup> Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), p < 0.05, based on valid patients, LOCF.

Comparison of the mean reduction and mean % reduction counts demonstrates that there is a statistically significant difference between treatment with Clindoxyl™ Gel and the vehicle. This is a clinical difference of 8 lesions, which converts to a 47 percent reduction. This may or may not be clinically meaningful, as the statistic is inflated by the small number of lesions at baseline. However, it is likely a real difference. In the comparison between the Clindoxyl™ Gel and clindamycin phosphate gel, there is only a difference of 4 lesions (p = 0.345) which represents a 32% reduction (p = 0.010). This is not clinically meaningful, and does not demonstrate clinical significance, although it is suggestive of a difference. In the comparison of

Clindoxyl™ Gel with benzoyl peroxide gel, the difference of 2.9 lesions ( $p = 0.508$ ) does not demonstrate a clinically significant difference from Clindoxyl™ Gel.

Results of Statistical Analyses of Inflammatory Lesion Counts in the Preferred Data Set of Study 150						
Treatment Comparison			Least Square Mean			
First	Second	Statistic <sup>b</sup>	First	Second	Difference	p-Value
Clindoxyl	Vehicle	Reduction at Week 11	17.0	8.1	8.9	0.040
		% Reduction at Week 11	66.5	19.2	47.3	0.000
Clindoxyl	Benzoyl	Reduction at Week 11	17.0	14.1	2.9	0.508
		% Reduction at Week 11	66.5	39.5	27.0	0.037
Clindoxyl	Clindamycin	Reduction at Week 11	17.0	13.0	4.0	0.345
		% Reduction at Week 11	66.5	34.5	32.0	0.010
Benzoyl	Vehicle	Reduction at Week 11	14.1	8.1	5.9	0.183
		% Reduction at Week 11	39.5	19.2	20.2	0.120
Clindamycin	Vehicle	Reduction at Week 11	13.0	8.1	4.9	0.250
		% Reduction at Week 11	34.5	19.2	15.3	0.218

<sup>b</sup> Reduction = baseline count - count at a later week

*Reviewer Comment: As measured by inflammatory lesions counts, Clindoxyl™ Gel has demonstrated clinical superiority over the vehicle. Study 150 is supportive of the superior efficacy of Clindoxyl™ Gel compared to clindamycin phosphate gel..*

#### Effect on Total Lesions

Study # 150					
Effect of Time and Treatment on Total Lesion Counts for the Preferred Data Set					
WEEK	STATISTIC	BZPO	CLINDAMYCIN	VEHICLE	CLINDOXYL
0	Mean Count	122.3	101.8	125.8	84.9
11	Mean Reduction	28.8	12.4	3.9	29.0
	Mean % Reduction	21.9	10.4	-1.4	41.5

Study # 150			
Results of Statistical Analysis of Total Count in Preferred Data Set			
Treatment Comparison		Statistic	p-Value
First	Second		
Clindoxyl	Vehicle	Reduction at week 11	0.023
		% reduction at week 11	0.000
Clindoxyl	Clindamycin	Reduction at week 11	0.125
		% reduction at week 11	0.003
Clindoxyl	BZPO	Reduction at week 11	0.985
		% reduction at week 11	0.066

The sponsor did not originally include the total lesion count as a primary efficacy variable. These counts were requested by the division and provided by the sponsor as an amendment. Analysis of per cent reduction at week 11 showed that Clindoxyl™ Gel treatment had significantly greater activity than the vehicle gel ( $p = 0.000$ ) and clindamycin phosphate gel ( $p = 0.003$ ). Both of these percent reductions also represents a clinical significant reduction in mean lesion count. The percent reduction comparison between Clindoxyl™ Gel and benzoyl peroxide

gel is **not** statistically significant ( $p = 0.066$ ), a statistic which is probably influenced by the large number of noninflammatory lesions and small number of inflammatory lesions in this study. The Clindoxyl™ Gel is unable to reach statistical significance in total lesion counts, due to the proportion of noninflammatory lesions and the relative lack of effect of the clindamycin component of Clindoxyl™ Gel upon these lesions.

*Reviewer comment: As measured by improvement in total lesion counts, Clindoxyl™ Gel is clinically superior to the vehicle gel and clindamycin phosphate gel, but is not clinically superior to benzoyl peroxide gel.*

Effect on Global Improvement

The percentage of patients with good to excellent improvement was consistently greater for the Clindoxyl™ Gel group. At week 11, significantly greater proportions of patients with good to excellent global improvement were observed in the Clindoxyl™ Gel group (75%) than in the vehicle group (15%) ( $p = 0.000$ ), the clindamycin phosphate gel group (38%) ( $p = 0.010$ ), and the benzoyl peroxide gel group (42%) ( $p = 0.030$ ).

Global Improvement of Patients in the Preferred Data Set of Study 150				
Week	Patients with Good to Excellent Global Improvement <sup>a</sup>			
	Clindoxyl	Clindamycin	Benzoyl Peroxide	Vehicle
2	1 (4.3%)	0	2 (8.7%)	1 (4.0%)
11	21 (75.0%)	11 (37.9%)	10 (41.7%)	4 (14.8%)

<sup>a</sup> Endpoint includes all patients with last observation carried forward

Once again, the benzoyl peroxide gel group ( $p= 0.066$ ) and the clindamycin phosphate gel group ( $p = 0.097$ ) did not reach statistical significance when compared with the vehicle in a comparison of global assessment outcomes, but they do **approach** significance.

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Chart to follow

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Comparisons of Treatment Effects on Proportion of Patients with Good to Excellent Global Improvement in the Preferred Data Set of Study 150 at Week 11					
Treatment Comparison		Proportion		Estimated Odds Ratio <sup>b</sup>	p-Value <sup>a</sup>
First	Second	First	Second		
Clindoxyl	Vehicle	0.75	0.15	16.09	0.000
Clindoxyl	Benzoyl Peroxide	0.75	0.42	4.08	0.030
Clindoxyl	Clindamycin	0.75	0.38	4.76	0.010
Benzoyl Peroxide	Vehicle	0.42	0.15	3.99	0.066
Clindamycin	Vehicle	0.38	0.15	3.44	0.097

<sup>a</sup> Obtained from logistic regression

*Reviewer Comment: The sponsor has demonstrated that the investigator's global perception of patients with good to excellent improvement is better with Clindoxyl™ Gel treatment than the perception of improvement for patients using clindamycin phosphate gel, benzoyl peroxide gel, or the vehicle gel.*

#### 8.1.1.4.3 SAFETY OUTCOMES

##### Exposure

Perfect patient compliance would have resulted in 77 applications of the drug product to the face of each patient with acne vulgaris. (applied once daily for 11 weeks). Overall, 83% of patients had an exposure of 71-84 applications. These exposures seem clinically reasonable, as in reality most patients are not able to achieve 100% compliance with medication dosing.

##### Adverse events

No patients dropped out of this study due to an adverse event. There were no clinically significant differences between drug and control groups with respect to the number of adverse events which occurred in each arm of the study. As one component of the sponsor's combination drug product (clindamycin phosphate) has known effects upon the gastrointestinal tract, it would have been appropriate for the sponsor to comment on the presence/absence of gastrointestinal symptoms in patients participating in this study. The sponsor has prepared a table (below) of adverse effects, but this does not include a sub-heading for gastrointestinal events. A review of the line listings of adverse event data in Study 150 shows that the headings in the table below are identical to the headings in the line listing, which indicates that no gastrointestinal events were reported.

Summary of Adverse Events in Study 150					
BODY SYSTEM / Event	Trt <sup>a</sup>	Number of Patients (% of total treated)			
		Related Mild	Not Related Mild	Moderate	Total
APPLICATION SITE / Paraesthesia	V	1 (3.3%)	0	0	1 (3.3%)
BODY AS A WHOLE / Fever	CX	0	1 (3.3%)	0	1 (3.3%)
/ Influenza-like symptoms	BPO	0	1 (3.3%)	0	1 (3.3%)
	CN	0	1 (3.3%)	0	1 (3.3%)
/ Varicella	CX	0	1 (3.3%)	0	1 (3.3%)
CENTRAL AND PERIPHERAL NERVOUS / Headache	BPO	0	2 (6.7%)	0	2 (6.7%)
	CN	0	1 (3.3%)	0	1 (3.3%)
	CX	0	1 (3.3%)	0	1 (3.3%)
FEMALE REPRODUCTIVE / Dysmenorrhea	CN	0	1 (3.3%)	0	1 (3.3%)
	V	0	1 (3.3%)	0	1 (3.3%)
	CX	0	2 (6.7%)	0	2 (6.7%)
/ Moniliasis genital	CX	0	1 (3.3%)	0	1 (3.3%)
/ Ovarian cysts	V	0	0	1 (3.3%)	1 (3.3%)
HEARING AND VESTIBULAR / Otitis media	CN	0	1 (3.3%)	0	1 (3.3%)
LIVER AND BILIARY / Biliary pain	CX	0	1 (3.3%)	0	1 (3.3%)
MUSCULO-SKELETAL / Myalgia	CX	0	1 (3.3%)	0	1 (3.3%)
PSYCHIATRIC / Anxiety	CN	0	1 (3.3%)	0	1 (3.3%)
RESPIRATORY / Bronchospasm	CN	0	1 (3.3%)	0	1 (3.3%)
/ Pharyngitis	BPO	0	2 (6.7%)	0	2 (6.7%)
	CN	0	1 (3.3%)	0	1 (3.3%)
/ Upper Resp Tract Infection	CN	0	1 (3.3%)	0	1 (3.3%)
	V	0	3 (10.0%)	0	3 (10.0%)
	CX	0	2 (6.7%)	0	2 (6.7%)
SKIN AND APPENDAGES / Dermatitis	V	0	1 (3.3%)	0	1 (3.3%)
/ Dermatitis contact	CX	0	1 (3.3%)	0	1 (3.3%)

<sup>a</sup> Treatment Codes: CX = Clindoxyl™ (n = 30), CN = Clindamycin (n = 30), BPO = Benzoyl Peroxide (n = 30), and V = Vehicle (n = 30). <sup>b</sup> Serious

**Reviewer Comment:** The sponsor should document pertinent positives AND pertinent negatives in categories which would be of concern with the use of this drug product (such as gastrointestinal events).

**Reviewer Comment:** Patients 56, 21, and 102 had symptoms which could also have been related to the gastrointestinal system and misinterpreted as menstrual/gall bladder pain. The sponsor should provide further clinical details which justify the classification for each of these patients.

The reviewer has compared the sponsor's original line listings (containing the adverse event description as noted by the investigator) with the transformed listing of adverse events presented above by the sponsor, and confirms that the sponsor has properly summarized the reported adverse events. All of the adverse events reported in the subjects on Clindoxyl™ Gel therapy have been tabulated by the reviewer with the start and stop days, cause, and outcome. This is presented below. These 8 events in 11 patients appear to be clinically insignificant.

Study Day	Subject #150	Adverse Event	Start	Stop	Cause	Outcome	Med Usage
010		Varicella	14	21		Recovered	No Change
115		Fever	50	52		Recovered	No Change
056		Headache	50	50		Recovered	No Change
056		Cold	9	13		Recovered	No Change
056		Menstrual Cramps	76	76	Concurrent	Recovered	No Change
021		Gall bladder pain	56	56	Concurrent	Recovered	No Change
021		Yeast Infection	21	26		Recovered	No Change
102		Menstrual Cramps	44	47	Concurrent	Recovered	No Change
023		Low back pain	44	51		Recovered	No Change
045		Cold	12	12		Recovered	No Change
094		Poison Ivy	69	73		Recovered	No Change

### Local Tolerance

Local tolerance to the study medication was determined by physician evaluation of erythema, peeling, and burning during each study visit. All four treatments were well tolerated, except for occasional mild or rarely moderate erythema, peeling, burning, or pruritus. For the benzoyl peroxide group the exception was that one patient (150/084) experienced severe erythema which was attributed to sunburn and not the study medication. Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment groups (see following table). There were no significant differences between the four treatment groups for change from baseline of signs and symptoms. Most treatment emergent signs and symptoms were modest and involved a single grade worsening (i.e. absent to mild or mild to moderate). This degree of worsening was also noted in 4 patients who had mild pruritus during the study - one (150/093) in the benzoyl peroxide gel

group, one (150/060) in the clindamycin phosphate gel group, and two (150/003 and 150/059) in the vehicle group. Substantial treatment emergent signs and symptoms, involving a 2 grade worsening, were observed in 2 patients in the benzoyl peroxide group (150/084-erythema and 150/078-peeling), in 1 patient in the clindamycin phosphate gel group (150/048-peeling), and in 3 patients in the vehicle group (150/016 and 150/095-erythema and 150/120-peeling). There were no patients in the Clindoxyl™ Gel group that had substantial treatment emergent signs and symptoms.

