CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

JUL 17 2000

NDA#/Drug class: 50-741/4S

Applicant: Stiefel Laboratories, Inc.
Coral Gables, Fl 33134

Name of Drug: Clindoxyl Gel (5% Benzoyl Peroxide and Clindamycin phosphate equivalent to 1% Clindamycin)

Indication: Topical treatment of facial acne vulgaris

Documents Reviewed: Volumes 5.1, 519-5.30 dated March 6, 2000

Medical Reviewer: Phyllis Huene, M.D. (HFD-540)

Statistical Reviewer: Valeria Freidlin, Ph.D. (HFD-725)

I. INTRODUCTION

Clindoxyl Gel is a combination product containing 5% Benzoyl Peroxide and Clindamycin phosphate equivalent to 1% Clindamycin. This Amendment was received in reference to a Not Approvable (NA) Letter issued for NDA 50-741 and dated May 14, 1997. The NA letter stated that the efficacy of Clindoxyl Gel has not been demonstrated over Benzoyl Peroxide gel alone in the treatment of lesions of acne vulgaris. The Agency recommended 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 over Benzoyl Peroxide gel alone.

In this submission, the sponsor provided reports of two adequate and well-controlled clinical studies conducted with Clindoxyl Gel (Studies 156 and 158) to determine safety and efficacy in the topical treatment of acne vulgaris. Throughout the review, the treatment name abbreviations Clindoxyl (Clx), Benzoyl (BPO), and Clindamycin (Cln) refer to combination product containing 5% Benzoyl Peroxide and Clindamycin phosphate equivalent to 1% Clindamycin, Benzoyl Peroxide gel, and Clindamycin phosphate gel (equivalent to 1% Clindamycin), respectively.

II. STUDY 156

The primary objective of the study was to determine the relative efficacy and safety of the use of Clindoxyl, Clindamycin, and Benzoyl in the topical treatment of acne vulgaris. This was a double-blind, active-controlled, parallel, multi-center study. Patients with acne vulgaris of the face were randomly assigned to once daily treatment with Clindoxyl, Clindamycin, or Benzoyl. Treatment occurred over an 11-week period with examinations of the patients at baseline (week 0), and at therapy weeks 2, 5, 8, and 11. Variation of this schedule of approximately five days was permitted provided that the investigator made sure that use of the test medication had been continued.

Study Population

Patients enrolled in this study had acne vulgaris of the face with a minimum of 25 inflammatory lesions (papules and/or pustules), a maximum of 55 inflammatory lesions, and a minimum of 12 non-inflammatory lesions (open and closed comedones), and no more than 3 facial cysts. Patients of any gender and race and 12 to 30 years of age were enrolled in this study.

Efficacy variables

According to the protocol, evaluation of efficacy was made by counting inflammatory and non-inflammatory lesions on the entire face, excluding the nose, at the initial visit (week 0) and at all subsequent visits (weeks 2, 5, 8, and 11). The degree of improvement was based on the percent reduction from baseline of lesion counts. In addition, a global assessment of improvement of the facial acne relative to the patient's initial condition was made by the Investigator at all subsequent visits. Investigator's Global used a scale of 0 to 4, where 0 = worsening, 1 = 0-25% improvement (poor), 2 = 26-50% improvement (fair), 3 = 51-75% improvement (good) and 4 = 76-100% improvement (excellent). Final Week 11 Global Assessment of improvement was dichotomized as success or not (good or excellent vs. fair, poor, or worsening).

In agreement with the Medical reviewer, this reviewer used the following **primary efficacy variables**: percent change from baseline to week 11 in two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and success rate in Investigator's Global assessment at Week 11. To support the efficacy, the difference between treatment groups in the actual change from baseline in lesion counts should also be clinically meaningful. In this review the following secondary efficacy variables were used: actual change from baseline in inflammatory, non-inflammatory, and total lesion counts at Week 11.

Safety

Evaluation of safety was made by reporting of adverse events by the patient and by observation of signs of excessive irritation, inflammation, or other unexpected or undesirable reactions by the investigator. At the final visit for each patient (Week 11 or earlier for dropouts), the overall tolerance to the test drug was assessed by the investigator. Overall tolerance was the primary safety variable.

Statistical methods

Two efficacy populations of patients were analyzed: the ITT and Per Protocol populations. The ITT data set consisted of all data collected on all patients. Missing values were replaced by carrying forward the last observation (ITT-LOCF analysis). The Per Protocol patients were those who completed 11 weeks of treatment without protocol violations. Safety analyses used the ITT data set.

Demographic and baseline characteristics sex, race, and local tolerance scores in the three treatment groups were compared via the CMH procedure with adjustment for site. Two-way ANOVA with interaction with effects for site and treatment was used to compare age and baseline counts of inflammatory and non-inflammatory lesions in treatment.

Specific comparisons planned in the analysis of the efficacy data in Study 156 are the Clindoxyl with Benzoyl and Clindamycin. For both non-inflammatory and inflammatory lesion counts, percent reduction from baseline to Week 11 was analyzed by the two-way ANOVA. The global improvement scores at Week 11 were collapsed to a dichotomous classification (good or excellent versus fair, poor, or worsening). The dichotomized global was analyzed using a logistic regression (PROC CATMOD).

The equality of the distributions of the overall tolerance scores in the four treatment groups was tested by a chi-square test. The percentage of patients experiencing at least one adverse event was compared by a Fisher's exact test

Reviewer's Comments:

- ***This reviewer used the following primary efficacy variables: percent change from baseline to week 11 in two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and success rate in Investigator's Global Assessment at Week 11.***
- ***To support the efficacy, the difference between treatment groups in the actual change from baseline in lesion counts should also be clinically meaningful. In this review the following secondary efficacy variables were used: actual change from baseline in inflammatory, non-inflammatory, and total lesion counts at Week 11.***
- ***In this review, the primary efficacy analysis is based on the ITT population. The sponsor's primary efficacy analysis was based on the Per Protocol population.***
- ***According to the regulatory requirement, as a combination drug, Clindoxyl must beat both active components. Therefore, no adjustment for multiple comparisons with Benzoyl and Clindamycin is required.***
- ***Clindoxyl is a combination drug indicated to cure two types of lesions: inflammatory and non-inflammatory. Benzoyl action is for non-inflammatory lesions and Clindamycin action is for inflammatory lesions. According to regulatory requirements, the sponsor must demonstrate that both components contribute to the efficacy of Clindoxyl in the treatment of acne vulgaris. Therefore, for approval, Clindoxyl must be no worse than Benzoyl and significantly better than Clindamycin relative to the percent reduction from baseline in non-inflammatory lesion count. Clindoxyl also must be no worse than Clindamycin and significantly better than Benzoyl relative to the percent reduction from baseline in inflammatory lesion count.***
- ***The major reason for issuing the May 1997 NA Letter was that the efficacy of Clindoxyl has not been demonstrated over Benzoyl alone (and, therefore, the contribution of Clindamycin to the efficacy of the combination was not supported). Therefore, this review will focus mostly on the comparison of the efficacy of Clindoxyl versus Benzoyl in the treatment of inflammatory lesions, in order to establish the contribution of Clindamycin to the efficacy of the combination.***

DISPOSITION OF SUBJECTS IN STUDY 156

A total of 288 subjects with acne vulgaris entered Study 158, with 36 subjects at each of the 8 sites. A total of 96 subjects were randomly assigned to the Benzoyl, Clindamycin, and Clindoxyl Gel groups. At the completion of the study a total of 257 subjects remained: 87 in the Benzoyl Peroxide Gel group, 85 in the Clindamycin Gel group, and 85 in the Clindoxyl Gel group, (p=0.87).

Eleven subjects in the Clindoxyl Gel group, 11 in the Clindamycin Gel group, and 9 in the Benzoyl

Peroxide Gel group did not complete the study and thus were considered not valid (non-evaluable) and excluded from analysis of the Per Protocol population (p= 0.87).

EFFICACY RESULTS of STUDY 156

Populations

Of the 288 subjects enrolled, 252 (88%) were considered valid. The Clindoxyl Gel group had 83 (86%) valid subjects, the Clindamycin Gel group had 84 (88%), and Benzoyl Peroxide Gel group had 85 (89%). There was no statistically significant difference between treatment groups relative to the proportion of valid patients (p=0.9).

Demographic and Baseline measurements

The baseline characteristics (sex, race, age, age range, baseline lesion counts, and baseline tolerance scores) of all subjects in each treatment group were not significantly different (p>0.05), although there were differences between sites for mean age and lesion counts (p<0.05). The subject population consisted primarily of Caucasian teenagers (72%) of either sex. The mean age was 17 years, range was from 12 to 30 years. The characteristics of the valid subjects were similar to those of all subjects enrolled (p>0.05). Mean baseline lesion counts by treatment group are shown in Table 1.

Table 1
Baseline Lesion Counts in Study 156

Treatment	Baseline Lesion Counts (mean +/- s.e.)		
	Inflammatory	Non-Inflammatory	Total
Benzoyl	34 +/- 0.9	46 +/- 3.5	79 +/- 3.9
Clindamycin	35 +/- 0.9	48 +/- 3.1	83 +/- 3.6
Clindoxyl	33 +/- 0.9	50 +/- 3.8	83 +/- 4.2
ALL	34 +/- 0.5	48 +/- 2.0	82 +/- 2.2

Efficacy Analysis in Study 156

Inflammatory Lesion Counts

Results of the statistical analysis for inflammatory lesion counts are given by treatment in Table 2. The comparison of Clindoxyl to Benzoyl was of primary interest. For inflammatory lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was not statistically significantly better than Benzoyl (p=0.845). Relative to the secondary efficacy variable, actual reduction from baseline, Clindoxyl also was not statistically significantly better than Benzoyl (p=0.764). The actual difference between the two treatment groups was 0.4 lesions. The results in the Per Protocol population were similar to those in the ITT population (p=0.867 for the percent reduction in inflammatory lesion count and p=0.725 for the actual reduction in the inflammatory lesion count).

TABLE 2
Inflammatory Lesion Counts in the ITT Population of Study 156

Treatment Comparison						
First	Second	Statistic	First	Second	Diff	p-Value
Clx	BPO	Reduction at Week 11	19	19	0.4	0.764
		% Reduction at Week 11	**58**	**57**	**0.8**	**0.845**
Clx	Cln	Reduction at Week 11	19	16	3	0.030
		% Reduction at Week 11	**58**	**49**	**9**	**0.030**
BPO	Cln	Reduction at Week 11	19	16	3	0.061
		% Reduction at Week 11	**57**	**49**	**8**	**0.048**

Non-Inflammatory Lesion Counts

Results of the statistical analysis for the non-inflammatory lesion counts are given by treatment in Table 3. For non-inflammatory lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was statistically significantly better than Clindamycin ($p<0.0001$). The results in the Per Protocol population were similar to those in the ITT population ($p<0.0001$).

TABLE 3
Non-Inflammatory Lesion Counts in the ITT Population of Study 156

Treatment Comparison						
First	Second	Statistic	First	Second	Diff	p-Value
Clx	BPO	Reduction at Week 11	18	14	4.4	0.070
		% Reduction at Week 11	**39**	**29**	**10**	**0.048**
Clx	Cln	Reduction at Week 11	18	9	9	0.000
		% Reduction at Week 11	**39**	**18**	**21**	**0.000**
BPO	Cln	Reduction at Week 11	14	9	5	0.046
		% Reduction at Week 11	**29**	**18**	**11**	**0.037**

Total Lesion Counts

Results of the statistical analysis for total lesion counts are given by treatment in Table 4. For total lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was only numerically better than Benzoyl ($p=0.080$). There was also no statistically significant difference between Clindoxyl and Benzoyl relative to the actual reduction in total lesions ($p=0.115$).

