CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-801

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-709 / 000
Drug Name:	Clindamycin Phosphate Foam, 1%
Indication(s):	Treatment of mild to moderate severity acne vulgaris
Applicant:	Connetics Corporation
Date(s):	Received 12/24/03, user fee (10 months) 10/24/04
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Keywords:
active control/non-inferiority, Cochran-Mantel-Haenszel, delta choice (active control)

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Sponsor is submitting NDA 21-709 for clindamycin phosphate foam, 1%, for topical application in the treatment of acne vulgaris under the Food, Drug, and Cosmetic Act, Section 505 (b) (2). Clindamycin phosphate foam was developed as a change in dosage form for the reference listed drug, Clindagel® (clindamycin phosphate) Topical Gel, 1%. The results are based on a single four armed, Phase 3 study, with treatment groups: 1) clindamycin foam, 2) Clindagel, 3) vehicle foam, and 4) vehicle gel. Treatment was to be applied once a day for 12 weeks. There was no untreated follow-up period. The primary endpoints specified in the protocol were the percent change from baseline in each of the non-inflammatory lesion counts, the inflammatory lesion counts, and the total lesion counts, plus a dichotomization of a six point Investigator's Static Global Assessment (ISGA), all computed in the intent-to-treat population. For all lesion count measures and the ISGA, clindamycin foam was shown to be statistically significantly superior to its vehicle and non-inferior to the gel formulation. In fact, for the percent change from baseline in non-inflammatory and total lesions, the foam was shown to be statistically significantly better than the gel formulation. A preliminary Bayesian analysis of the non-inferiority comparisons was consistent with these results (Appendix 7). Although results from the intent to treat population are emphasized, results from the per protocol and simple completer populations are similar.

In particular, in the Week 12 intent-to-treat (ITT) population, for each of the measures: percent change from baseline in non-inflammatory lesion counts, inflammatory lesion counts, and total lesion counts, plus the dichotomization of the six point Investigator's Static Global Assessment (ISGA) there were statistically significant differences between clindamycin foam and its vehicle ($p \leq 0.0014$, $p < 0.0001$, $p < 0.0001$, and $p \leq 0.0025$, respectively). Similarly, in each case clindamycin foam was found to be non-inferior to Clindagel. For the percent decrease in non-inflammatory lesion counts, a 95% confidence interval about the difference between clindamycin foam and Clindagel was computed as (3.1,13.5). Since the lower limit of this interval was greater than the non-inferiority bound of -10%, we would conclude that the hypothesis of non-inferiority was accepted. In fact, since the interval was uniformly greater than 0, we conclude that superiority is accepted (actual test of superiority has $p \leq 0.0019$). For percent reduction in inflammatory lesions, the interval about the difference is (-0.6, 9.7), again uniformly greater than -10%. For percent reduction in total lesions the confidence interval is (3.3, 11.7), once again uniformly greater than the -10% bound. As before, since the interval was greater than 0, we accept the hypothesis of superiority (test of superiority has $p \leq 0.0005$). Success on the ISGA was defined as a score of 0 or 1 on the six-point scale in the ITT population at 12 weeks. Success percentages were 31.1% in the clindamycin foam group versus 27.3% in the Clindagel group. The 95% confidence interval on the treatment difference was (-2.3,9.9), again greater than the -10% bound. Since all these intervals were above -10% bound, we accept the hypothesis of non-inferiority. Note results at the study endpoint seem to be quite consistent,

whether one uses the ITT population, the per protocol (PP) population, or just the group of subjects that completed the study. This suggests that drop-outs had no effect on conclusions.

1.2 Brief Overview of Clinical Studies

To study the efficacy and safety of clindamycin phosphate foam, 1%, for topical treatment of acne vulgaris, the Sponsor provided results from a Phase 3 randomized, double-blind, four-armed, multi-center, 12-week study (Study C.003). The results of this study were supported by a somewhat earlier, but slightly overlapping Phase 2, randomized, double-blind, three-armed, multi-center, 12-week studies (Study C.002). Detailed results on the primary endpoints in Study C.002 are given in Appendix 6. With the concurrence of the FDA, percent change from baseline in inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts, plus an Investigator's Static Global Assessment (ISGA) were specified as the primary endpoints.

Table 1 in Section 2.1 below provides a summary description of the two studies.

1.3 Statistical Issues and Findings

The Sponsor indicated that this submission was intended to demonstrate, using acne lesion count measures and an Investigator's Static Global Assessment, the non-inferiority of clindamycin phosphate foam, 1% (Clindamycin Foam), versus Clindagel® (clindamycin phosphate gel) Topical Gel, and the superiority of Clindamycin Foam versus vehicle foam. There were some issues in the analysis:

1. Note that at the Pre-IND meeting on April 10, 2002, the Sponsor was told that a non-inferiority bound of 11% would be acceptable. This was implicitly confirmed in the Special Protocol Assessment submitted 7 May 2002. However, current practice is to generally maintain at least a 10% bound. The latter value was used in this report. Note that this does not change any conclusions.