Local Tolerance (Change from Baseline of Signs and Symptoms) in Study 150 <sup>a</sup>						
Signs and		Number of Patients with Worsening Score				
Symptoms	Treatment	Week 2	Week 5	Week 8	Week 11	Any
		Erythema	Clindoxyl™	2 (8.3%)	1 (3.4%)	1 (3.6%)
	Clindamycin	1 (3.6%)	0	0	0	1 (3.3%)
	Benzoyl Peroxide	4 (14.3%)	3 (11.5%)	1 (3.8%)	2 (8.3%)	7 (23.3%)
	Vehicle	3 (11.1%)	4 (14.8%)	1 (3.6%)	2 (7.4%)	6 (20.7%)
Peeling	Clindoxyl™	6 (25.0%)	4 (13.8%)	3 (10.7%)	1 (3.6%)	10 (33.3%)
	Clindamycin	1 (3.6%)	2 (7.4%)	1 (3.4%)	0	3 (10.0%)
	Benzoyl Peroxide	2 (7.1%)	2 (7.7%)	2 (7.7%)	1 (4.2%)	6 (20.0%)
	Vehicle	5 (18.5%)	3 (11.1%)	0	0	8 (27.6%)
Burning	Clindoxyl™	0	0	0	0	0
	Clindamycin	0	0	0	0	0
	Benzoyl Peroxide	0	0	0	0	0
	Vehicle	0	1 (3.7%)	0	0	1 (3.7%)

<sup>a</sup> There were no significant differences between groups for any worsening when analyzed by Fisher's exact test ( $p > 0.05$ ).

### Overall tolerance

Overall tolerance is a global assessment made by the investigator on day 11. The investigator in study 150 has judged all but one subject to have an EXCELLENT tolerance, which raises a concern about the ability of this scale to adequately discriminate between different levels of subject tolerance. Perhaps successful completion of treatment is considered an excellent response? As the sponsor has not defined these levels, the reviewer can only surmise. Overall tolerance would not appear to be the best primary variable for evaluation of safety.

Distribution of Patients by Overall Tolerance Scores in Study 150				
Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)
Clindoxyl™	0	0	0	30 (100%)
Clindamycin	0	0	0	30 (100%)
Benzoyl Peroxide	0	0	1 (3.3%)	29 (96.7%)
Vehicle	0	0	0	29 (100%)

There was no significant difference between treatments when analyzed by Fisher's exact test ( $p > 0.05$ ).

## 8.1.1.5 REVIEWER'S CONCLUSIONS OF STUDY RESULTS

Efficacy

Summary of Study # 150 with Comparison of Results at Week 11 to Clindoxyl™ Gel				
Parameter	Clindoxyl™	Benzoyl Peroxide	Clindamycin	Vehicle™
Number of valid patients at week 11	28	24	29	27
Mean age in years (all patients)	19.2	19.0	17.2	18.4
Percent male/female (all patients)	33/67	47/53	37/63	37/63
<b>Noninflammatory Lesions</b>				
Mean Baseline count (all patients)	58.1	89.3	70.7	90.2
Mean reduction at week 11	12.0	14.7	-0.6	-4.3
p-values: comparison to Clindoxyl™	NA	0.738	0.105	0.040
Mean % reduction at week 11	26.5	14.2	-5.2	-12.6
p-values: comparison to Clindoxyl™	NA	0.309	0.007	0.001
<b>Inflammatory Lesions</b>				
Mean Baseline count (all patients)	26.8	33.0	31.1	35.6
Mean reduction at week 11	17.0	14.1	13.0	8.1
p-values: comparison to Clindoxyl™	NA	0.508	0.345	0.040
Mean % reduction at week 11	66.5	39.5	34.5	19.2
p-values: comparison to Clindoxyl™	NA	0.037	0.010	0.000
<b>Total Lesions</b>				
Mean baseline counts	84.9	122.3	101.8	125.8
Mean reduction at week 11	29.0	28.8	12.4	3.9
p-values: comparison to Clindoxyl	NA	0.985	0.125	0.023
Mean % reduction at week 11	41.5	21.9	10.4	-1.4
p-values: comparison to Clindoxyl™	NA	0.066	0.003	0.000
p-value: AUC of % reduction		0.146		
<b>Global Improvement at week 11</b>				
% of patients with good to excellent	75.0	41.7	37.9	14.8
p-values comparison to Clindoxyl	NA	0.030	0.010	0.000
<b>Overall Tolerance</b>				
% of patients with excellent	100	96.7	100	100

This study indicates that Clindoxyl™ Gel is more clinically effective than vehicle in the treatment of acne vulgaris, and provides supportive evidence that Clindoxyl™ Gel may be more effective than clindamycin phosphate gel and benzoyl peroxide gel. The superiority of Clindoxyl™ Gel in comparison with the vehicle is obvious in all four measurements: noninflammatory lesions counts, inflammatory lesion counts, total lesions counts, and global assessment.

The clindamycin phosphate gel arm is essentially ineffective against noninflammatory lesions (as demonstrated by a 5% increase in the percentage of lesions), while the Clindoxyl™ Gel arm shows a 26% reduction in these lesions ( $p = 0.007$ ). This demonstrates that the benzoyl peroxide in the combination is enhancing the effect on noninflammatory lesions. In the treatment of inflammatory lesions, the clindamycin phosphate gel arm shows approximately the same clinical reduction from baseline (31.1 minus 13) as the benzoyl peroxide gel arm (33 minus 14.1) and the Clindoxyl™ Gel arms (26.8 minus 17). Although the percent reduction reaches statistical significance, the mean

reduction p value does not. This study is supportive in demonstrating that the clinical efficacy of Clindoxyl™ Gel may be superior to benzoyl peroxide gel or clindamycin phosphate gel, but it does NOT robustly demonstrate the clinical superiority of Clindoxyl™ Gel compared with either component.

This is not a pivotal trial, as it is a single investigator study with less than 30 patients in each arm.

#### Safety

This study reassures the reviewer that Clindoxyl™ Gel is probably safe when used once daily for 11 weeks in the treatment of acne vulgaris. However, the sponsor must provide pharmacokinetic evidence that demonstrates that Clindoxyl™ Gel causes no greater absorption of clindamycin than clindamycin phosphate gel alone.

8.1.2 INDICATION # 1 REVIEWER'S TRIAL # 2 STUDY #151 SPONSOR'S PROTOCOL#9405  
TITLE: A MULTICENTER, DOUBLE-BLIND CLINICAL COMPARISON OF THE EFFICACY AND SAFETY OF CLINDOXYL™ GEL, CLINDAMYCIN PHOSPHATE GEL, BENZOYL PEROXIDE GEL, AND VEHICLE GEL IN THE ONCE DAILY TREATMENT OF ACNE VULGARIS FOR 11 WEEKS.

#### INVESTIGATORS:

Study Site 151A (20 Sept 94 to 02 Feb 95)  
Jane.S. Lindholm, M.D.  
Minnesota Clinical Study Center  
7205 University Avenue N.D.  
Fridley, Minnesota 55432

Study Site 151B (26 Oct 94 to 12 Jan 95)  
Christopher J. Huerter, M.D.  
Harris Laboratories Inc  
109 Applewood Mall- Center Mall  
Omaha, Nebraska 68105

Site 151C (26 Oct 94 to 09 Mar 95)  
Donald P.Lookingbill, M.D.  
Milton S. Hershey Medical Center  
P.O. Box 850  
Hershey, Pennsylvania 17033

Site 151D (13 Oct 94 to 19 Jun 95)  
J.M. Swinehart, M.D.  
Colorado Medical Research Center  
950 East Harvard Avenue  
Suite 630  
Denver, Colorado 80210

### 8.1.2.1 OBJECTIVE/RATIONALE

See Section 8.1.1.1

### 8.1.2.2 DESIGN

This study was a vehicle controlled, double-blind, parallel, randomized multicenter trial comparing Clindoxyl™ Gel, clindamycin phosphate gel, benzoyl peroxide gel, and vehicle gel. The medications were used concurrently in four groups randomly assigned in the order of entry so that approximately two sevenths of the study patients would be treated with Clindoxyl™ Gel, two sevenths with clindamycin phosphate gel, two sevenths with benzoyl peroxide gel, and one seventh with vehicle gel in a parallel fashion.

### 8.1.2.3 PROTOCOL

#### 8.1.2.3.1 POPULATION

Approximately 70 patients (20 patients/each active group and 10 patients/vehicle group) were to be selected for participation at each site, for a total of 280 patients. The inclusion/exclusion criteria and methods are the same as in study 150 (see 8.1.1.3.1)

#### 8.1.2.3.2 ENDPOINTS

See section 8.1.1.3.2

#### 8.1.2.3.3 STATISTICAL CONSIDERATIONS

As this was a multi-centered trial, the statistical methods applied included tests for site by treatment interaction, in addition to the statistical considerations discussed in Section 8.1.1.3.3

### 8.1.2.4 RESULTS

#### 8.1.2.4.1 POPULATIONS ENROLLED/ANALYZED

A total of 273 patients with acne vulgaris were entered into this study: 70 patients were entered at each site except Site 151D which only entered 63 patients after 6 months of recruiting. The sponsor decided to stop recruitment so that the study could be completed. Of the 273 subjects enrolled, 42 patients failed to complete the study with 9 dropouts in the Clindoxyl™ Gel group, 18 dropouts in the clindamycin phosphate gel group, 8 dropouts in the benzoyl peroxide gel group, and 7 dropouts in the vehicle gel group. The enrollment and dropouts by site and subject number are summarized below.

	Site 151A	Site 151B	Site 151C	Site 151D	Total
<b>Enrollment (ITT-W0)</b>	<b>n</b>	<b>n</b>	<b>n</b>	<b>n</b>	
BZPO	20	20	20	18	78
Clindamycin	20	20	20	18	78
Vehicle	10	10	10	9	39
Clindoxyl	20	20	20	18	78
				Sum of patients entered	=273
<b>Completed Study (Intent to treat, Week 11)</b>	<b>n Dropouts</b>	<b>n Dropouts</b>	<b>n Dropouts</b>	<b>n Dropouts</b>	<b>Dropout totals</b>
<b>BZPO - Completed wk 11:</b>	17	19	19	15	
Identity of dropouts:	05,24,52	07	64	37,49,55	8
<b>Clindamycin Complete 11</b>	17	15	16	12	
Identity of dropouts	16,29,60	06,23,25,52,62	05,08,42,70	07,11,29,36,56,58	18
<b>Vehicle Completed wk 11:</b>	7	10	9	6	
Identity of dropouts:	01,36,48		48	04,24,32	7
<b>Clindoxyl-Complete wk 11</b>	18	18	18	15	
Identity of dropouts	02,31	14,45	41,51	08,40,48	9
			Sum of dropouts		=42
			Remaining patients		=231

Five of the subjects that completed the study were then excluded from the population due to significant protocol violations, which are summarized below:

Arm	Site	Subject	Reason for exclusion
Vehicle	151B	58	Antibiotic Use
Clindoxyl	151B	63	Non Compliant Birth Control Usage
Clindoxyl	151D	46	Non Compliant Birth Control Usage
Benzoyl	151D	35	Non Compliant Birth Control Usage
Benzoyl	151C	26	Using wrong medication

The remaining subjects are the Preferred Data Set, and used for efficacy analysis. The reviewer has summarized below the numbers in the Intent to Treat group at baseline (ITTW0); the numbers in the Valid Case group (also known as the Preferred Data Set - PDS); and the subject numbers of the excluded cases (invalid patients). Review of the line listings/case report form summaries for the excluded cases indicates that all exclusions are reasonable.