TABLE 4
Total Lesion Counts in the ITT Population of Study 156

Treatment Comparison						
First	Second	Statistic	First	Second	Diff	p-Value
Clx	BPO	Reduction at Week 11	38	32	5	0.115
		% Reduction at Week 11	**50**	**43**	**7**	**0.080**
Clx	Cln	Reduction at Week 11	38	25	12	0.000
		% Reduction at Week 11	**50**	**33**	**17**	**0.000**
BPO	Cln	Reduction at Week 11	32	25	7	0.024
		% Reduction at Week 11	**43**	**33**	**10**	**0.008**

Global Improvement Scores

The comparisons of the proportion of subjects with good to excellent improvement at endpoint are shown in Table 5. There was no statistically significant difference between Clindoxyl and Benzoyl (p=0.213) or Clindoxyl and Clindamycin (p=0.088). The results in the Per Protocol population were similar to those in the ITT population (p=0.101 and p=0.051, respectively).

TABLE 5
Comparisons of Treatment Groups Relative to Percent of Patients with Good to Excellent Grades in the Global Improvement at Endpoint for the ITT population of Study 156

Treatment Comparison		Percentage of patients with Good to Excellent Grades		p-Value
First	Second	First	Second	
Clindoxyl	Benzoyl	64 %	54 %	0.213
Clindoxyl	Clindamycin	64 %	50 %	0.088
Benzoyl	Clindamycin	54 %	50 %	0.640

SAFETY RESULTS in STUDY 156

Of the 283 subjects with exposure data, 204 (72%) had 71-84 applications, which approximated the once daily application for 11 weeks. The tolerance of the study medication was determined by investigator evaluation of overall tolerance at the last visit for each subject. Analysis of the proportion of subjects classified as success in the overall tolerance score (good to excellent) demonstrated no significant differences (p=0.607) between the four treatment groups (Table 6).

TABLE 6 Distribution of Subjects by Overall Tolerance Score in Study 156					
Treatment (N)	Poor (0)	Fair (1)	Good (2)	Excellent (3)	Success (2 or 3)
Benzoyl Peroxide (96)	0	1 (1%)	5 (5 %)	89 (94%)	94 (99%)
Clindamycin (96)	0	0 (0 %)	4 (4 %)	91 (96%)	95 (100%)
Clindoxyl (96)	1 (1%)	0 (0%)	4 (4%)	87 (95%)	91 (99%)
There was no significant difference between treatment groups (p=0.607) for proportion with success (good to excellent).					

Adverse Events

A total of 91 adverse events were reported for 63 of 288 subjects during the study. Analysis of the frequencies of subjects with reported adverse events (Table 7) found no significant differences between treatment groups (p=0.378). The Clindoxyl Gel group had 18 (19%) subjects who reported a total of 28 adverse events.

TABLE 7 Number of Subjects Reporting Adverse Events in Study 156		
Treatment	# of subjects	# of events
Benzoyl Peroxide	23 (24%)	27
Clindamycin	22 (23%)	36
Clindoxyl	18 (19%)	28
ALL	63 (22%)	91
There was no significant difference between treatment groups (p=0.378). Reoccurring events were counted once.		

III. STUDY 158

The primary objective of the study was to determine the relative efficacy and safety of the use of Clindoxyl, Clindamycin, Benzoyl, and Vehicle in the topical treatment of acne vulgaris. This was a double-blind, parallel, multi-center study. Patients with acne vulgaris of the face were enrolled in 8 centers and randomly assigned at the 2:1:2:1 ratio to once daily treatment with Clindoxyl, Clindamycin, Benzoyl, or Vehicle. Treatment occurred over an 11-week period with examinations of the patients at baseline (week 0), and at therapy weeks 2, 5, 8, and 11. Variation of this schedule of approximately five days was permitted provided that the investigator made sure that use of the test medication had been continued.

Study Population

Patients enrolled in this study had acne vulgaris of the face with a minimum of 25 inflammatory lesions (papules and/or pustules), a maximum of 55 inflammatory lesions, and a minimum of 12 non-inflammatory lesions (open and closed comedones), and no more than 3 facial cysts. Patients of any race and 12 to 31 years of age were enrolled in 8 centers in this study.

Efficacy variables

Evaluation of efficacy was made by counting inflammatory and non-inflammatory lesions on the entire face, excluding the nose, at the initial visit (week 0) and at all subsequent visits (weeks 2, 5, 8, and 11). The degree of improvement was based on the percent reduction from baseline of lesion counts. In addition, a global assessment of improvement of the facial acne relative to the patient's initial condition was made by the Investigator at all subsequent visits. Investigator's Global used a scale of 0 to 4, where 0 = worsening, 1 = 0-25% improvement (poor), 2 = 26-50% improvement (fair), 3 = 51-75% improvement (good) and 4 = 76-100% improvement (excellent). Final Week 11 global assessment of improvement was dichotomized as success or not (good or excellent vs. fair, poor, or worsening).

This reviewer used the following **primary efficacy variables**: percent change from baseline to week 11 in two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and success rate in Investigator's Global assessment at Week 11. To support the efficacy, the difference between treatment groups in the actual change from baseline in lesion counts should also be clinically meaningful. In this review the following secondary efficacy variables were used: actual change from baseline in inflammatory, non-inflammatory, and total lesion counts at Week 11.

Safety

Evaluation of safety was made by reporting of adverse events by the patient and by observation of signs of excessive irritation, inflammation, or other unexpected or undesirable reactions by the investigator. At the final visit for each patient (Week 11 or earlier for dropouts), the overall tolerance to the test drug was assessed by the investigator. Overall tolerance was the primary safety variable.

Statistical methods

Statistical methods in Study 158 were the same as in Study 156.

Reviewer's Comments:

- ***This reviewer used the following primary efficacy variables: percent change from baseline to week 11 in two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and success rate in Investigator's Global Assessment at Week 11.***
- ***To support the efficacy, the difference between treatment groups in the actual change from baseline in lesion counts should also be clinically meaningful. In this review the following secondary efficacy variables were used: actual change from baseline in inflammatory, non-***

inflammatory, and total lesion counts at Week 11.

- ***In this review, the primary efficacy analysis is based on the ITT population. The sponsor's primary efficacy analysis was based on the Per Protocol population.***
- ***According to the regulatory requirement, as a combination drug, Clindoxyl must beat both active components and Vehicle. Therefore, no adjustment for multiple comparisons with Benzoyl, Clindamycin, and Vehicle is required.***
- ***For internal validity, Benzoyl must be statistically significantly better than Vehicle relative to reduction of non-inflammatory lesion count and Clindamycin must be statistically significantly better than Vehicle relative to reduction of inflammatory lesion count.***
- ***Clindoxyl is a combination drug indicated to cure two types of lesions: inflammatory and non-inflammatory. Benzoyl action is for non-inflammatory lesions and Clindamycin action is for inflammatory lesions. According to regulatory requirements, the sponsor must demonstrate that both components contribute to the efficacy of Clindoxyl in the treatment of acne vulgaris. Therefore, for approval, Clindoxyl must be statistically significantly better than Vehicle relative to the percent reduction from baseline in inflammatory and non-inflammatory lesion counts. Clindoxyl also must be no worse than Benzoyl and significantly better than Clindamycin relative to the percent reduction from baseline in non-inflammatory lesion count. Clindoxyl also must be no worse than Clindamycin and significantly better than Benzoyl relative to the percent reduction from baseline in inflammatory lesion count.***
- ***The major reason for issuing the May 1997 NA Letter was that the efficacy of Clindoxyl has not been demonstrated over Benzoyl alone (and, therefore, the contribution of Clindamycin to the efficacy of the combination was not supported). Therefore, this review will focus mostly on the comparison of the efficacy of Clindoxyl versus Benzoyl in the treatment of inflammatory lesions, in order to establish the contribution of Clindamycin to the efficacy of the combination.***

DISPOSITION OF SUBJECTS IN STUDY 158

A total of 358 subjects with acne vulgaris entered Study 158. Thirty to 50 subjects were entered at each site resulting in a total of 112 subjects randomly assigned to the Benzoyl Peroxide Gel group, 65 to the Clindamycin Gel group, 113 to the Clindoxyl Gel group, and 68 to the Vehicle Gel group. At the completion of the study a total of 289 subjects remained: 91 in the Benzoyl Peroxide Gel group, 52 in the Clindamycin Gel group, 92 in the Clindoxyl Gel group, and 54 in the Vehicle Gel group (p=1.0). Twenty-one subjects in the Clindoxyl Gel group, 13 in the Clindamycin Gel group, 21 in the Benzoyl Peroxide Gel group, and 14 in the Vehicle Gel group did not complete the study and thus were considered not valid (non-evaluable) and excluded from analysis of valid subjects (p= 1.0).

EFFICACY RESULTS of STUDY 158

Populations

Two populations were analyzed for efficacy: ITT and Per Protocol (valid subjects). Of the 358 subjects enrolled, 279 (78%) were considered valid. The Clindoxyl Gel group had 91 (81%) valid subjects, the Clindamycin Gel group had 50 (77%), the Benzoyl Peroxide Gel group had 87 (78%), and the Vehicle Gel group had 51 (75%). There was no statistically significant difference between treatment groups relative to the proportion of valid patients (p=0.83).

Demographic and Baseline measurements

The baseline characteristics (sex, race, age, age range, baseline lesion counts, and baseline tolerance scores) of all subjects in each treatment group were not significantly different ($p>0.05$), although there were differences between sites for mean age and lesion counts ($p<0.01$). The subject population consisted primarily of Caucasian teenagers (72%) of either sex. The mean age was 18 years, age range was from 12 to 31 years. The characteristics of the valid subjects were similar to those of all subjects enrolled. The baseline lesion counts in Study 158 are shown in Table 8.

Table 8
Baseline Lesion Counts in Study 158

Treatment	Baseline Lesion Counts (mean +/- s.e.) Inflammatory	Non-Inflammatory	Total
Benzoyl	31 +/- 0.7	34 +/- 2.2	65 +/- 2.5
Clindamycin	33 +/- 1.1	35 +/- 2.4	69 +/- 2.7
Clindoxyl	33 +/- 0.8	37 +/- 2.0	69 +/- 2.3
Vehicle	31 +/- 0.9	37 +/- 3.2	68 +/- 3.6
ALL	32 +/- 0.4	36 +/- 1.2	68 +/- 1.4

Efficacy Analysis in Study 158

Inflammatory Lesion Counts

Results of the statistical analysis for inflammatory lesion counts are given by treatment in Table 9.

TABLE 9
Inflammatory Lesion Counts in the ITT Population of Study 158

Treatment Comparison First	Second	Statistic	First	Second	Diff	p-Value
Clx	Veh	Reduction at Week 11	17	9	8	0.000
		% Reduction at Week 11	**53**	**29**	**24**	**0.000**
Clx	BPO	Reduction at Week 11	17	13	4	0.005
		% Reduction at Week 11	**53**	**41**	**12**	**0.008**
Clx	Cln	Reduction at Week 11	17	10	7	0.000
		% Reduction at Week 11	**53**	**33**	**20**	**0.000**
BPO	Veh	Reduction at Week 11	13	9	4	0.011
		% Reduction at Week 11	**41**	**29**	**12**	**0.019**
Cln	Veh	Reduction at Week 11	10	9	1	0.502
		% Reduction at Week 11	**33**	**29**	**4**	**0.487**

The comparison of Clindoxyl to Benzoyl was of primary interest. For inflammatory lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was statistically significantly better than Benzoyl (p=0.008). Relative to the secondary efficacy variable, actual reduction from baseline, Clindoxyl also was statistically significantly better than Benzoyl (p=0.005). The actual difference between the two treatment groups was 4 lesions. The results in the Per Protocol population were similar to those in the ITT population (p=0.005 for the percent reduction).

Non-Inflammatory Lesion Counts

Results of the statistical analysis for the non-inflammatory lesion counts are given by treatment in Table 10. For non-inflammatory lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was only numerically better than Clindamycin (p=0.316). The results in the Per Protocol population were similar to those in the ITT population (p=0.204).

TABLE 10
Non-Inflammatory Lesion Counts in the ITT population of Study 158

Treatment Comparison						
First	Second	Statistic	First	Second	Diff	p-Value
Clx	Veh	Reduction at Endpoint	12	2	11	0.000
		% Reduction at Endpoint	**25**	**-9**	**35**	**0.001**
Clx	BPO	Reduction at Endpoint	12	9	3	0.112
		% Reduction at Endpoint	**25**	**21**	**4**	**0.633**
Clx	Cln	Reduction at Endpoint	12	6	6	0.021
		% Reduction at Endpoint	**25**	**15**	**11**	**0.316**
BPO	Veh	Reduction at Endpoint	9	2	7	0.003
		% Reduction at Endpoint	**21**	**-9**	**30**	**0.004**
Cln	Veh	Reduction at Endpoint	6	2	5	0.078
		% Reduction at Endpoint	**15**	**-9**	**24**	**0.040**

Total Lesion Counts

Results of the statistical analysis for the total lesion counts are given by treatment in Table 11. For total lesion counts, relative to the primary efficacy variable, percent reduction from baseline, Clindoxyl was only numerically better than Benzoyl (p=0.109). The results in the Per Protocol population supported the results in the ITT population (p=0.076).

TABLE 11
Total Lesion Counts in the ITT Population of Study 158

Treatment Comparison First	Second	Statistic	First	Second	Diff	p-Value
Clx	Veh	Reduction at Week 11	29	10	19	0.000
		% Reduction at Week 11	**41**	**15**	**25**	**0.000**
Clx	BPO	Reduction at Week 11	29	22	8	0.011
		% Reduction at Week 11	**41**	**33**	**82**	**0.109**
Clx	Cln	Reduction at Week 11	29	16	13	0.001
		% Reduction at Week 11	**41**	**25**	**16**	**0.005**
BPO	Veh	Reduction at Week 11	22	10	11	0.001
		% Reduction at Week 11	**33**	**15**	**18**	**0.001**
Cln	Veh	Reduction at Week 11	16	10	6	0.114
		% Reduction at Week 11	**25**	**15**	**10**	**0.108**

Internal validity was not shown in Study 158. There was no statistically significant difference between Clindamycin and Vehicle relative to the percent reduction of the inflammatory and total lesion counts (p=0.487 and p=0.108, respectively) and actual reduction of the inflammatory and total lesion counts, (p=0.502 and p=0.114, respectively).

Global Improvement Scores

Proportions of subjects with good to excellent improvement at endpoint are shown in Table 12.

TABLE 12
Comparisons of Treatment Groups Relative to Percent of Patients with Good to Excellent Grades in the Global Improvement at Endpoint for the ITT population of Study 158

Treatment Comparison		Percentage of patients with Good to Excellent Grades		p-Value
First	Second	First	Second	
Clindoxyl	Vehicle	49 %	24%	0.001
Clindoxyl	Benzoyl	49 %	36 %	0.042
Clindoxyl	Clindamycin	49 %	25 %	0.001
Benzoyl	Vehicle	36 %	24 %	0.067
Clindamycin	Vehicle	25 %	24 %	0.876

Relative to the proportion of patients with good to excellent grades in the Global Improvement, the p-value for the difference between Clindoxyl and Benzoyl was close to the nominal (p=0.042). In

the Per Protocol population, the difference between Clindoxyl and Benzoyl relative to the proportion of patients with good to excellent grades in the Global Improvement was not statistically significant (p=0.059).

SAFETY RESULTS in STUDY 158

TABLE 13
Distribution of Subjects by Overall Tolerance Score in Study 158

Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)	Success (2 or 3)
Benzoyl Peroxide	0	2 (2%)	18 (17%)	84 (81%)	102 (98%)
Clindamycin	0	1 (2%)	12 (20%)	48 (79%)	60 (98%)
Clindoxyl	0	1 (1%)	21 (20%)	82 (79%)	103 (99%)
Vehicle	1 (2%)	1 (2%)	11 (17%)	53 (80%)	64 (97%)
ALL	1 (0.3%)	5 (2%)	62 (19%)	267 (80%)	329 (98%)

There was no significant difference between treatment groups (p=0.80) for proportion with success (good to excellent).

Of the 324 subjects with exposure data, 249 (74%) had 71-84 applications, which approximated the once daily application for 11 weeks. The tolerance of the study medication was determined by investigator evaluation of overall tolerance at the last visit for each subject. Analysis of the proportion of subjects classified as success in the overall tolerance score (good to excellent) demonstrated no significant differences (p=0.80) between the four treatment groups (Table 13).

Adverse Events

TABLE 14
Number of Subjects Reporting Adverse Events

Treatment	# of subjects	# of events
Benzoyl Peroxide	19 (17%)	24
Clindamycin	10 (15%)	10
Clindoxyl	26 (23%)	34
Vehicle	15 (22%)	22
ALL	70 (20%)	90

There was no significant difference between treatment groups (p=0.5). Reoccurring events were counted once.

A total of 90 adverse events were reported for 70 of 358 subjects during the study. Analysis of the frequencies of subjects with reported adverse events and of subjects with reported adverse events (Table 14) found no significant differences between treatment groups (p=0.5). The Clindoxyl Gel group had 26 (23%) subjects who reported a total of 34 adverse events. In comparison, in the Clindamycin group, 15% of patients reported adverse events. This difference between the two treatment groups was not statistically significant (p=0.21).

IV. REVIEWER'S CONCLUSIONS

This Amendment was received in reference to a NA letter issued for NDA 50-741 and dated May 14, 1997. The NA letter stated that the efficacy of Clindoxyl Gel has not been demonstrated over Benzoyl Peroxide gel alone in the treatment of lesions of acne vulgaris. The Agency recommended 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 over Benzoyl Peroxide gel alone. The sponsor submitted two pivotal studies (156 and 158) to support the claim that once daily use of Clindoxyl Gel is effective and safe in the treatment of acne vulgaris.

This reviewer used the following primary efficacy variables: percent change from baseline to week 11 in two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and success rate in Investigator's Global Assessment at Week 11. To support the efficacy, the difference between treatment groups in the actual change from baseline in lesion counts should also be clinically meaningful. In this review, the primary efficacy analysis is based on the ITT population. The sponsor's primary efficacy analysis was based on the Per Protocol population.

According to the regulatory requirement, as a combination drug, Clindoxyl must beat both active components. Therefore, no adjustment for multiple comparisons with Benzoyl and Clindamycin is required. Clindoxyl is a combination drug indicated to cure two types of lesions: inflammatory and non-inflammatory. Benzoyl action is for non-inflammatory lesions and, Clindamycin action is for inflammatory lesions. According to regulatory requirements, the sponsor must demonstrate that both components contribute to the efficacy of Clindoxyl in the treatment of acne vulgaris. Therefore, for approval, Clindoxyl must be no worse than Benzoyl and significantly better than Clindamycin relative to the percent reduction from baseline in non-inflammatory lesion count. Clindoxyl also must be no worse than Clindamycin and significantly better than Benzoyl relative to the percent reduction from baseline in inflammatory lesion count.

The major reason for issuing the May 1997 NA Letter was that the efficacy of Clindoxyl has not been demonstrated over Benzoyl alone (and, therefore, the contribution of Clindamycin to the efficacy of the combination was not established). Therefore, this review primarily examined comparison of the efficacy of Clindoxyl versus Benzoyl in the treatment of inflammatory lesions, in order to evaluate the contribution of Clindamycin to the efficacy of the combination.

Efficacy Results in Study 156

Study 156 failed to demonstrate that Clindamycin contributes to the efficacy of the combination. At the endpoint, there was no statistically significant difference between Clindoxyl and Benzoyl

Peroxide relative to the percent reduction of inflammatory and total lesion counts (p=0.845 and p=0.080, respectively). This was supported by the analysis of the actual reduction from baseline in lesion counts: there was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the actual reduction of inflammatory and total lesion counts (p=0.764 and p=0.115, respectively). Results in the Per Protocol population supported the results in the ITT population (p=0.867 and p=0.725 relative to the % reduction and actual reduction of inflammatory lesions, respectively)

Relative to the proportion of subjects with good to excellent improvement in the Investigator's Global Assessment at endpoint, there was no statistically significant difference between Clindoxyl and Benzoyl or Clindamycin (p=0.213 and p= and p=0.088, respectively). The results in the Per Protocol population were similar to those in the ITT population (p=0.101 and p=0.051, respectively).

Efficacy Results in Study 158

In Study 158, there was a statistically significant difference between Clindoxyl and Benzoyl groups relative to the percent reduction in inflammatory lesions (p=0.008). However, Study 158 failed to show that Clindoxyl is statistically significantly better than Benzoyl Peroxide relative to two of the three categories of lesion counts: there was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the percent reduction of total lesion counts (p=0.109). Results for the total lesions in the Per Protocol population supported the results in the ITT population (p=0.076).

For the difference between Clindoxyl and Benzoyl relative to the proportion of patients with good to excellent grades in the Global Improvement, the p-value was close to the nominal (49% vs. 36%, p=0.042). In the Per Protocol population, the difference between Clindoxyl and Benzoyl relative to the proportion of patients with good to excellent grades in the Global Improvement was not statistically significant (p=0.059).

Study 158 failed to demonstrate that Benzoyl contributes to the efficacy of the combination. There was no statistically significant difference between Clindoxyl and Clindamycin relative to percent reduction of non-inflammatory lesions (p=0.316). Results in the Per Protocol population supported the results in the ITT population (p=0.204).

Internal validity was not shown in Study 158. There was no statistically significant difference between Clindamycin and Vehicle relative to the percent reduction of the inflammatory and total lesion counts (p=0.487 and p=0.108, respectively) and actual reduction of the inflammatory and total lesion counts, (p=0.502 and p=0.114, respectively).

Safety Results of Studies 156 and 158

In either of the Studies 156 and 158, there was no statistically significant difference between treatment groups relative to the proportion of patients with good to excellent overall tolerance score ($p \geq 0.607$) or proportion of patient with at least one adverse event ($p \geq 0.378$).

Overall Reviewer's Conclusions (which may be conveyed to the sponsor):

The objective of this Amendment was to address the deficiencies stated in the NA Letter and to demonstrate that Clindamycin contributes to the efficacy of the combination. Study 156 failed to demonstrate that Clindamycin contributes to the efficacy of the combination: there was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the percent reduction or actual reduction in inflammatory lesions ($p \geq 0.764$), total lesions ($p \geq 0.08$), and proportion of subjects with good to excellent improvement in the Investigator's Global Assessment at endpoint ($p=0.213$).

In Study 158, there was a statistically significant difference between Clindoxyl and Benzoyl groups relative to the percent reduction in inflammatory lesions ($p=0.008$). However, Study 158 failed to show that Clindoxyl is statistically significantly better than Benzoyl Peroxide relative to two of the three categories of lesion counts: there was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the percent reduction of total lesion counts ($p=0.109$).

In Study 158, for the difference between Clindoxyl and Benzoyl relative to the proportion of patients with good to excellent grades in the Global Improvement, the p-value was close to the nominal (49% vs. 36%, $p=0.042$). In the Per Protocol population, the difference between Clindoxyl and Benzoyl was not statistically significant ($p=0.059$).

Study 158 failed to demonstrate that Benzoyl contributes to the efficacy of the combination. In this study, there was no statistically significant difference between Clindoxyl and Clindamycin relative to the percent reduction of non-inflammatory lesions ($p=0.316$). Results in the Per Protocol population were similar to the results in the ITT population ($p=0.204$).