PATIENTS WITH CONCOMITANT MEDICATION VIOLATIONS			
Site/Patient	Arm	Medication/not valid	Medication/retained as valid
<b>151A</b>			
01	Vehicle	Augmentin from 9/30/94	
47	Vehicle		Flagyl 1500mg 9 days
36	Vehicle	Amoxicillin 1500mg 11days	
48	Vehicle	Erythromycin Since 11/3/94	
22	Clindamycin		Penicillin 1000mg 11d
09	Clindoxyl		Penicillin 2000mg for 19d
31	Clindoxyl	Erythromycin 10 days, 2000mg	
56	Clindoxyl		Desogen since 9/17/94
<b>151B</b>			
23	Clindamycin	Amoxicillin Since 11/7/94	
52	Clindamycin	Multiple	
62	Clindamycin	Loracarbef	
14	Clindoxyl	Sulfamethoxazole	
<b>151C</b>			
64	BZPO	Amoxil 750 mg 10d	
42	Clindamycin	Keflex 1000mg 10 d	
70	Clindamycin	Erythromycin	
41	Clindoxyl	Zithromax	
51	Clindoxyl	Keflex 1000mg 10d Prednisone 6 days	
<b>151D</b>			
03	BZPO		Penicillin 3d
14	BZPO		Amoxicillin 1000mg 3d
55	BZPO	Amoxicillin 10d 1500mg	
24	Vehicle	Cephalexin 4d 1500mg Keflex 5d 1500mg Augmentin 14d 750mg	
19	Clindoxyl		Cephalexin 5d 1000mg
23	Clindoxyl		Amoxicillin 1500mg 3d

The demographic characteristics (sex, race, age, age range, baseline lesion counts, and baseline tolerance scores) of patients in each group of the intent-to-treat data set were not significantly different ( $P > 0.05$ ). The patient population consisted primarily of Caucasian teenagers of either sex.

#### 8.1.2.4.2 EFFICACY ENDPOINT OUTCOMES

##### Noninflammatory lesions

The baseline lesion counts are similar across treatment arms for all sites combined. Clindoxyl™ Gel shows a clinically and statistically ( $p = 0.000$ ) significant percent reduction in

noninflammatory lesion and mean reduction (18.5) counts at 11 week compared to vehicle (0.8 lesions/+9.6%) and clindamycin (8.2 lesions/15.3%). Clindoxyl™ Gel and benzoyl peroxide gel have essentially the same mean count at baseline (48) and show similar mean reductions (16/18) and percentage reductions (34/40). Clindoxyl™ Gel does not show any clinical superiority to the benzoyl peroxide gel arm in the treatment of noninflammatory lesions

Week	Statistic <sup>1</sup>	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl™
0	Mean Count	48.5	46.0	52.6	48.6
11	Mean Reduction	16.3 <sup>v</sup>	8.2	0.8	18.5 <sup>v,c</sup>
	Mean % Reduction	34.9 <sup>v</sup>	15.3 <sup>v</sup>	-9.6	40.4 <sup>v,c</sup>

<sup>1</sup> Reduction = baseline count - count at a later week  
<sup>v,c,b</sup> Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), p<0.05 based on valid patients, LOCF.

Statistical comparisons of Clindoxyl™ Gel with the other arms of the study are presented below. The p values derived from the mean reduction and the percentage reduction are considered together, and for these noninflammatory lesions they trend together.

Treatment Comparison		Statistic <sup>b</sup>	Least Sq Mean			p-Value
First	Second		First	Second	Difference	
Clindoxyl	Vehicle	Reduction at Week 11	18.3	1.1	17.2	0.001
		% Reduction at Week 11	40.1	-10.5	50.6	0.000
Clindoxyl	Benzoyl Peroxide	Reduction at Week 11	18.3	16.0	2.3	0.549
		% Reduction at Week 11	40.1	34.0	6.1	0.456
Clindoxyl	Clindamycin	Reduction at Week 11	18.3	8.1	10.2	0.012
		% Reduction at Week 11	40.1	14.5	25.6	0.003
Benzoyl Peroxide	Vehicle	Reduction at Week 11	16.0	1.1	14.9	0.003
		% Reduction at Week 11	34.0	-10.5	44.5	0.000
Clindamycin	Vehicle	Reduction at Week 11	8.1	1.1	7.0	0.166
		% Reduction at Week 11	14.5	-10.5	25.0	0.018

### Inflammatory lesions

The baseline lesions counts are again similar across all treatment arms for the combined centers, varying from 25.5 to 29.9, but the mean number of inflammatory lesions is significantly lower in this study than the mean number of noninflammatory lesions. Since these lesion counts are low, a small clinical difference in actual mean reduction, which may not be of any clinical significance, can translate into a fairly large percentage reduction.

Effect of Time and Treatment on Inflammatory Lesion Counts for the Preferred Data Set in Study 151					
Week	Statistic <sup>1</sup>	Benzoyl Peroxide N=68	Clindamycin N=60	Vehicle N=31	Clindoxyl™ N=67
0	Mean Count	29.9	25.5	28.0	25.8
11	Mean Reduction	12.4 <sup>v</sup>	8.3 <sup>v</sup>	-0.5	14.6 <sup>v,c</sup>
	Mean % Reduction	39.4 <sup>v</sup>	35.9 <sup>v</sup>	-7.6	58.4 <sup>v,c,b</sup>

<sup>1</sup> Reduction = baseline count - count at a later week  
<sup>v,c,b</sup> Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), p<0.05 based on valid patients, LOCF.

This is demonstrated below in the comparison of Clindoxyl™ Gel with benzoyl peroxide gel. A mean reduction in lesion count difference of 2.2 (p = 0.278) results in a percentage reduction of 19.3% (p = 0.003) This relatively insignificant clinical difference of only two actual lesions (well within the range of clinical error) translates into a statistically significant difference in the mean percentage reduction.

Results of Statistical Analyses of Inflammatory Lesion Counts in the Preferred Data Set <sup>a</sup> of Study 151						
Treatment Comparison			Least Square Mean			
First	Second	Statistic <sup>b</sup>	First	Second	Difference <sup>e</sup>	p-Value
Clindoxyl	Vehicle	Reduction at Week 11	14.5	-1.3	15.9	0.000
		% Reduction at Week 11	58.0	-10.7	68.6	0.000
Clindoxyl	BZPO	Reduction at Week 11	14.5	12.2	2.3	0.278
		% Reduction at Week 11	58.0	38.7	19.3	0.003
Clindoxyl	Clindamycin	Reduction at Week 11	14.5	8.1	6.4	0.005
		% Reduction at Week 11	58.0	34.6	23.4	0.000
BZPO	Vehicle	Reduction at Week 11	12.2	-1.3	13.5	0.000
		% Reduction at Week 11	38.7	-10.7	49.4	0.000
Clindamycin	Vehicle	Reduction at Week 11	8.1	-1.3	9.5	0.001
		% Reduction at Week 11	34.6	-10.7	45.2	0.000

<sup>a</sup> Site\*treatment interaction was not significant (p>0.1).  
<sup>b</sup> Reduction = baseline count - count at a later week

The Clindoxyl™ Gel arm is clinically superior to vehicle gel and also to clindamycin phosphate gel, which demonstrates the usefulness of the benzoyl peroxide component in the combination over clindamycin phosphate alone. The sponsor has not demonstrated that Clindoxyl™ Gel is superior to benzoyl peroxide gel, and therefore has not demonstrated the usefulness of the clindamycin phosphate in the combination product.

Total Lesion Counts:

The sponsor provided data on total lesion count analysis by amendment (8 Aug 96). In study 151 the order of both mean reduction and percent reduction was consistently Clindoxyl™ Gel>benzoyl peroxide gel>clindamycin phosphate gel> vehicle gel.

Study # 151					
Effect of Time and Treatment on Total Lesion Counts for the Preferred Data Set					
WEEK	STATISTIC	BZPO	CLINDAMYCIN	VEHICLE	CLINDOXYL
0	Mean Count	78.4	71.4	80.6	74.4
11	Mean Reduction	28.7	16.6	0.3	33.1
	Mean % Reduction	38.3	26.5	-6.0	47.7

Study # 151			
Results of Statistical Analysis of Total Count in Preferred Data Set			
Treatment Comparison		Statistic	p-Value
First	Second		
Clindoxyl	Vehicle	Reduction at week 11	0.000
		% reduction at week 11	0.000
		AUC of % reduction	0.000
Clindoxyl	Clindamycin	Reduction at week 11	0.001
		% reduction at week 11	0.001
		AUC of % reduction	0.000
Clindoxyl	BZPO	Reduction at week 11	0.344
		% reduction at week 11	0.097
		AUC of % reduction	0.020

Analysis of reduction and percent reduction at week 11 and AUC of percent reduction showed that the Clindoxyl™ Gel treatment had significantly greater activity clindamycin phosphate gel or vehicle gel, but the combination gel has again not demonstrated superiority to benzoyl peroxide. This may be due to the fact that the study has relatively low numbers of inflammatory lesions, and the clindamycin phosphate component does not have adequate efficacy to demonstrate its contribution with this small sample size of lesions.

Global Improvement:

The individual site data on global improvement are presented below. Once again, Clindoxyl™ Gel has the best overall outcome, followed by benzoyl peroxide gel and clindamycin phosphate gel, with the vehicle gel trailing.

Percentage of patients with good to excellent global improvement Study 151				
	151A	151B	151C	151D
Clindoxyl	66.7	70.6	61.1	50.0
BZPO	52.9	73.7	22.2	7.1
Clindamycin	52.9	46.7	25.0	8.3
Vehicle	14.3	0	0	16.7

Patients with good to excellent improvement in the preferred data set of study 151 at 11 weeks were distributed as follows: Vehicle - 2/31 (6.5%), Clindamycin phosphate -21/60 (35%), benzoyl peroxide 28/68 (41.1%), and Clindoxyl™ Gel 42/67 (62.7%). Statistical analysis showed that these differences were all significant at the  $p < 0.05$  level. The investigators were able to discriminate the clinical outcome between Clindoxyl™ Gel and the following: vehicle ( $p = 0.000$ ), benzoyl peroxide gel ( $p=0.013$ ) and clindamycin phosphate gel ( $p=0.002$ ). In addition, benzoyl peroxide ( $p=0.000$ ) and clindamycin phosphate ( $p=0.003$ ) were both statistically different from the vehicle.

Comparisons of Treatment Effects on Proportion of Patients with Good to Excellent Global Improvement in the Preferred Data Set at Week 11 <sup>a</sup> Study 151					
Treatment Comparison		Proportion		Estimated Odds Ratio <sup>b</sup>	p-Value <sup>b</sup>
First	Second	First	Second		
Clindoxyl	Vehicle	0.63	0.06	29.1	0.000
Clindoxyl	Benzoyl Peroxide	0.63	0.41	2.6	0.013
Clindoxyl	Clindamycin	0.63	0.35	3.5	0.002
Benzoyl Peroxide	Vehicle	0.41	0.06	11.1	0.000
Clindamycin	Vehicle	0.35	0.06	8.4	0.003

<sup>a</sup> Site\*treatment interaction was not significant ( $p>0.1$ )

<sup>b</sup> Obtained from logistic regression

This study has demonstrated that treatment with Clindoxyl™ Gel is superior to both clindamycin phosphate gel, benzoyl peroxide gel, and vehicle in the global assessment outcome of patients with acne vulgaris. These results should be expected, except in the comparison with benzoyl peroxide. Since this study did not show a meaningful difference in outcomes between Clindoxyl™ Gel and benzoyl peroxide gel in any of the lesion counts, it is unusual that the global assessment (which is based upon visual perception of lesion counts) would be significant.

## 8.1.2.4.3 SAFETY OUTCOME

Exposure

The extent of exposure to study medications is summarized below. Once daily treatment for 11 weeks would result in 77 exposures. Of the 226 patients in the preferred data set, 216 were able to apply the medication between 71 and 84 times.

Summary of Extent of Exposure to Medication in Study 151					
# of Applications	Distribution of Patients by # of Applications (planned exposure 77 applications in 77 days)				
	Benzoyl	Clindamycin	Vehicle	Clindoxyl™	ALL
0 to 14*	4 (5.1%)	12 (15.4%)	5 (12.8%)	5 (6.4%)	26 (9.5%)
15 to 28	0	1 (1.3%)	0	0	1 (0.4%)
29 to 42	2 (2.6%)	2 (2.6%)	2 (5.1%)	3 (3.8%)	9 (3.3%)
43 to 56	2 (2.6%)	2 (2.6%)	0	1 (1.3%)	5 (1.8%)
57 to 70	5 (6.4%)	2 (2.6%)	1 (2.6%)	8 (10.3%)	16 (5.9%)
71 to 84	65 (83.3%)	58 (74.4%)	30 (76.9%)	61 (78.2%)	214 (78.4%)
> 84	0	1 (1.3%)	1 (2.6%)	0	2 (0.7%)

\* Includes unknowns.