Internal validity was not shown in Study 158. There was no statistically significant difference between Clindamycin and Vehicle relative to the percent reduction of the inflammatory and total lesion counts ($p=0.487$ and $p=0.108$, respectively) and actual reduction of the inflammatory and total lesion counts, ($p=0.502$ and $p=0.114$, respectively).

This is a matter of the clinical judgement of the reviewing medical division to decide whether Clindoxyl should be approved given the efficacy issues described above.

/S/ 7.14.2000

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 7/17/2000

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III

cc:
Archival NDA 50-741, March 2000 Amendment
HFD-540
HFD-540/Mrs. Cintron
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-725/Dr. Huene
HFD-725/Dr. Al-Osh
HFD-725/Dr. Al-Osh
HFD-725/Dr. Huque
HFD-344/Dr. Carreras
Chron. (HFD-725)
This review contains 17 pages
Word/Clindoxyl2/CLNDX_r1/07-14-2000

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

NDA#/Drug class: 50-741/4S

FEB 10 1997

Applicant: Stiefel laboratories, Inc.
Coral Gables, Fl 33134

Name of Drug: Clindoxyl Gel (5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin, packaging Lot #292313)

Documents Reviewed: Volumes 1.17-1.26 dated May 14, 1996, and data on disks provided by the sponsor

Type of Report: Statistical/Clinical.

Indication: Topical treatment of facial acne vulgaris

Clinical Input: Susan Walker, M.D. (HFD-540)

CLINICAL STUDIES

INTRODUCTION

Three controlled clinical studies were conducted with clindoxyl gel to determine safety and efficacy in the topical treatment of acne vulgaris. Clindoxyl gel is a combination product containing 5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin. The clinical trials included 3 control groups, 5% benzoyl peroxide gel, clindamycin phosphate gel (equivalent to 1% clindamycin) and vehicle gel, with the purpose to compare the efficacy and safety of clindoxyl gel in the treatment of acne vulgaris with that of vehicle or either of the individual active components of the product.

Throughout the review, the terms 'Study 150', 'Study 151' and "Study 152' refer to the three clinical trials submitted by the sponsor, and the treatment name abbreviations Clindoxyl, Benzoyl, and Clindamycin refer to combination product containing 5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin, benzoyl peroxide gel, and clindamycin phosphate gel (equivalent to 1% clindamycin), respectively.

The three studies were similar in design with the exception of the randomization ratio and that studies 151 and 152 were multicenter studies and Study 150 had only one center. The next section describes design, materials, and methods in these three studies.

DESIGN, MATERIALS AND METHODS OF STUDIES 150, 151, AND 152.

OBJECTIVES

The primary objective of the study was to determine the relative efficacy and safety of the use of Clindoxyl, Clindamycin, Benzoyl, and Vehicle in the topical treatment of acne vulgaris.

INVESTIGATIONAL PLAN

Overall Plan

Study 150 had one center abd studies 151 and 152 were multicenter studies. Each of the studies was double-blind, parallel, vehicle controlled study in which patients with acne vulgaris of the face were randomly assigned to once daily treatment with either Clindoxyl, Clindamycin, Benzoyl, or Vehicle. Treatment occurred over an 11 week period with examinations of the patients initially (week 0), and at therapy weeks 2, 5, 8, and 11. Variation of this schedule of approximately ± five days was permitted provided that the investigator assured himself that use of the test medication had been continued.

Design and Control Group

Each study was a vehicle controlled clinical comparison of Clindoxyl, Clindamycin, Benzoyl, and Vehicle. The medications were used concurrently in four groups randomly assigned in the order of entry. In studies 151 and 152, approximately two sevenths of the study patients were be treated with Clindoxyl, two sevenths with Clindamycin, two sevenths with Benzoyl, and one seventh with Vehicle in a parallel fashion. In Study 150, approximately one quarter of the study patients was treated with Clindoxyl, one quarter with Clindamycin, one quarter with Benzoyl, and one quarter with Vehicle in a parallel fashion.

Study Population

Patients chosen for participation in each study were to have acne vulgaris of the face with a minimum of 12 inflammatory lesions (papules and/or pustules), a minimum of 12 non-inflammatory lesions (open and closed comedones), and no more than 3 facial nodulocystic lesions. Patients of any race and 13 to 30 years of age were to be selected for participation in this study. Patients were excluded if they 1) had utilized medicated shampoos or medicated cleansers of any type within one week of admission to the study, 2) had been treated with acne treatment of any type, systemic or topical antibiotics, systemic or topical corticosteroids or any medication that may have interfered with the study results within one month of admission to the study, 3) had been treated with oral isotretinoin within 6 months of admission to the study, 4) had a known history of hypersensitivity or idiosyncratic reaction to benzoyl peroxide, clindamycin, lincomycin, or any of the components of the study medications, 5) required any significant concomitant medication, 6) had a severe systemic disease or any other disease that would affect the evaluation of the study medication, 7) were

pregnant or lactating females, 8) were not using an effective form of contraception, including abstinence, for 3 months (6 months for oral contraception) before admission to the study, and 9) could not be reasonably agreeable to participate in the entire study program. All patients provided written informed consent prior to admission.

Dose Selection

Patients were instructed to apply the study medication to the entire face once a day, in the evening, for a period of 11 weeks. If excessive irritation or dryness developed, the investigator instructed the patient to temporarily decrease the frequency of application, in which case the investigator made note of the dosage change.

Blinding

Both the patient and the investigator/staff were unaware of which study medication was being used. The tubes, labels, and formulations looked identical. Each tube was labeled with patient and study number. The labels were affixed and the tubes were packed in numerical sequence.

Efficacy and Safety Variables

Evaluation of efficacy was made by counting inflammatory and non-inflammatory lesions on the entire face at the initial visit (week 0) and at all subsequent visits (weeks 2, 5, 8, 11). In addition a global assessment of improvement of the facial acne relative to the patient's initial condition was made at all subsequent visits using a scale of 0 to 4 where 0 = worsening, 1 = 0-25% improvement (poor), 2 = 26-50% improvement (fair), 3 = 51-75% improvement (good) and 4 = 76-100% improvement (excellent). Final Week 11 global assessment of improvement was dichotomized as success or not (good or excellent vs. fair, poor, or worsening).

Reviewer's Comment: ***It is these reviewer's opinion that the percent change from baseline is more meaningful than change from baseline. Therefore, in this review the following primary efficacy variables were used: percent change from baseline in inflammatory lesions and non-inflammatory lesions and success rate in global assessment at Week 11.***

In this review the following secondary efficacy parameters were used: change and percent change from baseline in inflammatory lesions and non-inflammatory lesions at earlier time points.

Evaluation of safety was made by reporting of adverse events by the patient and by observation of signs of excessive irritation, inflammation, or other unexpected or undesirable reactions by the investigator.

At the final visit for each patient (Week 11 or earlier for dropouts), the overall tolerance to the test medication was assessed by the investigator using a scale of 0 to 3 where 0 = poor, 1 = fair, 2 = good, and 3 = excellent. Overall tolerance was the primary safety variable.

Observations of the local tolerance of the topical medications were made by the investigator at each study visit by scoring facial erythema, peeling, burning, or other effects using the scale of 0 to 3 where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. These local observations were made on the initial visit to provide a baseline measurement for treatment comparisons. Changes from baseline of local tolerance scores for erythema, peeling, and burning and adverse event frequency were used as secondary safety variables.

Patient Compliance

At the first study visit, each patient was given detailed instructions concerning proper application of the study medication which included making their first application under observation.

Concomitant Therapy

Concomitant therapy which would affect the evaluation of the study medication was not permitted. Other concomitant medication which was required and previously used for conditions unrelated to acne vulgaris was continued and recorded.

Removal of Patients from the Study or Analysis

Patients who were uncooperative, had suffered adverse events severe enough to require discontinuation of study medication, required concomitant medication not permitted by the protocol design, or in the investigator's opinion should not continue the study for any reason, were dropped from the study. Patients that missed two sequential visits were dropped from the study. Patients that did not complete the study or had protocol violations were excluded from the efficacy analyses of the preferred data set.

Statistical methods

Two populations of patients were analyzed: all patients (ITT data set) and valid patients (Preferred data set). Valid patients were those who completed 11 weeks of treatment without protocol violations. The preferred data set consists of data actually collected on valid patients; the intent-to-treat (ITT) data set consists of all data collected on all patients. Missing values were replaced by carrying forward the last observation (ITT-LOCF analysis). Safety analyses used the intent-to-treat data set.

Demographic and baseline characteristics sex, race, and local tolerance scores in the four treatment groups were compared via the CMH procedure with adjustment for site in studies 151 and 152 and via Fisher's exact test in Study 150. Two-way ANOVA with interaction with effects for site and treatment was used to compare age and baseline counts of inflammatory and non-inflammatory lesions in treatment groups (one-way ANOVA was used in Study 150).

The five specific comparisons planned in the analysis of the efficacy data are the Clindoxyl with the Benzoyl and Clindamycin and these same three active treatment

groups to the Vehicle.

Reviewer's Comment: ***According to regulatory requirement, as a combination drug, Clindoxyl has to beat both its components and Vehicle. Therefore, no adjustment for multiple comparisons with Benzoyl, Clindamycin, and Vehicle was not required.***

For both non-inflammatory and inflammatory lesion counts, the following measures were analyzed by two-way ANOVA (one-way ANOVA in Study 150): percent reduction from baseline to Week 11 (primary variable) and both reduction and percent reduction from baseline at weeks 2, 5, and 8.

The global improvement scores at Week 11 were collapsed to a dichotomous classification (good or excellent versus fair, poor, or worsening).

Each local tolerance score at each time was collapsed to a dichotomous classification (worsening versus same or improved). The equality of the proportion worsening for all four treatment groups was tested by Fisher's exact test. The equality of the distributions of the overall tolerance scores in the four treatment groups was tested by a chi-square test. Also, the numbers of patients experiencing at least one adverse event were tested for equality of the treatment groups by a Fisher's exact test. Patients with missing data were excluded from these analyses.

RESULTS OF Study 150

DISPOSITION OF PATIENTS ENTERED

The disposition of patients in Study 150 is summarized in Table 150.1. A total of 120 patients entered this study and each patient had a diagnosis of acne vulgaris. All entry criteria were satisfied. Thirty patients were assigned to each of the following four groups in a random fashion: Clindoxyl, Clindamycin, Benzoyl, and Vehicle. At the completion of the study a total of 108 patients remained: 28 patients in the Clindoxyl, 29 patients in the Clindamycin group, 24 patients in the Benzoyl group, and 27 patients in the Vehicle group (P=0.3). A summary of reasons for premature withdrawal from the study is presented in Table 150.2. All 12 patients withdrew because of use of an excluded concomitant medication or did not return for follow up.

TABLE 150. 1
Disposition of Patients Entered in Study 150

	Clindoxyl	Clindamycin	Benzoyl Peroxide	Vehicle	ALL
Entered	30	30	30	30	120
Completed	28	29	24	27	108

TABLE 150.2
Reasons for Premature Withdrawal in Study 150

REASON	Distribution of Patients by Treatment and Reason				
	Clindoxyl	Clindamycin	Benzoyl Peroxide	Vehicle	All
Did not return or lost to follow up	2	1	4	2	9
Concomitant medication violation	0	0	2	1	3
ALL REASONS	2	1	6	3	12

Patient Conduct

Patient compliance was monitored by the return of used tubes of medication and by questioning each patient as to the number of missed applications of study medication since the previous visit. Over 96% of the patients in the preferred data set used their medication at a compliance level of 90% or more of the protocol specified once daily dose. At the completion of the study, the site conducted a study medication accountability for the return of clinical supplies to the sponsor. The sponsor verified that the return of medication from the site was 96.0%.

Two patients in the Clindoxyl treatment group, 1 patient in the Clindamycin treatment group, 6 patients in the Benzoyl treatment group, and 3 patients in the Vehicle treatment group were non-evaluable and excluded from the preferred data set (P=0.3). Patients from all four treatment groups were excluded because they did not complete the entire treatment period or for protocol violations. Two patients (150/093 and 150/103) in the Benzoyl group and 1 patient (150/089) in the Vehicle group had protocol violations for antibiotic use.

Protocol Conduct

There were some deviations from the protocol, such as procedures not done within the time constraints specified in the protocol and concomitant antibiotic or corticosteroid usage, which did not cause the patients to be disqualified. These protocol deviations did not affect the interpretation of the study results. One patient applied Vehicle every other day for most of the study due to intermittent burning as prescribed by the investigator and allowed by the protocol.

EFFICACY RESULTS

Data Sets Analyzed

Only patients completing the study and compliant with the protocol were considered valid, and their data were included in the preferred data set. All patients with data were included in the intent-to-treat data set (Table 150.3). The Clindoxyl group had 28 patients, the Clindamycin group had 29 patients, the Benzoyl group had 24 patients, and the Vehicle group had 27 patients in the preferred data set at the completion of treatment at Week 11 (P=0.3). The Benzoyl group had more missing data at the end of the study than the other groups due to the larger number (6) of

patient withdrawals but this difference was not statistically significant with P=0.3 (Table 150. 2).

TABLE 150.3
Number of Patients with Evaluable Data in Study 150

	Preferred Data Set					Intent-to-Treat Data Set				
Treatment	W0	W2	W5	W8	W11	W0	W2	W5	W8	W11
Clindoxyl	28	23	28	28	28	30	24	29	28	28
Clindamycin	29	27	27	29	29	30	28	27	29	29
Benzoyl Peroxide	24	23	23	24	24	30	28	26	26	24
Vehicle	27	25	27	27	27	30	27	27	28	27
All	108	98	105	108	108	120	107	109	111	108

Demographic and Baseline Features

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 (Table 150.5) were not significantly different (P>0.05). The characteristics of the patients in the preferred data set were similar to those of the intent-to-treat data set (P>0.05). The patient population consisted primarily of Caucasian teenagers of either sex.

TABLE 150.5
Characteristics and Baseline Features of All Patients Entered in Study 150*

	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) [b]	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 [b]	26.5±2.6	30.5±2.7	34.0±3.6	34.7±3.5	31.4 ± 1.6
Noninflamm. Lesion Count [b]	58.7±8.2	69.2±7.7	88.3±10.6	85.4±11.3	75.4 ± 4.9
Erythema Baseline Score [c]	8 (26.7%)*	11 (36.7%)	10(33%)	8 (26.7%)	37 (30.9%)
Peeling Baseline Score [c]	5 (16.7%)	4 (13.3%)	1 (3.3%)*	2 (6.7%)	12 (10.0%)
Burning Baseline Score [c]	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	5 (4.2%)

* There were no significant differences between groups (p > 0.05).
[b] Data expressed as mean ± s.e.
[c] Number (%) of patients with mild score (none were severe). * One patient was moderate.

Analysis of Each Efficacy Measure

Efficacy was determined by counting non-inflammatory and inflammatory lesions and grading global improvement throughout the study. The treatment by sex interactions in the efficacy analyses were not significant ($P>0.1$).

1. Non-Inflammatory Lesion Counts

As can be seen from Figure 150.1, non-inflammatory lesion counts declined in the Benzoyl and Clindoxyl groups as time of treatment increased but did not decline in the Clindamycin or Vehicle groups. The percent reduction in non-inflammatory lesions was greater for the Clindoxyl group than the other groups throughout the study (Figure 150.1). The mean percent reduction at 11 weeks was 26.5 for the Clindoxyl group, 14.2 for the Benzoyl group, -5.2 (i.e. an increase in lesions) for the Clindamycin group and -12.6 for the Vehicle Group (Table 150.6). The Clindoxyl group had a significantly ($P\leq 0.007$) greater percent reduction than the Clindamycin and Vehicle groups (Tables 150.6 and 150.7). However, Clindoxyl did not produce significantly better percent reduction than Benzoyl at Week 11 ($P=0.3$). When the same comparisons were made with the intent-to-treat data set, similar results were obtained (Clindoxyl was superior to Clindamycin and Vehicle with $P\leq 0.007$).

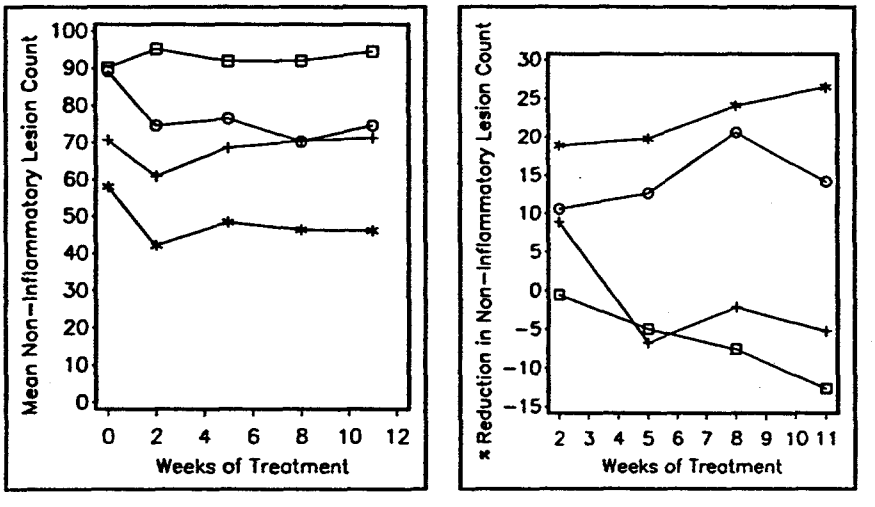

Figure 150.1: Mean non-inflammatory lesion count and mean percent reduction in the preferred data set during 11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*)

TABLE 150.6
Effect of Time and Treatment on Non-Inflammatory Lesion Counts for the Preferred Data Set in Study 150

Week	Statistic[1]	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	89.3	70.7	90.2	58.1
2	Mean Reduction	11.6[v]	5.8	-1.1	10.0[v]
	Mean % Reduction	10.6	8.9	-0.5	18.9[v]
5	Mean Reduction	12.9[v]	-0.5	-1.7	9.7
	Mean % Reduction	12.7[v]	-6.7	-4.9	19.8[v,c]
8	Mean Reduction	19.1[v]	0.2	-1.8	11.8
	Mean % Reduction	20.6[v]	-2.1	-7.5	24.1[v,c]
11	Mean Reduction	14.7[v]	-0.6	-4.3	12.0[v]
	Mean % Reduction	14.2[v]	-5.2	-12.6	26.5[v,c]
ITT-LOCF	Mean Reduction	14.0[v]	-0.4	-3.3	12.7[v]
	Mean % Reduction	12.4[v]	-4.4	-9.4	27.1[v,c]

[1] Reduction = baseline count - count at a later week
[v,c,b] Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), $p<0.05$

TABLE 150. 7
Results of Statistical Analyses of Non-Inflammatory Lesion Counts in the Preferred Data Set of Study 150

Treatment Comparison			Least Square Mean			
First	Second	Statistic[b]	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
Benzoyl Peroxide	Vehicle	Reduction at Week 11	14.7	-4.3	19.0	0.021
		% Reduction at Week 11	14.2	-12.6	26.8	0.030
Clindamycin	Vehicle	Reduction at Week 11	-0.6	-4.3	3.7	0.633
		% Reduction at Week 11	-5.2	-12.6	7.3	0.527

[b] Reduction = baseline count - count at a later week

Inflammatory Lesion Counts

As can be seen from Figure 150.2, inflammatory lesion counts declined in all groups as time of treatment increased. The percent reduction in inflammatory lesions was consistently greater for the Clindoxyl group than the other groups throughout the study (Figure 150.2). The mean percent reduction at Week 11 was 66.5 for the Clindoxyl group, 39.5 for the Benzoyl group, 34.5 for the Clindamycin group, and 19.2 for the Vehicle group (Table 150.8). As can be seen from Tables 150.8 and 150.9, at Week 11 the Clindoxyl group had a significantly greater percent reduction than the Vehicle group ($P<0.001$), the Benzoyl group ($P=0.037$), and the Clindamycin group ($P=0.01$).

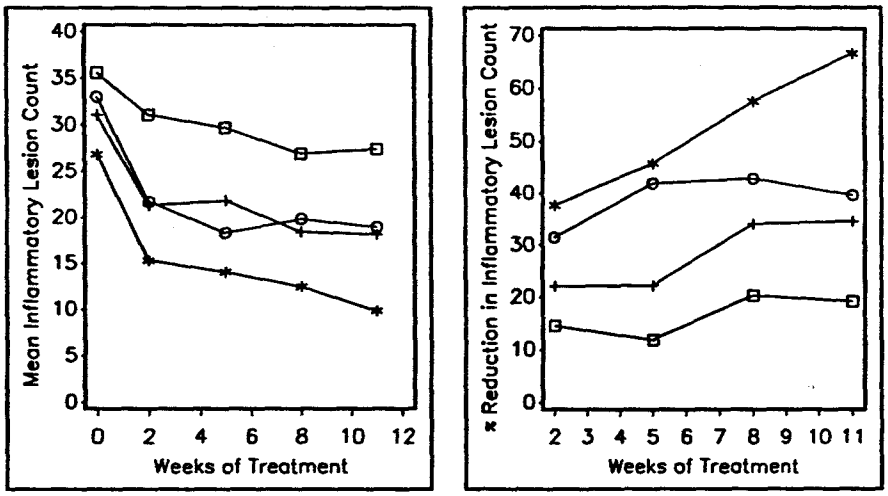

Figure 150.2: Mean inflammatory lesion count and mean percent reduction in the preferred data set during 11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

TABLE 150.8
Effect of Time and Treatment on Inflammatory Lesion Counts for the Preferred Data Set of Study 150

Week	Statistic[1]	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	33.0	31.1	35.6	26.8
2	Mean Reduction	11.5[v]	9.3	5.3	10.3
	Mean % Reduction	31.4	22.0	14.5	37.6[v]
5	Mean Reduction	15.3[v]	8.9	5.9	12.8
	Mean % Reduction	41.8[v]	22.2	11.9	45.7[v,c]
8	Mean Reduction	13.2	12.7	8.7	14.4
	Mean % Reduction	42.7[v]	34.0	20.3	57.4[v,c]
11	Mean Reduction	14.1	13.0	8.1	17.0[v]
	Mean % Reduction	39.5	34.5	19.2	66.5[v,c,b]
ITT-LOCF	Mean Reduction	13.3	12.7	8.3	16.4[v]
	Mean % Reduction	36.4	33.9	19.4	64.8[v,c,b]

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

TABLE 150.9
Results of Statistical Analyses of Inflammatory Lesion Counts
in the Preferred Data Set of Study 150

Treatment Comparison			Least Square Mean			
First	Second	Statistic[b]	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

[b] Reduction = baseline count - count at a later week

Global Improvement Scores

As can be seen from Figure 150.3, the percentage of patients with good to excellent global improvement increased in all groups. This percentage was consistently greater for the Clindoxyl group than the other groups throughout the study (Figure 150.3). The percentage of patients with good to excellent global improvement at 11 weeks was 75.0% for the Clindoxyl group, 41.7 for the Benzoyl group, 37.9 for the Clindamycin group, and 14.8 for the Vehicle group (Table 150.10). As can be seen from Table 150.11, significantly ($P \leq 0.03$) greater proportions of patients with good to excellent global improvement were observed in the Clindoxyl group than all other groups at Week 11. When the same comparisons were made with the ITT-LOCF data set, similar results were obtained.