Overall Tolerance

Overall tolerance was identified by the sponsor as the primary safety variable. The distribution of patients by overall tolerance scores is presented below. There were no significant differences in the distribution of patients by treatment and overall tolerance scores. The majority of patients in all arms received scores of excellent. Subject 151D/49, who dropped out because of the adverse event of "rash on face, burning, and stinging after application" should have been classified as Poor. As there are no subjects in the Poor category, it is unclear where this patient was classified. The sponsor has not accounted for all patients in the intent to treat group at week 0, which is 273 patients.

*Reviewer Comment: Since the sponsor did not define the levels of this scale (Poor, Fair, Good, and Excellent), the outcomes are not useful. See sections 8.1.1.3.2. and 8.1.2.3.2.*

Distribution of Patients by Overall Tolerance Score <sup>a</sup> in Study 151 n=263				
Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)
Benzoyl Peroxide	0	0	6 (7.8%)	71 (92.2%)
Clindamycin	0	1 (1.4%)	4 (5.6%)	67 (93.1%)
Vehicle	0	1 (2.7%)	2 (5.4%)	34 (91.9%)
Clindoxyl™	0	0	6 (7.8%)	71 (92.2%)

<sup>a</sup> There was no significant difference between treatment groups (p>0.05) when analyzed by Fisher's exact test



Adverse Events Recorded in Patients on Clindoxyl in Study 151					
Study/Subj	Event	Duration	Related?	Rx Usage	Outcome
Whole Body					
151A/09	Slight tingling with medication application	Few Seconds	Yes	No change	Recovered
151A/10	Ache (concurrent illness)	1 day	No	No change	Recovered
151B/03	Flu	8 days	No	No change	Recovered
151B/53	Flu	3 days	No	No change	Recovered
151D/19	Liposuction of abdomen	3hrs	No	No change	Recovered
151D/23	Allergic reaction to fish (rash)	3 days	No	No change	Recovered
CNS					
151A/49	Headache	1 day	No	No change	Recovered
151B/08	Headache	.5 hr	No	No change	Recovered
151B/08	Headache	2hrs	No	No change	Recovered
151B/24	Headache	40min	No	No change	Recovered
151B/32	Headache	3 hrs	No	No change	Recovered
151B/27	Headache	7 hrs	No	No change	Recovered
151 B/27	Headache	6hrs	No	No change	Recovered
151B/43	Headache	45 min	No	No change	Recovered
151B/66	Headache	8hrs	No	No change	Recovered
151C/31	Headache	3hrs	No	No change	Recovered
151D/57	Headache	6hrs	No	No change	Recovered
Female Repro					
151A/42	Cramps	7 days	No	No change	Recovered
151B/63	Ovarian Cyst(considered valid patient) Ortho 28 for 64 days/Cataflam prn	Unknown	No	No change	Unknown
Gastrointestinal					
151A/09	Wisdom tooth extraction pain	18d	No	No change	Recovered
151A/09	Tooth abscess	6d	No	No change	Recovered
151A/09	Tooth abscess	7d	No	No change	Recovered
151A/15	Wisdom tooth pulled	1d	No	No change	Recovered
151B/14	Diarrhea(with n/v listed below) E.Coli	9d	No	Discontinue	Recovered
151B/14	Nausea	9d	No	Discontinue	Recovered
151B/14	Vomiting	9d	No	Discontinue	Recovered
151B/63	Irritable bowel, intermittent Treated with Dicyclomine 40mg prn since 1/3/95	Unknown	No	No change	Unknown
151D/46	Diarrhea	4hrs	No	No Change	Recovered
Musculoskeletal					
151A/49	Heel Pain	24hrs	No	No change	Recovered
	Knee pain(Entry error p203, Vol 1.27)	2 days	No	No change	Recovered
151A/49	Arm Ace	1 day	No	No change	Recovered
151C/35	Broken Toe	20 d	No	No change	Recovered
141C/41	Broken Finger	4 weeks	No	No change	Recovered
Respiratory					
16 patients	Common cold symptoms, once ea		No	No change	Recovered
1 patient 3x	Cold symptoms		No	No change	Recovered
Skin					
151D/19	Mole removal (routine)	10min	No	No change	Recovered

### Local Tolerance

Comments on the local tolerance category have been previously detailed under Study 150 and 151, Sections 8.1.1.3.2. and 8.1.2.3.2

Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment arms. There were no significant differences in the distribution of patients by treatment and treatment emergent signs and symptoms except for peeling where the benzoyl peroxide gel and Clindoxyl™ Gel groups had a significantly higher incidence (20%) in worsening peeling scores. This could reasonably be expected, as peeling is a well known side effect of benzoyl peroxide. In general, emergent peeling was more frequent at the earlier evaluations (weeks 2, 5, and 8) for these 2 groups, which is also clinically expected. Little or no emergent burning or pruritus was observed, but some patients (6-12%) had emergent erythema and dryness in all active groups. Most treatment emergent signs and symptoms involved a modest (1 grade) worsening. Five patients had a substantial (>1 grade) worsening of pruritus, dryness, or peeling but only two of these patients (dryness and peeling) were in the Clindoxyl™ Gel group. All of these events are clinically expected and acceptable as a potential side effects of acne treatment.

Local Tolerance (Change from Baseline of Signs and Symptoms) in Study 151						
		Number of Patients with Worsening Score				
Signs and Symptoms	Treatment	Week 2	Week 5	Week 8	Week 11	Any <sup>a</sup>
Erythema	Benzoyl	4(5.2%)	5(6.9%)	3(4.5%)	2(2.9%)	8(10.4%)
	Clindamycin	3(4.2%)	2(3.0%)	1(1.7%)	2(3.3%)	6(8.3%)
	Vehicle	0	0	0	1(3.1%)	1(2.7%)
	Clindoxyl	2(2.6%)	5(7.1%)	2(3.0%)	1(1.4%)	5(6.5%)
Peeling <sup>a</sup>	Benzoyl	8(10.4%)	12(16.7%)	9(13.4%)	5(7.1%)	16(20.8%)
	Clindamycin	2(2.8%)	4(6.1%)	3(5.0%)	3(5.0%)	5(6.9%)
	Vehicle	0	1(2.9%)	1(3.0%)	1(3.1%)	2(5.4%)
	Clindoxyl	8(10.4%)	8(11.4%)	6(9.1%)	3(4.4%)	14(18.2%)
Burning	Benzoyl	0	1(1.4%)	0	0	1(1.3%)
	Clindamycin	0	0	0	0	0
	Vehicle	0	0	0	0	0
	Clindoxyl	1(1.3%)	0	1(1.5%)	0	2(2.6%)
Dryness	Benzoyl	4(5.2%)	5(6.9%)	3(4.5%)	4(5.7%)	8(10.4%)
	Clindamycin	4(5.6%)	4(6.1%)	1(1.7%)	1(1.7%)	6(8.3%)
	Vehicle	1(2.7%)	2(5.9%)	1(3.0%)	1(3.1%)	2(5.4%)
	Clindoxyl	3(3.9%)	4(5.7%)	5(7.6%)	4(5.8%)	9(11.7%)

<sup>a</sup> A significance difference was seen in the distribution of any worsening of peeling when analyzed by Fisher's exact test (p=0.02). There were no significant differences seen for any worsening of erythema, burning, or dryness (p>0.05)

## 8.1.2.5 REVIEWER'S CONCLUSIONS OF STUDY RESULTS

Efficacy

Both mean reductions and mean percentage reductions were considered in the analysis. As described in detail previously, Clindoxyl™ Gel has demonstrated superior efficacy than vehicle and clindamycin phosphate gel in the treatment of noninflammatory lesions, inflammatory lesions, total lesion counts, and in the investigator's global assessment.

Summary of Study # 151 with Comparison of Results at Week 11 to Clindoxyl™ Gel				
Parameter	Clindoxyl™	Benzoyl Peroxide	Clindamycin	Vehicle
	N=67	N=68	N=60	N=31
Number of valid patients at week 11	67	68	60	31
Mean age in years (all patients)	17.7	18.8	19.2	18.0
Percent male/female (all patients)	50/50	54/46	55/45	54/46
<b>Noninflammatory Lesions</b>				
Mean baseline count (all patients)	45.9	48.1	44.7	51.7
Mean reduction at week 11	18.5	16.3	8.2	0.8
p-values: comparison to Clindoxyl™	NA	0.549	0.012	0.001
Mean % reduction at week 11	40.4	34.9	15.3	-9.6
p-values: comparison to Clindoxyl™	NA	0.456	0.003	0.000
<b>Inflammatory Lesions</b>				
Mean baseline count (all patients)	26.4	29.2	25.5	27.6
Mean reduction at week 11	14.6	12.4	8.3	-0.5
p-values: comparison to Clindoxyl™	NA	0.278	0.005	0.000
Mean % reduction at week 11	58.4	39.4	35.9	-7.6
p-values: comparison to Clindoxyl™	NA	0.003	0.000	0.000
<b>Total Lesions</b>				
Mean baseline counts	74.4	78.4	71.4	80.6
Mean reduction at week 11	33.1	28.7	16.6	0.3
p-values: comparison to Clindoxyl™	NA	0.344	0.001	0.000
Mean % reduction at week 11	47.7	38.3	26.5	-6.0
p-values: comparison to Clindoxyl™	NA	0.097	0.001	0.000
p-value: AUC of % reduction	NA	0.020	0.000	0.000
<b>Global Improvement at week 11</b>				
% of patients with good to excellent	62.7	41.2	35.0	6.5
p-values: comparison to Clindoxyl™	NA	0.013	0.002	0.000
<b>Overall Tolerance</b>				
% of patients with excellent	92.2	92.2	93.1	91.9

This study demonstrates that Clindoxyl™ Gel is clinically and statistically superior to both clindamycin phosphate gel and the vehicle gel in the treatment of acne vulgaris. However, the study has not demonstrated the superiority of Clindoxyl™ Gel when compared with benzoyl peroxide gel alone in the reduction of noninflammatory lesion counts, inflammatory lesion counts, or total lesion counts. The study did demonstrate the superiority of Clindoxyl™ Gel compared to benzoyl peroxide gel in global assessment.

### Safety

The study presents no data which would indicate that there are any safety concerns related to the use of Clindoxyl™ Gel for 11 weeks as a daily application for the treatment of acne vulgaris. However, as previously discussed, the sponsor should provide additional pharmacokinetic data addressing the absorption of Clindoxyl™ Gel following topical treatment.

#### 8.1.3 INDICATION #1 REVIEWER'S TRIAL #3 STUDY #152 SPONSOR'S PROTOCOL # 9406

TITLE: A TWO CENTER, DOUBLE BLIND CLINICAL COMPARISON OF THE EFFICACY AND SAFETY OF CLINDOXYL™ GEL, CLINDAMYCIN PHOSPHATE GEL, BENZOYL PEROXIDE GEL, AND VEHICLE GEL IN THE ONCE DAILY TREATMENT OF ACNE VULGARIS FOR 11 WEEKS.

#### INVESTIGATORS:

Site 152A: 26 Sept 94 to 01 Mar 95  
Michael T. Jarratt, M.D.  
Pharmaco LSR, HRC  
2901 N. IH-35  
Austin, Texas 78722

Site 152B: 03 Oct 94 to 22 Dec 94  
Richard Berger, M.D.  
Hill Top Research, Inc.  
223 Route 18, Suite 203  
East Brunswick, New Jersey 08816

#### 8.1.3.1 OBJECTIVE/RATIONALE

See section 8.1.1.1

#### 8.1.3.2 DESIGN

This is a controlled, double-blind, parallel, randomized, multicenter trial (two centers).

#### 8.1.3.3 PROTOCOL

See Section 8.1.2.3

### 8.1.3.3.1 POPULATION

Approximately 140 patients (40 patient each active group and 20 patients/vehicle group) were to be selected at each of the two sites for a total sample size of 280. The remainder of the population description is identical to that in studies 150 and 151.

### 8.1.3.3.2 ENDPOINTS

See Section 8.1.2.3.2

### 8.1.3.3.3 STATISTICAL CONSIDERATIONS

See previous statistical sections and statistician's review.

### 8.1.3.4 RESULTS

#### 8.1.3.4.1 POPULATIONS ENROLLED/ANALYZED

A total of 280 patients entered the study, with 140 being randomized at each site. The characteristics of sex, race, age range, and baseline lesion counts of patients in the intent to treat data set were not significantly different. However, there were highly significant differences in the baseline noninflammatory lesion counts ( $p < 0.001$ ) where Site 152A enrolled patients with nearly twice as many noninflammatory lesions as Site 152B.