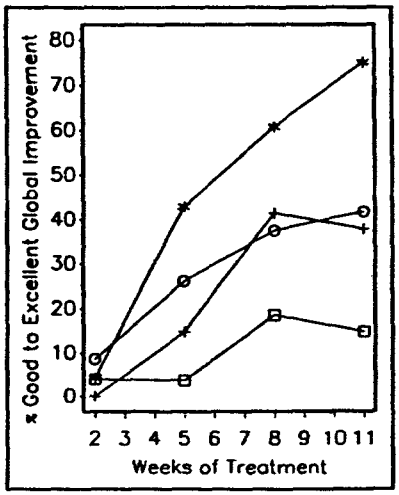

Figure 150.3: Percent of patients with good to excellent global improvement in the preferred data set after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

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TABLE 150.10
Global Improvement of Patients in the Preferred Data Set of Study 150

	Patients with Good to Excellent Global Improvement[a]			
Week	Clindoxyl	Clindamycin	Benzoyl Peroxide	Vehicle
2	1 (4.3%)	0	2 (8.7%)	1 (4.0%)
5	12 (42.9%)	4 (14.8%)	6 (26.1%)	1 (3.7%)
8	17 (60.7%)	12 (41.4%)	9 (37.5%)	5 (18.5%)
11	21 (75.0%)	11 (37.9%)	10 (41.7%)	4 (14.8%)
ITT-LOCF[a]	21 (70.0%)	11 (36.7%)	12 (40.0%)	5 (16.7%)

[a] Endpoint includes all patients with last observation carried forward

TABLE 150.11
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[b]	p-Value[a]
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

[a] Obtained from logistic regression

CONCLUSIONS ON EFFICACY IN STUDY 150

The primary efficacy variables were the percent change from baseline for non-inflammatory and inflammatory lesions and success with global improvement scores at Week 11. The Clindoxyl group had significantly greater percent reductions in inflammatory and non-inflammatory lesions than the Clindamycin and Vehicle groups at 11 weeks ($P \leq 0.01$). Compared to the Benzoyl group, the Clindoxyl group had significantly greater percent reduction at Week 11 in inflammatory lesions ($P = 0.037$) and numerically greater percent reduction in non-inflammatory lesions ($P = 0.3$). The Clindoxyl group had a significantly ($P \leq 0.03$) greater proportion of patients (75%) with good to excellent global improvement at Week 11 than the Clindamycin group (38%), the Benzoyl group (42%), or the Vehicle group (15%). The ITT-LOCF analysis supported the results of the preferred analysis.

Overall Study 150 supports the sponsor's claim that once daily use of Clindoxyl is an effective regimen for the treatment of acne vulgaris. Clindoxyl treatment was significantly ($P \leq 0.01$) more effective than Vehicle or Clindamycin treatments relative to the percent reduction of inflammatory or non-inflammatory lesions and in global improvement. Clindoxyl also was significantly ($P \leq 0.037$) better than Benzoyl

with the exception of the percent reduction of non-inflammatory lesions (P=0.3). The ITT-LOCF analysis supported the results of the preferred analysis.

RESULTS OF Study 151

DISPOSITION OF PATIENTS ENTERED

The disposition of patients in Study 151 is summarized in Table 151.1. A total of 273 patients with acne vulgaris entered this multicenter study: 70 patients were entered at each site with the exception of Site 151D which only entered 63 patients of the protocol required 70 patients after about 6 months of recruiting. It was decided that recruitment should stop so that the study could be completed before the summer. Seventy-eight patients were assigned to each of the following three active groups in a random fashion: Benzoyl, Clindamycin, and Clindoxyl. Twenty patients were assigned to each active group at each site, with the exception of Site 151D which assigned 18 patients to each active group. Thirty-nine patients were assigned randomly to the Vehicle group, 10 patients at each site, with the exception of Site 151D which assigned 9 patients to the Vehicle group. At the completion of the study a total of 231 patients remained: 70 patients in the Benzoyl group, 60 patients in the Clindamycin group, 32 patients in the Vehicle group and 69 patients in the Clindoxyl group (P=0.1).

TABLE 151.1
Disposition of Patients Entered in Study 151

Site	Disposition	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl	ALL
151A	Entered	20	20	10	20	70
	Completed	17	17	7	18	59
151B	Entered	20	20	10	20	70
	Completed	19	15	10	18	62
151C	Entered	20	20	10	20	70
	Completed	19	16	9	18	62
151D	Entered	18	18	9	18	63
	Completed	15	12	6	15	48
ALL	Entered	78	78	39	78	273
	Completed	70	60	32	69	231

Most patients (33 of 42) withdrew because of use of an excluded concomitant medication or other protocol violations or did not return for follow up.

Patient Conduct

Patient compliance was monitored by the return of used tubes of medication and by questioning each patient as to the number of missed applications of study medication since the previous visit. Overall 96% of the patients in the preferred data set used their medication at a compliance level of 90% or more of the protocol specified once daily dose (Table 151.3). Depending on the site and treatment group 89 to 100% of the patients achieved this level of compliance. At the completion of the study, the site conducted a study medication accountability for the return of clinical supplies to the sponsor. The sponsor verified that the return of medication was 97.5% for Site 151A, 98.2% for Site 151B, 97.9% for Site 151C, 97.1% for Site 151D, and 97.6% for overall return.

Nine patients in the Clindoxyl group, 18 patients in the Clindamycin group, 8 patients in the Benzoyl group, and 7 patients in the Vehicle group did not complete the study (Table 151.1) and thus were considered not valid (non-evaluable) and excluded from the preferred data set. There was no significant difference between treatment group relative to the number of patients not completed the study (P=0.1). Eighteen of these patients did not complete the entire treatment period because of protocol violations which included use of excluded concomitant medication during the study (15 patients) or on entry (2 patients) and becoming pregnant for 1 patient (151D/37). In addition, 5 patients that completed the study were also considered not valid because of antibiotic use (1 patient in the Vehicle group - 151B/58), non-compliant birth control pill use (2 patients in the Clindoxyl group - 151B/63 and 151D/46 and 1 patient in the Benzoyl group - 151D/35), and 1 patient (151C/26) for using the wrong medication in the Benzoyl group.

TABLE 151.3
Number (%) of Valid Patients Compliant at 90 to 110% of Planned Dosing
(77 applications in 77 days)

Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl	ALL
151A	17 (100)	17 (100)	7 (100)	17 (94.4)	58 (98.3)
151B	19 (100)	14 (93.3)	8 (88.9)	17 (100)	58 (96.7)
151C	17 (94.4)	16 (100)	8 (88.9)	17 (94.4)	58 (95.1)
151D	14 (100)	11 (91.7)	6 (100)	13 (92.9)	44 (95.7)
ALL	67 (98.5)	58 (96.7)	29 (93.5)	64 (95.5)	218 (96.5)

Protocol Conduct

There were some deviations from the protocol, such as procedures not done within the time constraints specified in the protocol and concomitant antibiotic usage, which did not cause the patients to be disqualified. Twenty-eight valid patients deviated from the ± 5 day schedule variation by 1 to 5 days including 13 patients in the Clindoxyl group, 8 patients in the Clindamycin group, 5 patients in the Benzoyl group, and 2 patients in the Vehicle group (P=0.1). Seven valid patients had concomitant short

term antibiotic usage which the investigator did not consider as having an effect on acne. One patient in the Clindoxyl group was enrolled out of sequential order and was only on birth control pills for two months before entry which the investigator stated would not affect her acne. These protocol deviations did not affect the interpretation of the study results.

EFFICACY RESULTS OF Study 151

Data Sets Analyzed

Only patients completing the study and compliant with the protocol were considered valid, and their data were included in the preferred data set (Table 151.4). All patients with data were included in the intent-to-treat data set (Table 151.4).

TABLE 151.4
Number of Patients with Evaluable Data in Study 151

Site	Treatment	Preferred Data Set					Intent to Treat Data Set				
		W0	W2	W5	W8	W11	W0	W2	W5	W8	W11
151A	Benzoyl Peroxide	17	17	17	14	17	20	20	18	15	17
	Clindamycin	17	17	17	17	17	20	18	18	17	17
	Vehicle	7	7	7	7	7	10	9	8	7	7
	Clindoxyl	18	18	18	16	18	20	20	19	16	18
	ALL	59	59	59	54	59	70	67	63	55	59
151B	Benzoyl Peroxide	19	19	19	17	19	20	20	19	17	19
	Clindamycin	15	15	15	14	15	20	18	17	16	15
	Vehicle	9	9	8	9	9	10	10	9	10	10
	Clindoxyl	17	17	16	17	17	20	20	18	19	18
	ALL	60	60	58	57	60	70	68	63	62	62
151C	Benzoyl Peroxide	18	18	18	18	18	20	20	20	20	19
	Clindamycin	16	16	16	15	16	20	20	17	16	16
	Vehicle	9	9	9	9	9	10	10	10	9	9
	Clindoxyl	18	18	16	16	18	20	20	17	16	18
	ALL	61	61	59	58	61	70	70	64	61	62
151D	Benzoyl Peroxide	14	14	13	14	14	18	17	15	15	15
	Clindamycin	12	12	12	11	12	18	15	14	11	12
	Vehicle	6	6	6	6	6	9	8	7	7	6
	Clindoxyl	14	14	13	14	14	18	17	16	15	15
	ALL	46	46	44	45	46	63	57	52	48	48
ALL	Benzoyl Peroxide	68	68	67	63	68	78	77	72	67	70
	Clindamycin	60	60	60	57	60	78	71	66	60	60
	Vehicle	31	31	30	31	31	39	37	34	33	32
	Clindoxyl	67	67	63	63	67	78	77	70	66	69
	ALL	226	226	220	214	226	273	262	242	226	231

The Clindoxyl group had 67 patients, the Clindamycin group had 60 patients, the Benzoyl group had 68 patients, and the Vehicle group had 31 patients in the preferred data set at the completion of treatment (Week 11). There was no significant difference between treatment groups in the proportion of patient included in the preferred data set (P=0.3). There were 1 to 2 more patients in each group (except for the Clindamycin group) in the intent-to-treat data set at the completion of treatment (Week 11) than in the preferred data set due to exclusion of five patients. The number of excluded patients were similar for all groups (P=0.3).

TABLE 151.7
Baseline Features of All Patients Entered in Study 151

		Week 0 Lesion Counts[a] (mean ± s.e.)		Week 0 Local Tolerance Scores (# of patients with mild or moderate scores[c])			
Site	Treatment[b]	Inflammatory	Non-Inflammatory	Erythema	Burning	Peeling	Dryness
151A	BPO	25.7 ± 4.3	45.8 ± 8.0	4	1	0	2
	Clindamycin	21.4 ± 1.7	46.0 ± 6.5	3	0	0	0
	Vehicle	21.1 ± 3.4	39.0 ± 7.4	3	0	0	0
	Clindoxyl	20.8 ± 2.2	45.9 ± 5.6	2	0	0	0
	ALL	22.4 ± 1.5	44.9 ± 3.4	12 (17.1%)	1 (1.4%)	0 (0.0%)	2 (2.9%)
151B	BPO	30.6 ± 3.0	32.8 ± 4.4	5	0	0	0
	Clindamycin	22.7 ± 2.0	31.8 ± 4.7	1	0	0	0
	Vehicle	34.1 ± 4.8	37.4 ± 5.2	0	0	0	0
	Clindoxyl	33.1 ± 4.1	28.2 ± 2.2	2	0	0	0
	ALL	29.6 ± 1.8	31.9 ± 2.1	8 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
151C	BPO	30.5 ± 3.4	69.8 ± 10.7	1	0	0	0
	Clindamycin	30.6 ± 3.9	66.1 ± 8.2	2	0	0	0
	Vehicle	33.6 ± 3.6	92.5 ± 14.1	1	0	0	0
	Clindoxyl	27.2 ± 3.1	75.8 ± 12.1	4	0	0	0
	ALL	30.0 ± 1.8	73.7 ± 5.5	8 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
151D	BPO	29.9 ± 3.6	43.3 ± 5.9	10	0	0	1
	Clindamycin	27.4 ± 4.1	33.6 ± 5.3	5	0	0	0
	Vehicle	21.1 ± 3.9	36.2 ± 6.0	3	0	0	0
	Clindoxyl	24.2 ± 2.4	32.4 ± 5.3	5	0	0	0
	ALL	26.3 ± 1.8	36.4 ± 2.8	23 (36.5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
ALL	BPO	29.2 ± 1.8	48.1 ± 4.1	20	1	0	3
	Clindamycin	25.5 ± 1.6	44.7 ± 3.5	11	0	0	0
	Vehicle	27.6 ± 2.2	51.7 ± 5.8	7	0	0	0
	Clindoxyl	26.4 ± 1.6	45.9 ± 4.2	13	0	0	0
	ALL	27.1 ± 0.9	47.0 ± 2.1	51 (18.7%)	1 (0.4%)	0 (0.0%)	3 (1.1%)

[a] There were no significant differences (p>0.05) between groups
[b] BPO = Benzoyl Peroxide. [c] There were no severe scores.

Demographic and Baseline Features

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 (Table 151.7) were not significantly different ($P>0.05$). The patient population consisted primarily of Caucasian teenagers of either sex.

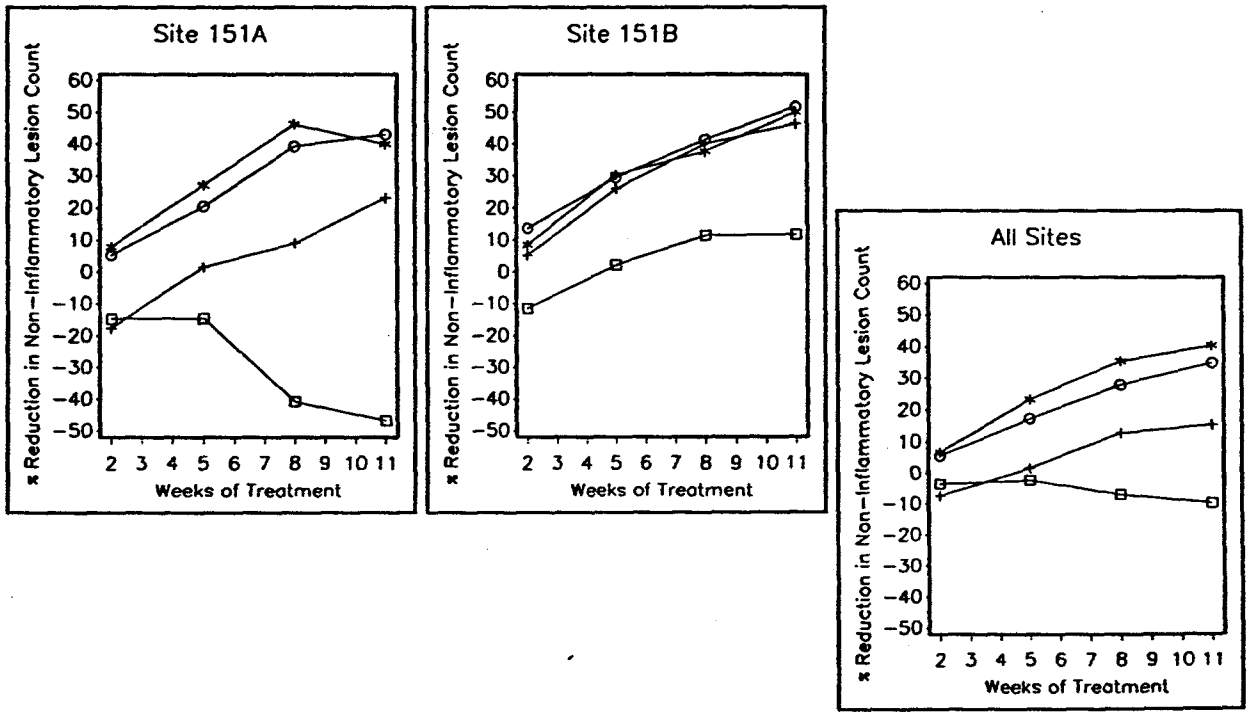
Analysis of Each Efficacy Measure

Efficacy was determined by counting non-inflammatory and inflammatory lesions and grading global improvement throughout the study. The treatment by site or sex interactions in the efficacy analyses were not significant ($P>0.1$).

Non-Inflammatory Lesion Counts

As can be seen from Figure 151.1, the percent reduction in non-inflammatory lesions was usually greater for the Clindoxyl group than the other groups throughout the study for each site or all sites combined.

The mean percent reduction at 11 weeks was 40.4 for the Clindoxyl group, 34.9 for the Benzoyl group, 15.3 for the Clindamycin group and -9.6 (i.e. an increase in lesions) for the Vehicle group (Table 151.8). The Clindoxyl group had a significantly ($P<0.003$) greater percent reduction than the Clindamycin and Vehicle groups at Week 11 (Tables 151.8 and 151.9). However the difference in the percent reduction between Clindoxyl and Benzoyl groups was not statistically significant ($P=0.5$). When the same comparisons were made with the ITT-LOCF data set, similar results were obtained.



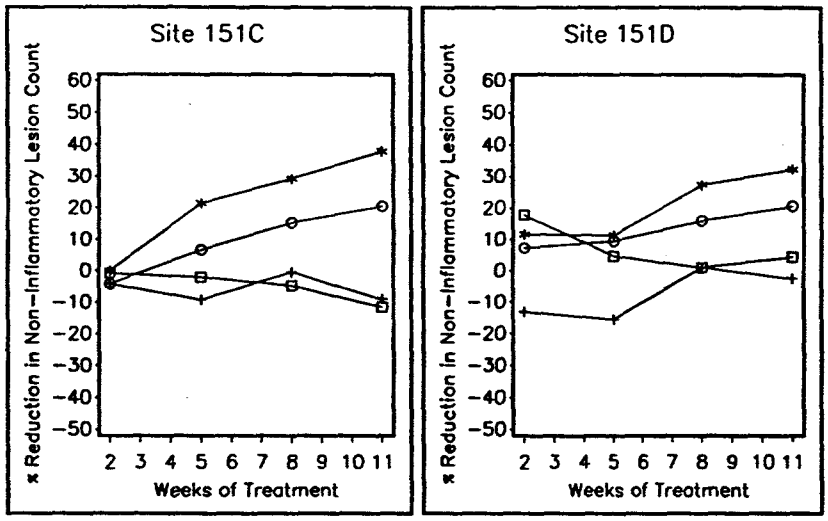


Figure 151.1: Mean percent reduction in non-inflammatory lesion count in the preferred data set by site and all sites combined after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

TABLE 151.8
Effect of Time and Treatment on Non-Inflammatory Lesion Counts for the Preferred Data Set in Study 151

Week	Statistic[1]	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	48.5	46.0	52.6	48.6
2	Mean Reduction	1.8	-3.2	-0.2	2.8[c]
	Mean % Reduction	5.6	-7.4	-3.4	6.7[c]
5	Mean Reduction	7.6	1.2	1.0	11.6[v,c]
	Mean % Reduction	17.2[v]	1.5	-2.4	23.3[v,c]
8	Mean Reduction	13.3[v]	6.6	0.3	16.1[v,c]
	Mean % Reduction	27.9[v]	12.7[v]	-7.0	35.4[v,c]
11	Mean Reduction	16.3[v]	8.2	0.8	18.5[v,c]
	Mean % Reduction	34.9[v]	15.3[v]	-9.6	40.4[v,c]
ITT-LOCF	Mean Reduction	14.3[v]	6.3	2.9	16.8[v,c]
	Mean % Reduction	30.4[v]	12.6	-5.2	37.2[v,c]

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

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TABLE 151.9

Results of Statistical Analyses of Non-Inflammatory Lesion Counts in the Preferred Data Set[a] of Study 151

Treatment Comparison			Least Square Mean			
First	Second	Statistic[b]	First	Second	Difference	p-Value
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

[a] Site*treatment interaction was not significant ($p>0.1$).
[b] Reduction = baseline count - count at a later week.

Inflammatory Lesion Counts

Inflammatory lesion counts declined in all groups as time of treatment increased except for the Vehicle group. As can be seen from Figure 151.2, the percent reduction in inflammatory lesions was consistently greater for the Clindoxyl group than the other groups throughout the study for each site or all sites combined. The mean percent reduction at 11 weeks was 58.4 for the Clindoxyl group, 39.4 for the Benzoyl group, 35.9 for the Clindamycin group, and -7.6 (i.e. an increase in lesions) for the Vehicle group (Table 151.10). The Clindoxyl group had a significantly ($P\leq 0.003$) greater percent reduction than the Clindamycin, Vehicle and Benzoyl groups at Week 11 (Tables 151.10 and 151.11). When the same comparisons were made with the ITT-LOCF data set, similar results were obtained.

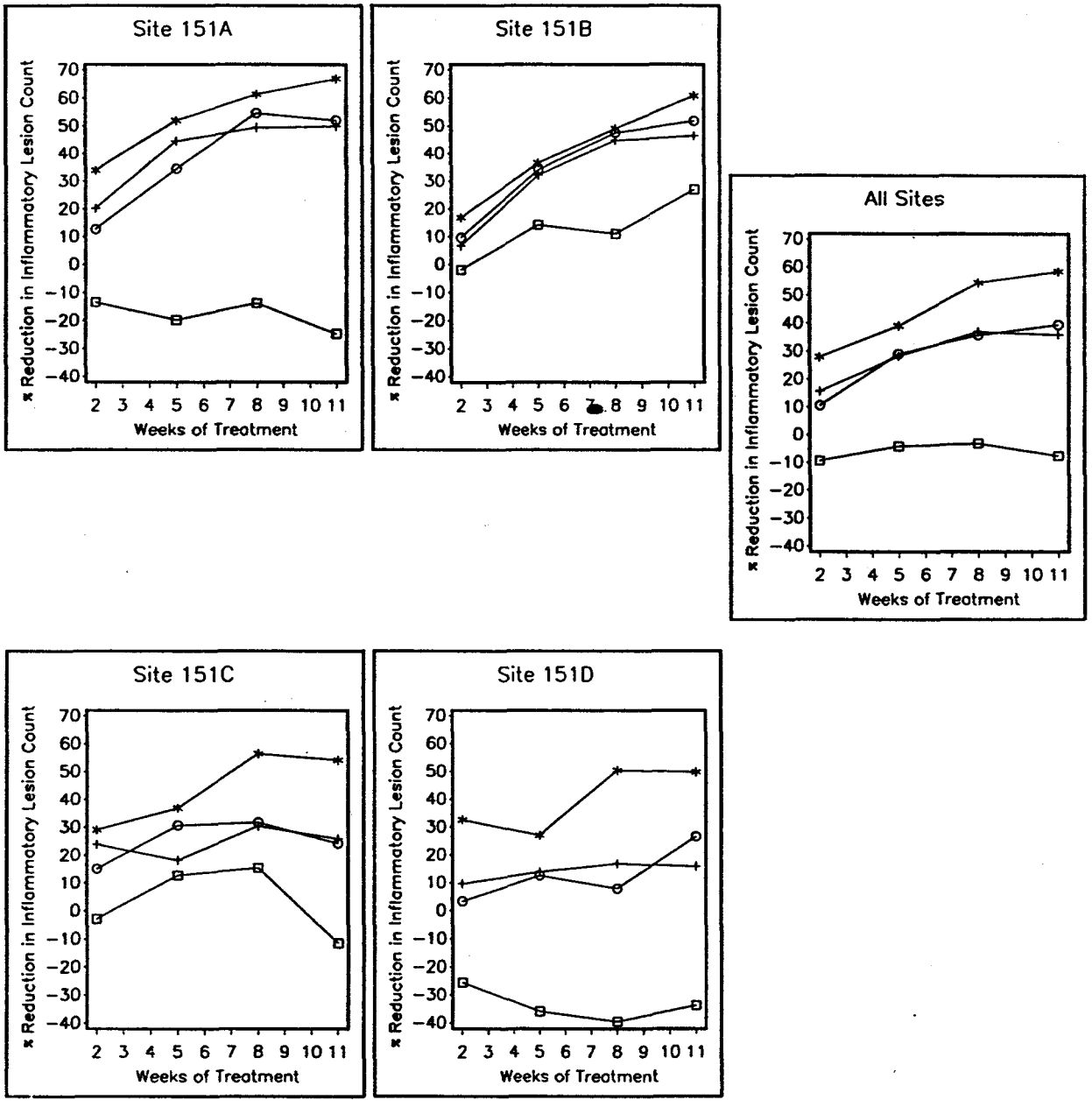

Figure 151.2: Mean percent reduction in inflammatory lesion count in the preferred data set by site and all sites combined after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