#### 8.1.3.4.2 EFFICACY ENDPOINT OUTCOMES

##### Noninflammatory Lesions

The mean baseline noninflammatory lesion counts are approximately the same at each site, ranging from 34.1 to 41.6. At week 11, the mean reduction and percent mean reduction of counts for Clindoxyl™ Gel is 12.5/ 25.7%, for benzoyl peroxide gel is 8.7/18.8%, for clindamycin phosphate gel is 4.5/11.2% and for vehicle gel is 5.5/15.4%.

Effect of Time and Treatment on Non-Inflammatory Lesion Counts for the Preferred Data Set in Study 152						
Week	Statistic <sup>1</sup>	Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl™
0	Mean Count	152A	51.0	44.2	52.1	59.4
		152B	23.4	24.5	26.9	24.2
		ALL	37.2	34.1	39.8	41.6
11	Mean Reduction	152A	16.2	6.2	7.8	23.0 <sup>v,c</sup>
		152B	1.2 <sup>v</sup>	2.9	3.2	2.2
		ALL	8.7	4.5	5.5	12.5 <sup>v,c</sup>
	Mean Reduction	% 152A	31.5(35)	9.0(34)	17.4(19)	41.8 <sup>v,c(36)</sup>
		152B	6.2(35)	13.3(36)	13.3(18)	10.0(37)
		ALL	18.8	11.2	15.4	25.7 <sup>v,c</sup>

<sup>1</sup> Reduction = baseline count - count at a later week  
<sup>v,c,b</sup> Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b),  $p < 0.05$  (Tables 152.9a&b)

Pairwise comparisons demonstrate that Clindoxyl™ Gel is statistically superior to vehicle gel (reduction  $p = 0.008$ / percent reduction  $p = 0.037$ ) and to clindamycin phosphate gel (reduction  $p = 0.000$ / percent  $p = 0.000$ ). However, once again, Clindoxyl™ Gel is not statistically superior to benzoyl peroxide gel.

Week 11 - Non-Inflammatory Lesion Counts in Study 152						
Results of Statistical Analyses in the Preferred Data Set <sup>a</sup>						
Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle					
	Reduction	ALL	12.6	5.5	7.1	0.008
	% Reduction	ALL	25.9	15.3	10.5	0.037
Clindoxyl	BZPO					
	Reduction	ALL	12.6	8.7	3.9	0.079
	% Reduction	ALL	25.9	18.8	7.0	0.091
Clindoxyl	Clindamycin					
	Reduction	ALL	12.6	4.5	8.1	0.000
	% Reduction	ALL	25.9	11.1	14.7	0.000
Benzoyl Peroxide	Vehicle					
	Reduction	ALL	8.7	5.5	3.2	0.234
	% Reduction	ALL	18.8	15.3	3.5	0.490
Clindamycin	Vehicle					
	Reduction	ALL	4.5	5.5	-0.9	0.731
	% Reduction	ALL	11.1	15.3	-4.2	0.406

<sup>a</sup> Site\*treatment interaction was significant ( $p=0.0001$ ).  
Reduction = baseline count - count at a later week.

### Inflammatory Lesions

The mean baseline inflammatory counts are similar across the treatment arms, and range closely from 20.2 to 21.2. At week 11, it is obvious that at each site there is a reduction of

Effect of Time and Treatment on Inflammatory Lesion Counts for the Preferred Data Set of Study 152						
Week	Statistic <sup>1</sup>	Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl™
0	Mean Count	152A	21.5	22.4	23.1	21.1
		152B	20.5	18.2	19.2	19.6
		ALL	21.0	20.2	21.2	20.4
11	Mean Reduction	152A	10.3 <sup>v</sup>	6.9	4.4	11.5 <sup>v,c</sup>
		152B	3.7 <sup>v</sup>	9.2	7.2	6.1 <sup>b,c</sup>
		ALL	7.0	8.1	5.8	8.8 <sup>v</sup>
	Mean % Reduction	152A	46.1 <sup>v</sup>	28.2	18.5	54.4 <sup>v,c</sup>
		152B	21.0 <sup>v</sup>	50.8	39.2	32.7 <sup>b,c</sup>
		ALL	33.5	39.8	28.6	43.4

<sup>1</sup> Reduction = baseline count - count at a later week  
v,c,b Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b),  $p < 0.05$  (Tables 152.11a&b, based on valid patients, LOCF).

approximately 8 lesions, with virtually no clinical difference at all between the treatment arms.

In analyzing the pairwise comparisons, comparing both the mean reduction and mean percent reduction, there is no statistical difference demonstrated between ANY of the four arms of the study. The vehicle gel arm reaches statistical significance in mean reduction, but this is only three lesions and is not truly meaningful. The sponsor was queried concerning possible discrepancies at the trial site, but was unable to provide an explanation for these results. They may possibly be due to chance alone.

Week 11 of Inflammatory Lesion Counts in Study 152						
Results of Statistical Analyses in the Preferred Data Set <sup>a</sup>						
Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle					
	Mean Reduction	ALL	8.8	5.8	3.0	0.046
	Percent Reduction	ALL	43.5	28.9	14.7	0.051
Clindoxyl	Benzoyl Peroxide					
	Mean Reduction	ALL	8.8	7.0	1.8	0.151
	Percent Reduction	ALL	43.5	33.5	10.0	0.107
Clindoxyl	Clindamycin					
	Mean Reduction	ALL	8.8	8.0	0.8	0.538
	Percent Reduction	ALL	43.5	39.5	4.0	0.517
Benzoyl Peroxide	Vehicle					
	Mean Reduction	ALL	7.0	5.8	1.2	0.420
	Percent Reduction	ALL	33.5	28.9	4.7	0.537
Clindamycin	Vehicle					
	Mean Reduction	ALL	8.0	5.8	2.2	0.139
	Percent Reduction	ALL	39.5	28.9	10.7	0.158

Total Lesion Counts

The total lesion counts at baseline were similar across treatment arms, and ranged from 54.3 to 62.0. Clindoxyl™ Gel demonstrated the most significant reduction, followed by benzoyl peroxide gel, clindamycin phosphate gel and the vehicle gel.

Study # 152					
Effect of Time and Treatment on Total Lesion Counts for the Preferred Data Set					
WEEK	STATISTIC	BZPO	CLINDAMYCIN	VEHICLE	CLINDOXYL
0	Mean Count	58.2	54.3	61.0	62.0
11	Mean Reduction	15.7	12.6	11.3	21.2
	Mean % Reduction	25.5	23.5	20.6	32.5

Clindoxyl™ Gel was able to demonstrate clinical and statistical superiority to the vehicle gel and to clindamycin phosphate gel in both the reduction and percent reduction in lesion counts at week 11. This again demonstrates the improved efficacy of the benzoyl peroxide/clindamycin



Comparisons of Treatment Effects on Proportion of Patients with Good to Excellent Global Improvement in the Preferred Data Set of Study 152 at Week 11 <sup>a</sup>						
Treatment Comparison			Proportion		Estimated Odds Ratio <sup>b</sup>	p-Value <sup>b</sup>
First	Second	Site	First	Second		
Clindoxyl	Vehicle	152A	0.47	0.26	2.51	0.340
		152B	0.16	0.44	0.24	0.119
		ALL	0.32	0.35	0.78	0.577
Clindoxyl	Benzoyl Peroxide	152A	0.47	0.43	1.19	0.821
		152B	0.16	0.23	0.65	0.602
		ALL	0.32	0.33	0.88	0.745
Clindoxyl	Clindamycin	152A	0.47	0.18	4.18	0.095
		152B	0.16	0.69	0.09	0.002
		ALL	0.32	0.44	0.60	0.197
Benzoyl Peroxide	Vehicle	152A	0.43	0.26	2.10	0.234
		152B	0.23	0.44	0.37	0.110
		ALL	0.33	0.35	0.88	0.775
Clindamycin	Vehicle	152A	0.18	0.26	0.60	0.458
		152B	0.69	0.44	2.84	0.080
		ALL	0.44	0.35	1.31	0.558

<sup>a</sup> Site\*treatment interaction was significant (p<0.001)

<sup>b</sup> Obtained from logistic regression

#### 8.1.3.4.3 SAFETY OUTCOMES

##### Extent of Exposure

The extent of exposure to study medication for all patients at this site is summarized below. The extent of full exposure was greatest to Clindoxyl™ Gel, which adds a measure of reassurance that the study will capture any significant side effects of this drug.

Summary of Extent of Exposure to Medication in Study 152					
# of Applications	Distribution of Patients by # of Applications (planned exposure 77 applications in 77 days)				
	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl	ALL
0 to 14*	4 (5.0%)	5 (6.2%)	0	3 (3.8%)	12 (4.3%)
15 to 28	2 (2.5%)	3 (3.8%)	0	1 (1.2%)	6 (2.1%)
29 to 42	1 (1.2%)	0	1 (2.5%)	1 (1.2%)	3 (1.1%)
43 to 56	2 (2.5%)	1 (1.2%)	0	0	3 (1.1%)
57 to 70	5 (6.2%)	1 (1.2%)	2 (5.0%)	0	8 (2.9%)
71 to 84	66 (82.5%)	70 (87.5%)	37 (92.5%)	74 (92.5%)	247 (88.2%)
> 84	0	0	0	1 (1.2%)	1 (0.4%)

\* Includes unknowns.

Overall tolerance

Previous sections of this review contain a discussion of concerns about the sponsor's lack of description of this safety parameter, and will not be repeated here.

Adverse Events

Adverse events were reported by 36 (45.9%) patients in the Clindoxyl™ Gel group, 28 (35.0%) patients in the clindamycin phosphate gel group, 36 (45.0%) patients in the benzoyl peroxide gel group, and 16 (40.0%) patients in the vehicle gel group.

Number of Patients Reporting Adverse Events <sup>a</sup>		
Treatment	# of patients	# of events <sup>b</sup>
Benzoyl Peroxide	36 (45.9%)	49
Clindamycin	28 (35.0%)	38
Vehicle	16 (40.0%)	19
Clindoxyl™	36 (45.0%)	53
ALL	116 (41.4%)	159

<sup>a</sup> There was no significant difference between treatment groups when analyzed by Fisher's exact test,  $p > 0.05$       <sup>b</sup> Reoccurring events were counted once.

There were no significant differences between treatments in the incidence of patients with adverse events. The line listings of adverse events listed by patients in the Clindoxyl™ Gel arm have been individually reviewed, and are similar in type to those presented in detail for study 151. Of the 53 adverse events in the Clindoxyl™ Gel group, 8 events (in 4 patients) were attributed to the study medication, and are presented below.

Summary of Adverse Events in Study 152								
BODY SYSTEM / Event <sup>a</sup>	Trt <sup>b</sup>	Number of Patients (% of total treated)						
		Related (*Probable, **Possible)			Not Related			Total
		Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	
<b>APPLICATION SITE</b>								
/ Acne	X	1(1.2%)**	0	0	0	0	0	1(1.2%)
	C	1(1.2%)**	0	0	0	0	0	1(1.2%)
/ Dermatitis Contact	X	0	0	0	1(1.2%)	0	0	1(1.2%)
	B	0	1(1.2%)*	0	0	0	0	1(1.2%)
/ Pruritus	C	1(1.2%)**	0	0	0	0	0	1(1.2%)
	X	1(1.2%)**	2(2.5%)*,**	0	0	0	0	3(3.8%)
/ Rash	B	1(1.2%)**	0	0	0	0	0	1(1.2%)
	C	0	1(1.2%)*	0	0	0	0	1(1.2%)
/ Rash Erythematous	X	0	2(2.5%)*,**	0	0	0	0	2(2.5%)
	V	1(2.5%)**	0	0	1(2.5%)	0	0	2(5.0%)
	X	1(1.2%)**	1(1.2%)*	0	0	0	0	2(2.5%)