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TABLE 151.10
Effect of Time and Treatment on Inflammatory Lesion Counts for the Preferred Data Set in Study 151

Week	Statistic[1]	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	29.9	25.5	28.0	25.8
2	Mean Reduction	4.0[v]	4.6[v]	-1.0	7.1[v,b]
	Mean % Reduction	10.6[v]	15.7[v]	-9.3	28.0[v,c,b]
5	Mean Reduction	8.4[v]	6.5[v]	0.6	9.9[v,c]
	Mean % Reduction	29.1[v]	28.3[v]	-4.1	39.1[v]
8	Mean Reduction	11.6[v]	8.8[v]	0.9	13.5[v,c]
	Mean % Reduction	35.8[v]	37.0[v]	-3.0	54.4[v,c,b]
11	Mean Reduction	12.4[v]	8.3[v]	-0.5	14.6[v,c]
	Mean % Reduction	39.4[v]	35.9[v]	-7.6	58.4[v,c,b]
ITT-LOCF	Mean Reduction	11.4[v]	6.9[v]	1.2	14.0[v,c]
	Mean % Reduction	37.1[v]	29.6[v]	-0.4	55.6[v,c,b]

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

TABLE 151.11
Results of Statistical Analyses of Inflammatory Lesion Counts in the Preferred Data Set[a] of Study 151

Treatment Comparison			Least Square Mean			
First	Second	Statistic[b]	First	Second	Difference	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	Benzoyl Peroxide	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
Benzoyl Peroxide	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

[a] Site*treatment interaction was not significant ($p>0.1$).
[b] Reduction = baseline count - count at a later week

Global Improvement Scores

As can be seen from Figure 151.3, the percentage of patients with good to excellent global improvement increased in all groups except for the Vehicle group. This

percentage was consistently greater for the Clindoxyl group than the other groups throughout the study for each site or all sites combined (Figure 151.3). The percentage of patients with good to excellent global improvement at Week 11 was

62.7 for the Clindoxyl group, 41.2 for the Benzoyl group, 35.0 for the Clindamycin group, and 6.5 for the Vehicle group (Table 151.12). At Week 11, significantly ($P \leq 0.013$) greater proportions of patients with good to excellent global improvement were observed in the Clindoxyl group than all other groups (Table 151.13). When the same comparisons were made with the ITT-LOCF data set, similar results were obtained.

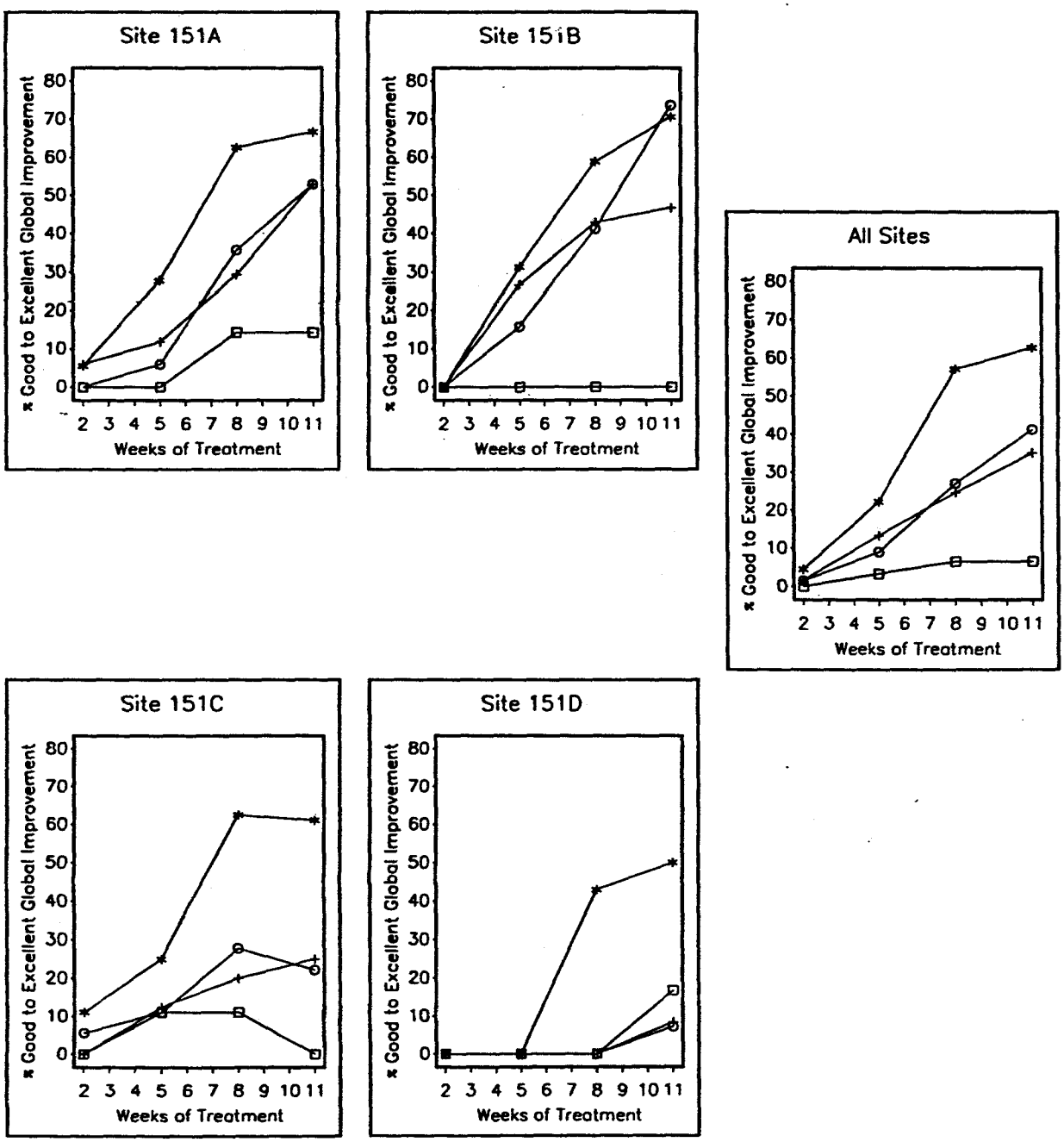

Figure 151.3: Percent of patients with good to excellent global improvement in the preferred data set by site and all sites combined after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*)

TABLE 151.12
Patients with Good to Excellent Global Improvement in the Preferred Data Set of Study 151

Week	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
2	1 (1.5%)	1 (1.7%)	0 (0.0%)	3 (4.5%)
5	6 (9.0%)	8 (13.3%)	1 (3.3%)	14 (22.2%)
8	17 (27.0%)	14 (24.6%)	2 (6.5%)	36 (57.1%)
11	28 (41.2%)	21 (35.0%)	2 (6.5%)	42 (62.7%)
ITT-LOCF[a]	30 (38.5%)	22 (28.2%)	2 (5.1%)	43 (55.1%)

[a] ITT-LOCF includes all patients with last observation carried forward.

TABLE 151.13
Comparisons of Treatment Effects on Proportion of Patients with Good to Excellent Global Improvement in the Preferred Data Set at Week 11[a] Study 151

Treatment Comparison		Proportion		Estimated Odds Ratio[b]	p-Value[b]
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

[a] Site*treatment interaction was not significant ($p > 0.1$)
[b] Obtained from logistic regression

CONCLUSIONS ON EFFICACY IN Study 151

The percent change from baseline of non-inflammatory and inflammatory lesions and success with global improvement scores at Week 11 were considered primary efficacy variables. The Clindoxyl group had significantly greater percent reductions in inflammatory and non-inflammatory lesions than the Clindamycin and Vehicle groups at Week 11 ($P \leq 0.003$). Compared to the Benzoyl group, the Clindoxyl group had significantly greater percent reduction in inflammatory lesions than the Benzoyl group at Week 11 ($P = 0.003$) and numerically greater percent reduction in non-inflammatory lesions ($P = 0.5$). In addition, the Clindoxyl group had a significantly ($P \leq 0.013$) greater proportion of patients (63%) with good to excellent global improvement at Week 11 than the Clindamycin group (35%), the Benzoyl group (41%), or the Vehicle group (6%).

Overall Study 151 supports the sponsor's claim that once daily use of Clindoxyl is an effective regimen for the treatment of acne vulgaris. A significantly greater proportion of patients in the Clindoxyl group had good to excellent global improvement at Week 11 than in the Vehicle, Benzoyl, or Clindamycin groups ($P \leq 0.013$). Clindoxyl treatment for 11 weeks produced significantly greater percent reductions in

inflammatory lesions than Vehicle, Benzoyl and Clindamycin (P<0.003) and significantly greater percent reductions in non-inflammatory lesions than Clindamycin and Vehicle (P≤0.003). Greater lesion count reductions and greater global improvements in the Clindoxyl group were observed at earlier visits throughout the study. The ITT-LOCF analysis supported the results of the preferred analysis.

RESULTS OF Study 152

DISPOSITION OF PATIENTS ENTERED

The disposition of patients entered in Study 152 is summarized in Table 152.1. A total of 280 patients with acne vulgaris entered this two center study: 140 patients were entered at each site. Eighty patients (40 patients at each site) were assigned to each of the following three active groups in a random fashion: Benzoyl, Clindamycin, and Clindoxyl. Forty patients (20 patients at each site) were assigned randomly to the Vehicle group . At the completion of the study, a total of 255 patients remained: 71 patients in the Benzoyl group, 71 patients in the Clindamycin group, 38 patients in the Vehicle group and 75 patients in the Clindoxyl group The difference between treatment groups was not significant (P=0.5).

TABLE 152.1
Disposition of Patients Entered in Study 152

Site	Disposition	Benzoyl	Clindamycin	Vehicle	Clindoxyl	ALL
152A	Entered	40	40	20	40	140
	Completed	36	35	20	38	129
152B	Entered	40	40	20	40	140
	Completed	35	36	18	37	126
ALL	Entered	80	80	40	80	280
	Completed	71	71	38	75	255

Most patients (17 of 25) withdrew because they were no longer able to participate, did not return for follow up, or had an adverse event related to their study medication.

COMPLIANCE

Patient Conduct

Patient compliance was monitored by the return of used tubes of medication and by questioning each patient as to the number of missed applications of study medication since the previous visit. Overall 98% of the patients in the preferred data set used their medication at a compliance level of 90% or more of the protocol specified once daily dose (Table 152.3). Depending on the site and treatment group 94 to 100% of the patients achieved this level of compliance. At the completion of the study, the site conducted a study medication accountability for the return of clinical supplies to the