BODY SYSTEM / Event <sup>a</sup>	Trt <sup>b</sup>	Number of Patients (% of total treated)						Total
		Related (*Probable, **Possible)			Not Related			
		Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	
<b>BODY AS A WHOLE</b>								
/ Back Pain	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Fatigue	X	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Fever	B	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Influenza-like Symptoms	B	0	0	0	1(1.2%)	2(2.5%)	1(1.2%)	4(5.0%)
	C	0	0	0	1(1.2%)	1(1.2%)	0	2(2.5%)
	X	0	0	0	2(2.5%)	1(1.2%)	0	3(3.8%)
/ Pain	X	0	0	0	0	1(1.2%)	0	1(1.2%)
<b>CENTRAL AND PERIPHERAL NERVOUS</b>								
/ Headache	B	0	0	0	3(3.8%)	1(1.2%)	0	4(5.0%)
	C	0	0	0	2(2.5%)	3(3.8%)	0	5(6.2%)
	V	0	0	0	1(2.5%)	0	0	1(2.5%)
	X	0	0	0	1(1.2%)	3(3.8%)	1(1.2%)	5(6.2%)
<b>FEMALE REPRODUCTIVE</b>								
/ Dysmenorrhea	X	0	0	0	1(1.2%)	1(1.2%)	0	2(2.5%)
/ Ovarian Cyst	V	0	0	0	1(2.5%)	0	0	1(2.5%)
<b>GASTRO-INTESTINAL</b>								
/ Abdominal Pain	X	0	0	0	1(1.2%)	0	0	1(1.2%)
	C	0	0	0	0	2(2.5%)	0	2(2.5%)
/ Diarrhea	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Dyspepsia	B	0	0	0	1(1.2%)	1(1.2%)	0	2(2.5%)
	X	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Infection Viral	X	0	0	0	2(2.5%)	2(2.5%)	0	4(5.0%)
	C	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Nausea	X	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Vomiting	C	0	0	0	0	0	1(1.2%)	1(1.2%)
	X	0	0	0	0	0	1(1.2%)	1(1.2%)
<b>HEARING AND VESTIBULAR</b>								
/ Earache	B	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Infection	B	0	0	0	1(1.2%)	0	0	1(1.2%)
	X	0	0	0	0	1(1.2%)	0	1(1.2%)
<b>MUSCULO-SKELETAL</b>								
/ Fracture Pathological	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Myalgia	B	0	0	0	1(1.2%)	0	0	1(1.2%)
	X	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Sprain	C	0	0	0	0	1(1.2%)	0	1(1.2%)
	X	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Surgery	V	0	0	0	0	1(2.5%)	0	1(2.5%)
/ Wound	X	0	0	0	0	0	1(1.2%)	1(1.2%)
<b>PSYCHIATRIC</b>								
/ Depression	C	0	0	0	0	0	1(1.2%)	1(1.2%)
/ Insomnia	C	0	0	0	1(1.2%)	0	0	1(1.2%)
<b>RESPIRATORY</b>								
/ Bronchitis	X	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Coughing	B	0	0	0	1(1.2%)	0	0	1(1.2%)
	V	0	0	0	1(2.5%)	0	0	1(2.5%)
	C	0	0	0	0	2(2.5%)	0	2(2.5%)
/ Pharyngitis	B	0	0	0	2(2.5%)	5(6.2%)	0	7(8.8%)
	V	0	0	0	1(2.5%)	0	1(2.5%)	2(5.0%)
	X	0	0	0	4(5.0%)	0	0	4(5.0%)
	C	0	0	0	0	0	1(1.2%)	1(1.2%)
/ Rhinitis	B	0	0	0	1(1.2%)	0	0	1(1.2%)
	V	0	0	0	1(2.5%)	0	0	1(2.5%)
	X	0	0	0	3(3.8%)	0	0	3(3.8%)
	C	0	0	0	0	3(3.8%)	0	3(3.8%)
/ Sinusitis	C	0	0	0	2(2.5%)	0	0	2(2.5%)
	V	0	0	0	0	2(5.0%)	0	2(5.0%)
/ Upper Respiratory Tract (URI)	B	0	0	0	11(13.8%)	4(5.0%)	0	15(18.8%)
	C	0	0	0	6(7.5%)	2(2.5%)	0	8(10.0%)
	V	0	0	0	6(15.0%)	1(2.5%)	0	7(17.5%)

BODY SYSTEM / Event <sup>a</sup>	Trt <sup>b</sup>	Number of Patients (% of total treated)						Total
		Related (*Probable, **Possible)			Not Related			
		Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	Mild	Mod <sup>c</sup>	Sev <sup>c</sup>	
<b>SKIN AND APPENDAGES</b>								
/ Herpes Simplex	X	0	0	0	0	1(1.2%)	0	1(1.2%)
/ Nail Disorder	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Pruritus	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Rash	B	0	0	0	1(1.2%)	0	0	1(1.2%)
	C	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Skin Dry	B	0	0	0	1(1.2%)	0	0	1(1.2%)
/ Surgery	B	0	0	0	0	1(1.2%)	0	1(1.2%)
<b>VASCULAR (Extra Cardiac)</b>								
/ Hematoma	C	0	0	0	1(1.2%)	0	0	1(1.2%)
<b>VISION</b>								
/ Allergy Aggravated	V	0	0	0	1(2.5%)	0	0	1(2.5%)
/ Wound	B	0	0	0	0	1(1.2%)	0	1(1.2%)

<sup>a</sup> Event listed using preferred term (see Appendix D, Table D.10 for investigator terms).

<sup>b</sup> Treatment Codes: B = Benzoyl Peroxide (n = 80), C = Clindamycin (n = 80), V = Vehicle (n = 40), X = Clindoxyl (n = 80).

<sup>c</sup> Mod = Moderate, Sev = Severe.

There were 13 patients (3 in the benzoyl peroxide gel group, 4 in the clindamycin phosphate gel group, and 6 in the Clindoxyl™ Gel group) who complained of 15 gastrointestinal symptoms, and these were all attributed to concurrent illness. There were no medication alterations required for any of these patients, and all events resolved.

Subject	Event	Duration	Outcome
152A/099	Acne worsening,	9 days	Discontinued
152A/012	Dryness, itching	1 day	Recovered
152A/024	Red area, itching	3 days	Recovered
152A/085	Dryness, itching, erythema	11-18 days	Recovered

### Local Tolerance

Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment groups. In general, all four treatments were well tolerated, except for occasional mild or rarely moderate erythema, peeling, burning, dryness, edema or pruritus. Six patients had a > grade 1 worsening of signs, but only two of these patients (erythema and burning) were in the Clindoxyl™ Gel Group.

### 8.1.3.5 REVIEWER'S CONCLUSIONS OF STUDY RESULTS

Study 152 demonstrates that Clindoxyl™ Gel is superior to both vehicle and clindamycin phosphate gel in the treatment of acne vulgaris, but is not superior to benzoyl peroxide gel.

## 9. OVERVIEW OF EFFICACY

A combination product must demonstrate superiority to both of its active components.

### Comparisons with clindamycin phosphate

In two controlled multi-center trials (151 and 152), Clindoxyl™ Gel has demonstrated superiority to clindamycin phosphate gel in the reduction at least one subtype of acne lesions (inflammatory or noninflammatory) and in the reduction of total lesion counts. In Study 151, Clindoxyl™ Gel was superior to clindamycin phosphate gel in the reduction of noninflammatory lesion counts, inflammatory lesion counts, total lesion counts, and the global assessment. In Study 152, Clindoxyl™ Gel was superior to clindamycin phosphate gel in the reduction of noninflammatory lesion counts and total lesion counts. In addition, the superior efficacy of Clindoxyl™ Gel is supported by the results of a single investigator study (Site 150) in which Clindoxyl™ Gel demonstrated superiority in the reduction of total lesion counts and in the global assessment.

### Comparisons with benzoyl peroxide

In two controlled multi-center trials (151 and 152), Clindoxyl™ Gel has failed to demonstrate superiority to benzoyl peroxide gel in the treatment of acne vulgaris. It has failed to demonstrate superiority over benzoyl peroxide gel in the reduction of inflammatory lesions, noninflammatory lesions, or total lesions. Clindoxyl™ Gel did demonstrate superiority over benzoyl peroxide gel in the global assessment in Study 151. The combination might not be expected to be superior to benzoyl peroxide gel in the treatment of noninflammatory lesions, but it should then be superior in the treatment of inflammatory lesions in order to justify adding clindamycin phosphate in a combination product. There is not persuasive evidence that the addition of clindamycin phosphate is more effective than benzoyl peroxide alone in the treatment of acne, especially inflammatory lesions. This may be due to the fact that the lesion counts for inflammatory acne were generally low in this study, and the effectiveness of the combination product could not be demonstrated with such low numbers of inflammatory lesions.

Pairwise Comparisons of Treatment Arms vs Clindoxyl™ Gel									
Clindoxyl™ Gel vs:	BZPO	BZPO	BZPO	Clinda mycin	Clinda mycin	Clinda mycin	Vehicle	Vehicle	Vehicle
	Study 150 n=120	Study 151 n=273	Study 152 n=280	Study 150	Study 151	Study 152	Study 150	Study 151	Study 152
Noninflammatory Lesion Count % reduction	Does not show efficacy	Does not show efficacy	Does not show efficacy	Supportive	Shows efficacy	Shows efficacy	Shows efficacy	Shows efficacy	Shows efficacy
Inflammatory Lesion Count % reduction	Supportive	Does not show efficacy	Does not show efficacy	Supportive	Shows efficacy	Does not show efficacy	Shows efficacy	Shows efficacy	Supportive
Total Lesion Count % decrease	Does not show efficacy	Does not show efficacy	Does not show efficacy	Shows efficacy	Shows efficacy	Shows efficacy	Shows efficacy	Shows efficacy	Shows efficacy
Global Assessment	Shows efficacy	Shows efficacy	Does not show efficacy	Shows efficacy	Shows efficacy	Does not show efficacy	Shows efficacy	Shows efficacy	Does not show efficacy

## 10. OVERVIEW OF SAFETY

These clinical trials have demonstrated no significant safety concern for patients who would use Clindoxyl™ Gel for the treatment of acne vulgaris.

Local tolerance information was collected by tabulating the treatment emergent signs and symptoms (erythema, peeling, and burning) collected on the Case Report Form at each visit. Occasionally the investigators also added dryness and pruritus to these observations in a "fill in the blank" space on the CRF. The Adverse Event tabulations collected similar data under the general heading "Application Site", in which the investigator recorded adverse events including rash-erythematous, paraesthesia, skin-dry, and pruritus.

The sponsors report of the Clindoxyl™ Gel group in the clinical trials describes the signs/symptoms of local tolerance such as erythema (7.0%), burning (2.2%), peeling (15.1%), dryness (6.5%) and pruritus (1.6%); but also describes these same clinical events under the adverse event tabulation as rash erythematous (1.1%), paraesthesia (0.5%), peeling (not listed), skin dry (1.1%), and pruritus (1.6%). The separation of identical clinical signs/symptoms (erythema, peeling, dryness, burning, itching) into two distinct groups (local tolerance and adverse events) is misleading, as the true incidence of events would be the sum of these groups if the groups are mutually exclusive. Indeed, the following paragraph demonstrates the mutual exclusivity of these groups.

Patient 151D/49 has an adverse event noted - "rash on face after application, burning after application, and stinging after application", but has no record in the local tolerance section that there was any problem with erythema or burning. Conversely, patient 152B/19 has local tolerance scores on the second visit of 2 in erythema, and 1 in burning, edema, and dryness but has only "Pruritic Rash" coded as an Adverse event.

*Reviewer Comment: The sponsor's current tabulation of adverse event and local tolerance data is not sufficiently meaningful to construct a clinically accurate and useful label. This is because the same clinical signs/symptoms are tabulated under different "headings". The sponsor should present the data in a format such that all similar clinical events are grouped together and represented with only one statistic (i.e one percentage for erythema, one percentage for edema etc.)*

### 10.1 SIGNIFICANT/POTENTIALLY SIGNIFICANT EVENTS

Clindamycin phosphate gel, currently marketed as a single agent, has the potential for significant gastrointestinal events, including diarrhea and pseudomembranous colitis. The sponsor's proposed labeling for the combination product parallels the warnings currently printed on the Cleocin products (topical clindamycin phosphate).

Benzoyl peroxide is not now considered a carcinogen. However, data from a study using mice known to be susceptible to cancer suggested that benzoyl peroxide acted as a tumor promoter. The clinical significance of this finding is not known. No report published in the scientific literature or

brought to the attention of the Over the Counter Drugs Division has shown conclusive evidence of a causal relationship between benzoyl peroxide in the treatment of acne and the development or enhancement of human skin tumors.

#### 10.1.1 DEATHS

There were no subject deaths during these trials.

#### 10.1.2 OTHER SIGNIFICANT/POTENTIALLY SIGNIFICANT EVENTS

The expected significant events related to use of Clindoxyl™ Gel are all effects of local usage on the skin: erythema, dryness, peeling, burning, stinging, and pruritus. These are covered in the safety section.

#### 10.1.3 OVERDOSE EXPERIENCE

There is no overdose experience data available for this drug product.

### 10.2 OTHER SAFETY FINDINGS

#### 10.2.1 ADR INCIDENCE TABLES

Adverse incidence tables will not be summarized in this review, as they should be updated by the sponsor prior to labeling.

#### 10.2.2 LABORATORY FINDINGS, VITAL SIGNS, ECGS

There were no laboratory evaluations during these clinical trials.

#### 10.2.3 SPECIAL STUDIES

The usual studies required to demonstrate topical safety include 1) cumulative irritancy, 2) contact sensitization, 3) phototoxic potential and 4) photocontact allergic potential. Cumulative irritancy and contact sensitization are often combined into one study. Irritancy and toxicity are dose-dependent pharmacodynamic endpoints that occur in almost everyone (if they occur at all) given sufficient duration of exposure and concentration. Thus, small numbers of patients (25-30) are sufficient to provide valid tests for contact irritancy and phototoxicity. Allergenicity is more of a quantal phenomenon and depends upon host sensitivity - it occurs in only a small subset of the population. To rule out an incidence of greater than a 1.5% reaction rate, approximately 200 subjects are needed. Photoallergenicity has routinely been tested in only 30 subjects, which is a compromise because of the much greater expense involved, unless there is substantial evidence to require more subjects.

#### **Study #153 CLX9505.153 29 Dec 95 Protocol # 9505**

Title: A Clinical Evaluation of the Phototoxic Potential of Clindoxyl™ Gel

Investigator: Kays Kaidbey, M.D.  
Ivy Laboratories (KGL, Inc)  
University City Science Center

3401 Market St  
Suite 226  
Philadelphia, PA 19104

Study Dates: Study Initiation - 23 Oct 1995  
Study Completion - 3 Nov 1995

Ten subjects with fair skin types I, II, or III were enrolled and completed this single center study without protocol violations. Clindoxyl™ Gel and the vehicle gel (80mg) were applied under semi-occlusive patches to duplicate skin sites measuring 2x2cm on the mid or lower back of these subjects. After 24 hours the patches were removed and the test sites and an untreated adjacent skin site (irradiated control) were

filter was added to remove residual reflected infrared and visible radiation. The size of the irradiated field was approximately a \_\_\_\_\_ diameter circle. UVA irradiance at skin level was \_\_\_\_\_

The other set of patches served us unirradiated controls. The phototoxic potential was evaluated by grading test sites within 5 to 10 minutes of irradiation and again at 24 and 48 hours. (A phototoxic material will produce a wheal and flare response immediately after exposure, or intense erythema and edema 24 and 48 hours later). Skin evaluations were done by a blinded expert grader who did not participate in applying the patches or administering UVA. Delayed erythema and edema were evaluated using a five point scale in which 0 = no reaction, 1 = minimal visible erythema, 2 = deeper erythema with clear distinct borders, 3 = intense erythema and edema, and 4 = vesicular or blistering reaction.

**Results:**

No patients in either the Clindoxyl™ Gel or vehicle gel groups demonstrated any reaction either immediately, or at 24hrs or 48hrs.

**Study #154 CLX9506.154 Protocol # 9506**

Title: A Clinical Evaluation of the Potential of Clindoxyl™ Gel for Photocontact Allergy

Investigator: Kays Kaidbey, M.D.  
Ivy Laboratories (KGL, Inc)  
University City Science Center  
3401 Market St  
Suite 226  
Philadelphia, PA 19104

Study Dates: Study Initiation - 19 Oct 95  
Study Completion - 1 Dec 95

28 subjects were enrolled in this single center study. In order to determine the potential of Clindoxyl™ Gel for photocontact allergy, the product was first studied in an induction phase, where 80mg of Clindoxyl™ Gel was applied under a semiocclusive patch on the mid or lower back of each subject. After 24 hours, the patch was removed, and the test site was irradiated with three predetermined minimal erythema doses. The site was then left open for a 48 hour period,

following which the patch was reapplied to the same designated test site under a semi-occlusive dressing. Twenty four hours later the patch was again removed and the site reexposed to another dose of \_\_\_\_\_ of solar simulated radiation. This application/irradiation procedure was repeated to the same test site for two exposures per week for three weeks. The second phase, challenge phase, was initiated 17 days after removal of the last induction patch. The subjects were challenged by application of 80mg of Clindoxyl™ Gel to two sites on the mid or lower back which were not previously treated. These sites were covered with a semi-occlusive patch. After 24 hours one of the two patches was removed, the exposed site and an untreated site were irradiated with ultraviolet A light (\_\_\_\_). After irradiation the remaining patch was removed. Reactions at all 3 test sites were graded 48 and 72 hours after irradiation, using a standard grading system, as follows: 0 = Not sensitized (may include irritant reaction), 1 = Mild sensitization (erythema and some edema), 2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation), 3 = Strong sensitization (large, vesiculo-bullous reactions).

#### Results:

26 subjects completed the investigation as outlined in the protocol. No immediate or delayed reactions were seen at any of the test sites. No adverse or other unexpected side effects were encountered in any of the panelists.

#### Study #155 CLX9507.155 Protocol # 9507

Title: A Clinical Evaluation of the Potential of Clindoxyl™ Gel for Inducing Contact Sensitization.

Investigator: Kays Kaidbey, M.D.  
Ivy Laboratories (KGL, Inc)  
University City Science Center  
3401 Market St  
Suite 226  
Philadelphia, PA 19104

Study Dates: Study Initiation -30 Oct 95  
Study Completion - 8 Dec 95

This single center study enrolled 27 subjects. In order to determine the potential of Clindoxyl™ Gel for inducing contact sensitization, the product was first studied in an induction phase, where 0.1ml of Clindoxyl™ Gel was applied to a circular (15mm diameter) test site under a semi-occlusive patch on the back of each subject. After 24 hours the patch was removed, and the test site was graded approximately 15 minutes later for irritation. The grading scale used was 0 = No erythema, 1 = Minimally visible (flat) erythema, 2 = Moderate erythema with sharply defined borders, 3 = Intense erythema with edema (elevated lesion), 4 = Intense erythema with edema and vesicles or erosions. This cumulative application/grading procedure was repeated daily Monday through Friday to the same test site for three weeks (15 applications/14 gradings occurred). The second phase, the challenge phase, was initiated 14 days after removal of the last induction patch, when the subjects were challenged by application of 0.1ml of each of Clindoxyl™ Gel, benzoyl peroxide gel, clindamycin phosphate gel, and vehicle gel to individual sites on the back which had not been previously treated. These treated sites were covered with a

semi-occlusive patch. After 48 hours the patches were removed and the potential for inducing a contact sensitization was evaluated by grading test sites at 30 to 60 minutes and 2 days following patch removal using a standard grading system: 0 = Not sensitized (may include irritant reaction), 1 = Mild sensitization (erythema and some edema), 2 = Moderate sensitization (erythema with infiltration, raised, spreading reaction beyond the borders of the patch, with or without vesiculation), 3 = Strong sensitization (large, vesiculo-bullous, vividly red, infiltrated plaques)

#### Results:

No adverse or other unexplained side effects were observed in any of the subjects. The cumulative scores for each subject were low and ranged from 0-10 (mean 1.2). The individual daily scores ranged from 0 to 1. There were no delayed contact sensitizations seen in any of the test sites either to the complete product or to its individual components.

*Reviewer Comment: The phototoxicity and photoallergenicity studies are adequate to support safety in these areas. Study #155 (Protocol #9507) is adequate to demonstrate that Clindoxyl™ Gel does not have significant potential for cumulative irritancy, but is inadequate to demonstrate that the product does not have significant potential to induce contact sensitization. A study with at least 200 subjects is required.*

#### 10.2.4 DRUG-DEMOGRAPHIC INTERACTIONS

There were no data presented which indicated the presence of any drug-demographic interactions which might predict greater risk of adverse effects with this drug..

#### 10.2.5 DRUG-DRUG INTERACTIONS

The reviewer agrees with the sponsor that concomitant use of Clindoxyl Gel and other therapeutic agents should not cause any adverse drug interactions, although concomitant use of Clindoxyl Gel with irritating products may lead to increased irritation. Patients took many different concomitant medications during the clinical studies. Most medications were OTC pain or cough/cold medications. A number of female patients were taking oral contraceptives. No interactions were evident.

#### 10.2.6 PHENOMENA/ABUSE POTENTIAL

This drug product should have little to no abuse potential.

#### 10.2.7 HUMAN REPRODUCTION DATA

There were no human reproduction data obtained during drug development.

### 11. LABELING REVIEW

This section will not be completed at this time as the application is pending NOT APPROVABLE due to Chemistry, Manufacturing and Controls deficiencies.

this trial be successful, the manufacturer will have demonstrated both 1) the clinical efficacy of clindamycin produced under GMP and 2) the contribution to the efficacy of the combination drug product by the clindamycin component. It would not be necessary to repeat the arms of the trial in which Clindoxyl™ Gel is compared to clindamycin phosphate gel or vehicle.

This New Drug Application HAS NOT demonstrated that Clindoxyl™ Gel is more efficacious than its components in the treatment of acne vulgaris. It also HAS NOT demonstrated that Clindoxyl™ Gel is SAFE for use in the treatment of acne vulgaris. However, the combination of clindamycin phosphate and benzoyl peroxide could provide a significant improvement in patient convenience and could be a useful addition to the dermatologic therapeutic armamentarium should the sponsor fulfill the statutory requirements for the demonstration of safety and efficacy.

### 13. RECOMMENDATIONS

It is recommended that a Not Approvable action be taken on New Drug Application 50-741, Clindoxyl™ Gel, based upon:

- 1) Failure of the manufacturer to use components which were produced in accordance with Good Manufacturing Practices.
- 2) Failure to characterize the metabolic and oxidative products of clindamycin phosphate when combined with benzoyl peroxide.
- 3) Failure to demonstrate that Clindoxyl™ Gel has no greater potential for absorption of clindamycin than clindamycin phosphate gel alone.
- 4) Failure to prove efficacy over benzoyl peroxide gel alone in the treatment of lesions of acne vulgaris.
- 5) Failure to demonstrate that Clindoxyl™ Gel poses minimal safety hazard to the patient as a contact sensitizer.

  
Susan J. Walker, MD  
Medical Officer

13 MAY 94

cc:  
Archival NDA 50-741  
HFD-540  
540/Wilkin/Division Director  
540/Toombs/Dermatology Team Leader  
540/Walker/Medical Officer  
540/White/Project Manager  
725/Srinivasan/Biostatistics Team Leader  
725/Freidlin/Biostatistician

HFD-540 Trac No:  
Document ID: AZ

Correspondence date: February 22, 2002  
CDER Stamp date: February 26, 2002

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 50-741  
MAJOR AMENDMENT

DATE: June 17, 2002

SPONSOR: Stiefel Laboratories  
Oak Hill, NY

DRUG: Clindoxyl Gel

ACTIVE INGREDIENTS: Clindamycin phosphate equivalent to 1%  
clindamycin, and 5% benzoyl peroxide.

PROPOSED INDICATION: Acne

Labeling indication: 'Clindoxyl Gel is indicated for the topical  
treatment of inflammatory ~~acne~~ acne vulgaris.'

REASON FOR AMENDMENT: Response to the 9/6/2000 Not Approvable letter;  
change in the labeling indication from 'for the topical treatment of  
acne vulgaris' to 'for the topical treatment of inflammatory  
acne vulgaris'.

Executive summary

- 1) Recommendations: It is recommended that the application be approved  
for the treatment of the inflammatory lesions of acne.
- 2) Summary of clinical studies: Clindoxyl Gel is a combination of 1%  
clindamycin and 5% benzoyl peroxide. In the original submission of  
NDA 50-741 the labeling indication was for the treatment of acne.  
In order to demonstrate the effectiveness of a combination product  
for acne, the sponsor needs to show that the combination is  
superior to each of its active ingredients in the percent reduction  
of two of three types of lesion counts (inflammatory, non-  
inflammatory, and total counts) and in the investigator's global  
evaluation.

In the original submission and a resubmission of the NDA, the  
sponsor provided the results of five clinical studies. The  
conclusions of the clinical and statistical reviewers was that  
these studies adequately demonstrated superiority of the  
combination to clindamycin, but not to benzoyl peroxide. In this  
amendment the sponsor has provided revised labeling, with a  
labeling indication for the treatment of only the inflammatory  
acne, and has provided a re-analysis of the data in the  
ITT population to support this indication.

**APPEARS THIS WAY  
ON ORIGINAL**

The data show that in three of the five studies, Clindoxyl Gel was significantly superior to benzoyl peroxide in the percent reduction of inflammatory lesions, and in the global evaluation. The conclusions of both the clinical and statistical reviewers are that the data adequately support the effectiveness of the labeling indication for the treatment of the inflammatory lesions of acne.

#### Prior submissions

The sequence of prior submissions and communications regarding NDA 50-741 was as follows.

- 1) Original submission: The original submission of NDA 50-741 was on May 15, 1996. The clinical studies in acne provided in this submission were Studies 150, 151, and 152. All were double blind, randomized, parallel group comparisons, with applications once daily for 11 weeks. The characteristics of these studies were as follows.

Study #	# centers	# pts	Treatment groups
150	1	120	Clindoxyl Gel 1% clindamycin phosphate gel 5% benzoyl peroxide gel vehicle gel
151	4	273	Clindoxyl Gel 1% clindamycin phosphate gel 5% benzoyl peroxide gel vehicle gel
152	2	280	Clindoxyl Gel 1% clindamycin phosphate gel 5% benzoyl peroxide gel vehicle gel

The efficacy parameters in each study were counts of inflammatory and non-inflammatory lesions, and a global assessment of the percentage improvement from baseline. The criteria for a determination of efficacy were a demonstration of the superiority of Clindoxyl Gel to clindamycin gel and benzoyl peroxide gel in the percent reduction of two of the three lesion counts (inflammatory, non-inflammatory, and total lesions), and in the percentage of patients with a rating of Good or Excellent (corresponding to 51% or greater improvement) in the global assessment. Analyses of the results were performed on the Preferred Data Set (Per Protocol population) rather than the ITT population; the ITT population is preferred by the FDA.

The clinical reviewer, Dr. Susan Walker, considered Studies 151 and 152 to be pivotal studies, and Study 150, because it was a single

center study, to be a supportive study. Dr Walker states in her conclusion that the superiority of Clindoxyl Gel has been demonstrated when compared to both clindamycin phosphate gel and the vehicle gel, but has not been demonstrated over benzoyl peroxide gel. She felt that in order to demonstrate the contribution of clindamycin, a trial could be one in which Clindoxyl gel is shown to be more efficacious than benzoyl peroxide in the treatment of inflammatory lesions only, because clindamycin appears to have very little activity in the treatment of non-inflammatory lesions.

- 2) Not Approvable letter of 5/14/97: The clinical portion of this letter included a statement that 'The efficacy of Clindoxyl Gel has not been demonstrated over benzoyl peroxide gel alone in the treatment of acne vulgaris. We recommend an additional clinical trial investigating the safety and efficacy of Clindoxyl Gel versus benzoyl peroxide gel in the treatment of acne vulgaris, in order to establish the clinical superiority of Clindoxyl Gel over benzoyl peroxide gel alone.'
- 3) Resubmission of 3/3/2000: The clinical studies provided in this submission were Studies 156 and 158. As in the original submission, these were double blind, randomized, parallel group comparisons, with applications once daily for 11 weeks. The characteristics of these studies were as follows.

Study #	# centers	# pts	Treatment groups
156	8	288	Clindoxyl Gel 1% clindamycin phosphate gel 5% benzoyl peroxide gel
158	8	358	Clindoxyl Gel 1% clindamycin phosphate gel 5% benzoyl peroxide gel vehicle gel

The efficacy parameters and the criteria for the determination of efficacy were the same as for Studies 150, 151, and 152. Analyses of the results were performed on the ITT population, defined as all patients enrolled.

The clinical reviewer, Dr. Phyllis Huene, felt that neither study demonstrated the effectiveness of Clindoxyl Gel, because the superiority over benzoyl peroxide had not been shown. In Study 156 Clindoxyl Gel was superior to benzoyl peroxide only in the percent reduction of non-inflammatory lesions, and was not superior in the percent reduction of other lesion counts nor in the global evaluation. In Study 158, Clindoxyl Gel was superior to benzoyl peroxide in the percent reduction of inflammatory lesions and in the global evaluation, but was not superior in the percent reduction of other lesion counts.

- 4) Not Approvable letter of 9/6/2000: The clinical portion of the letter included the following statement: 'The clinical studies submitted (Studies 156 and 158) did not demonstrate that Clindoxyl Gel is superior in effectiveness to the benzoyl peroxide gel alone. We recommend an adequate and well-controlled, additional clinical trial evaluating the safety and efficacy of Clindoxyl Gel versus benzoyl peroxide gel in the treatment of acne vulgaris. Such a study would have to demonstrate clinical superiority of the Clindoxyl Gel over the benzoyl peroxide gel alone.'
- 5) Current submission: The sponsor has provided in this amendment an analysis of the percent reduction of inflammatory, non-inflammatory, and total lesion counts, and of the global improvement, in the ITT population for Studies 150, 151, and 152. They have also revised their labeled indication to specify that treatment is for the inflammatory lesions of acne only.

The sponsor states that the labeling has been reformatted and/or updated to be in accordance with the recently approved BenzaClin Topical Gel.

Review of current submission

In this submission the sponsor has provided analyses of Studies 150, 151, and 152 in the ITT/LOCF population. In accordance with the revised labeling indication, i.e., for the treatment of inflammatory lesions of acne, this review is only of the percent reduction of inflammatory lesions, and the investigator's global evaluation. The sponsor has provided the results as the mean percent reduction in inflammatory lesion counts at week 11, and as the proportion of patients with 'Success' in the global evaluation, defined as those with a rating of Good or Excellent, in the ITT population.

A. Study 150.

Mean percent reduction in inflammatory lesion counts Study 150			
Clindoxyl n=30	Benzoyl peroxide n=30	Clindamycin n=30	Vehicle n=30
65%	36%	34%	19%

Success rate, global evaluation Study 150			
Clindoxyl n=30	Benzoyl peroxide n=30	Clindamycin n=30	Vehicle n=30
70%	40%	37%	17%

p values Study 150			
	Clindoxyl vs benzoyl peroxide	Clindoxyl vs clindamycin	Clindoxyl vs vehicle
Mean % reduction Inflamm.lesions	0.0169	0.0095	0.0002
Treatment Success	0.0217	0.0112	0.0001

## B. Study 151.

Mean percent reduction in inflammatory lesion counts Study 151			
Clindoxyl n=78	Benzoyl peroxide n=78	Clindamycin n=78	Vehicle n=39
55%	37%	29%	-1%

Success rate, global evaluation Study 151			
Clindoxyl n=78	Benzoyl peroxide n=78	Clindamycin n=78	Vehicle n=39
55%	37%	26%	4%

p values Study 151			
	Clindoxyl vs benzoyl peroxide	Clindoxyl vs clindamycin	Clindoxyl vs vehicle
Mean % reduction Inflamm.lesions	0.0019	<0.0001	<0.0001
Treatment Success	0.0299	0.0005	<0.0001

## C. Study 152.

Mean percent reduction in inflammatory lesion counts Study 152			
Clindoxyl n=80	Benzoyl peroxide n=80	Clindamycin n=80	Vehicle n=40
42%	32%	38%	29%

Success rate, global evaluation Study 152			
Clindoxyl n=80	Benzoyl peroxide n=80	Clindamycin n=80	Vehicle n=40
29%	30%	40%	35%

p values Study 152			
	Clindoxyl vs benzoyl peroxide	Clindoxyl vs clindamycin	Clindoxyl vs vehicle
Mean % reduction Inflamm. lesions	0.0820	0.4743	0.0784
Treatment Success	0.8622	0.1354	0.4852

Review of Studies 156 and 158

Analyses for the mean percent reduction in inflammatory lesions and the rate of Treatment Success for Studies 156 and 158 are taken from the review of the submission of 3/3/2000, as follows.

## A. Study 156.

Mean percent reduction in inflammatory lesion counts Study 156		
Clindoxyl n=96	Benzoyl peroxide n=96	Clindamycin n=96
57%	57%	49%

Success rate, global evaluation Study 156		
Clindoxyl n=96	Benzoyl peroxide n=96	Clindamycin n=96
60%	52%	49%

p values Study 156		
	Clindoxyl vs benzoyl peroxide	Clindoxyl vs clindamycin
Mean % reduction Inflamm. lesions	0.0845	0.030
Treatment Success	0.213	0.088

## B. Study 158.

Mean percent reduction in inflammatory lesion counts Study 158			
Clindoxyl n=113	Benzoyl peroxide n=112	Clindamycin n=65	Vehicle n=68
52%	41%	33%	29%

Success rate, global evaluation Study 158			
Clindoxyl n=113	Benzoyl peroxide n=112	Clindamycin n=65	Vehicle n=68
49%	36%	25%	24%

p values Study 158			
	Clindoxyl vs benzoyl peroxide	Clindoxyl vs clindamycin	Clindoxyl vs vehicle
Mean % reduction Inflamm. lesions	0.008	0.000	0.000
Treatment Success	0.042	0.001	0.001

Summary of results

Since the conclusions of the reviews of the previous submissions were that the superiority of Clindoxyl Gel over clindamycin and the vehicle has been adequately demonstrated, the most pertinent analyses at this time are the comparison of Clindoxyl Gel with benzoyl peroxide in the percent reduction of inflammatory lesion counts and in the rate of Treatment Success, in the ITT population. The p values for these comparisons in the five studies are summarized as follows. (Bolded values are statistically significant.)

p values Clindoxyl Gel vs benzoyl peroxide All studies		
Study #	% reduction - Inflammatory lesions	Treatment Success
150	<b>0.0169</b>	<b>0.0217</b> ✓
151	<b>0.0019</b>	<b>0.0299</b> ✓
152	0.0820	0.8622
156	0.0845	0.213
158	<b>0.008</b>	<b>0.042</b> ✓

In summary, Clindoxyl Gel was superior to benzoyl peroxide gel in both the percent reduction in inflammatory lesion counts and in the rate of Treatment Success in three of the five studies.

Reviewer's evaluation: It is felt the data are adequate to demonstrate the superiority of Clindoxyl gel over its components in the percent reduction of inflammatory lesion counts and in the investigator's global evaluation of Treatment Success.

Recommendations: It is recommended that the application be approved for the treatment of the inflammatory lesions of acne.

Phyllis A. Huene, M.D.

cc: HFD-540/Wilkin  
HFD-540/Luke  
HFD-540/Huene  
HFD-725/Alosh  
HFD-725/Fritsch  
HFD-540/Vidra  
HFD-540/Lutwak

n50741.az

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/s/

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Phyllis Huene  
6/24/02 12:24:21 PM  
MEDICAL OFFICER

Markham Luke  
6/24/02 03:53:42 PM  
MEDICAL OFFICER  
Response to 9/6/2000 NA letter with Amendment for narrower  
indication: "for the topical treatment of inflammatory lesions  
of acne vulgaris" only.

Jonathan Wilkin  
7/21/02 08:06:55 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

**REQUEST FOR CONSULTATION**

TO (Division/Office):

FROM:

Vickey Lutwak, Project Manager  
HFD-540

HFD-520

Albert Sheldon, Ph.D., Team leader  
Harold Silver, Ph.D.  
Fran LeSane, SCSO  
Division of Antiinfective Drug Products, HFD-520

DATE July 16, 2002	IND NO.	NDA NO. 50-741	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT 2/26/02
NAME OF DRUG Clindoxyl Gel	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 7/19/02 Labeling meeting on Monday 7/22/02	

NAME OF FIRM: Stiefel Labs

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Label Review. NA on Sept 8, 2000. Resubmitted February 26, 2002. There was no label review with the original submission.

label sent via e-mail attachment 7/16/02.

Other needs, please call me at 7-2073. Thank you.

SIGNATURE OF REQUESTER Victoria Lutwak		METHOD OF DELIVERY (Check one)	
SIGNATURE OF RECEIVER		<input type="checkbox"/> MAIL e-mail DFS	<input type="checkbox"/> HAND
		SIGNATURE OF DELIVERER	

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this page is the manifestation of the electronic signature.**  
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/s/  
-----

Harold Silver  
7/24/02 04:21:19 PM  
MICROBIOLOGIST

Please sign off on the Clinical Microbiology Consult (DDDDP/HFD-540)  
Labeling Review for NDA 50-741.

Albert Sheldon  
7/25/02 07:49:17 AM  
MICROBIOLOGIST

This is a consult for 540.

Lillian Gavrilovich  
8/5/02 03:30:24 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**