2. Residuals from the linear models for the lesion count measures were clearly not normal. The protocol specified a Shapiro-Wilk test of normality, though it is not clear if this is to be applied to the residuals or the original observations. However, the distributions of the residuals tended to be strongly unimodal, thin tailed, and only moderately skewed to the right. So with these large sample sizes analysis of variance on these measures should be appropriate. While not reviewed here, normit transformed ranks seemed to give much the same test results as the original responses, confirming this observation.

3. The non-inferiority analysis in the percent change from baseline in the various lesion count measures use confidence intervals based on contrasts in an analysis of variance with factors for center and treatment. In these ANOVA's center by treatment interaction was never statistically significant. The protocol specified that under such circumstances the interaction term should be dropped from the model. However, there are two problems with such an approach:

1) The confidence intervals are then conditional confidence intervals and the true unconditional confidence level is not clear.
2) When estimating contrasts in the center by treatment layouts, effectively this means that in the full space associated with the factorial design, the basis for the contrast terms are effectively orthogonalized to the subspace spanned by the center by treatment interaction contrasts. This reviewer would prefer the simpler interpretation of the contrasts prior to this orthogonalization to the generally greater power associated with this transformation.
Hence, the contrasts used to define the non-inferiority comparisons in the FDA analysis include, and are balanced over these interactions, not orthogonalized to the interactions. For the non-inferiority comparisons this deviation from the protocol has no effect on conclusions.

4. As discussed in Appendix 5, when computing confidence intervals for the non-inferiority comparisons in binary responses like success on ISGA, there are a number of reasonable choices, including whether or not the analysis is stratified by center and the type of error variance used. For the FDA analysis three different intervals are displayed, but note that they are all close to each other, and all lead to the same conclusions.

2. INTRODUCTION

2.1 Overview

Clindamycin phosphate foam, 1%, is a topical antibiotic anti-acne product in an aerosol foam vehicle. The Sponsor, Connetics Corporation, claims that the foam delivery system offers some advantages in drug delivery over the older gel system, in particular less residue.

Pre-IND meetings were held on 16 August 2001 and 10 April 2002, followed by a Special Protocol Assessment, IND 64, 577 / 001, submitted by the Sponsor on 7 May 2002.

For the submitted clinical studies, C.002 and C.003, the primary endpoints for acne were based on lesion counts and an Investigator's Static Global Assessment.

Table 1 below provides a summary description of the clinical studies.

Table 1. Description of Studies

Study Protocol	Study Type	# Centers locations	Treatment Arm	# of ITT subjects/arm	Individual Study Duration	Overall Study Duration
C.003	Phase 3	18 U.S.	Clindamycin Foam. Clindagel Vehicle Foam Vehicle Gel.	386 385 127 128	12 weeks	12 September 2002 to 5 August 2003
C.002	Phase 2	8 U.S.	Clindamycin Foam. Clindagel Vehicle Foam	53 50 27	12 weeks	June 2002 To November 2002

In addition to the phase 3 and phase 2 studies reviewed here, studies C.003 and C.002 respectively, the Sponsor submitted reports for a Phase 1 bioavailability study (Study C.001) and

a Phase 1 irritation and sensitization study (Study C.004). These are not reviewed here. An analysis of the primary endpoints for the phase 2 study (Study C.002) is presented in Appendix 6.

Note the overlap in study periods in the clinical studies above. On the basis of the Sponsor's analysis of the results from the Phase 2 study, during the study period for Study C.003, the sample size was increased from 848 to 1016. The protocol specified four primary endpoints: the percent change from baseline in each of 1) non-inflammatory lesion counts, 2) the inflammatory lesion counts, and 3) total lesion counts, plus 4) a dichotomization of a six point Investigator's Static Global Assessment (ISGA).

Subject demographics and disposition are summarized in Appendix 4.

2.2 Data Sources

The Sponsor reports that data monitoring was performed by personnel from [redacted] In addition, Connetics Corporation personnel performed co-monitoring at various study sites during the conduct of the study. There was no data safety monitoring board.

Data for Study C.003 were provided in the FDA electronic data room with 30 SAS transport data sets in the directory:
\\Cdsesub1\n21709\N_000\2003-12-22\crt\datasets\cln.c.003

Data for Study C.002 were provided in the FDA electronic data room with 26 SAS transport data sets in the directory:
\\Cdsesub1\n21709\N_000\2003-12-22\crt\datasets\cln.c.002

Most of the data were stratified by visit number, visit 1 through 5, with visits a nominal three weeks apart. For four subjects in Study C.003 and one subject in Study C.002 the FDA analysis specified visit numbers that were greater than the Sponsor's to reflect the fact that there was a multiple of three weeks between consecutive visits. In the analysis of the remaining, vast majority of subjects, the FDA analysis followed the visit numbers assigned by the Sponsor.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Sponsor indicates that this is a 505 (b) (2) submission. This objective of the current submission was to demonstrate, using acne lesion count measures and an Investigator's Static Global Assessment, the non-inferiority of clindamycin phosphate foam, 1%, versus Clindagel® (clindamycin phosphate gel) Topical Gel and the superiority of clindamycin foam versus vehicle foam. The primary support for these objectives is in a single Phase 3 study:

In both the Phase 3 study, C.003, and the earlier, supporting Phase 2 study, C.002, efficacy assessments were collected at week 0 (baseline), and at Weeks 3, 6, 9, and 12 (end of treatment/ end of study). Study C.002 was only designed to get reasonable estimates of effects for use in power computations for the Phase 3 study, C.003. Since it was not powered to detect treatment differences the lack of statistically significant treatment differences is not surprising. Results for Study C.002 are summarized in Appendix 6.

3.1.1 Patient Populations and centers

Three different populations were defined for the FDA analysis:

1. Intent-to-Treat Population: The ITT population consisted of all patients who were randomized and dispensed study medication, and is the primary analysis population.

2. Completers Population: All patients with data at that visit.

3. Sponsor defined Per-Protocol (PP) Population, i.e., the subset of study compliant completers

The Sponsor's analyses used the ITT and the PP populations.

There were 18 investigative sites (i.e., actual centers). The Sponsor states that they pooled sites by locality and climate so as have at least 10 subjects per vehicle arm and 30 subjects per active arm. This resulted in pooling actual centers to new nominal, pooled centers as described in the following table:

Table 2. Pooled Centers

Actual Center	Nominal Center	Actual Center	Nominal Center	Actual Center	Nominal Center
C08	N01	C05,C12	N05	C11	N09
C09,C14	N02	C04	N06	C17	N10
C10,C18	N03	C01,C15	N07	C03	N11
C06	N04	C13,C16	N08	C02,C07	N12

These pooled, nominal centers were the centers specified by the protocol to be used as factors or stratification variables in the analyses. Although the analyses reported here follow this recoding, results of analyses using the original centers were similar.

3.1.2 Primary Endpoints

The primary efficacy variables included lesion counts (total, inflammatory, and non-inflammatory) and the Investigator's Static Global Assessments (ISGA). The primary endpoints for lesion counts specified by the protocol for analysis were the percent change in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12 (end of treatment). For Study C.003 the ISGA was defined as follows:

Table 3. Investigator's Static Global Assessment

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyper-pigmented, though not pink-red) requiring no further treatment in the Investigator's opinion.
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions
Grade 3	Non-inflamd matory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and there may or may not be one small nodulo-cystic lesions
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

The primary endpoint used to analyze the ISGA was the proportion of subjects who had an ISGA of 0 or 1 at Week 12. In Study C.002 the ISGA was scored on a somewhat different five- point scale. However, in that study, at Week 12, the six-point scale above was also evaluated. (Please see Appendix 6.)

Secondary endpoints specified by the protocol were as follows:
1. The absolute change in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12.
2. The proportion of subjects who had an Subjects Global Assessment (SGA) score of 0 or 1 at Week 12 (end of treatment). (See Appendix A.3 for the definition of the SGA)
3. The change in the Subject's Global Assessment from Baseline to Week 12.

The Medical team indicated that the results from the SGA had no regulatory utility. However since it was specified as a secondary endpoint in the protocol, simple descriptive results using this endpoint are described in Appendix A.3. However no formal testing was done. Results for the absolute change in lesion counts are provided below.

3.1.3 Results for Study C.003

Study C.003 was a Phase 3 study designed to demonstrate dual objectives of 1) the non-inferiority of clindamycin phosphate foam, 1%, versus Clindagel® (clindamycin phosphate gel) Topical Gel, 1% (Clindagel) and 2) the superiority of clindamycin foam versus vehicle foam based on lesion counts and an Investigator's Static Global Assessment. The designated treatment was to be applied once a day for 12 weeks. Eligible subjects were to be 12 years of age or older, with an Investigator's Static Global Assessment grade of 2 or 3 at baseline and no active nodulo-cystic lesions. In addition, they were to have 17-40 facial inflammatory lesions (papules and pustules) and 20-75 facial non-inflammatory lesions (open and closed comedones), where the latter excluded nasal lesions. Note that at the pre-IND meetings and in the Special Protocol review the Division of Dermatological and Dental Drug Products recommended a minimum of 20 of each lesion type as an entry criterion.

Subjects were instructed to apply a sufficient amount of study drug to cover the entire face (including the forehead, nose, cheeks and chin). After Baseline (Visit 1) visit, visits to assess efficacy were conducted at Week 3 (Visit 2), Week 6 (Visit 3), Week 9 (Visit 4) and Week 12 (Visit 5).

The following tables (Tables 4, 5, 6, and 7) provide profiles over time of the primary endpoints. The entries under "p-value" are the statistical significance levels of the tests of superiority of the listed active drug to its vehicle. The other entries denote the mean and standard deviation of the percent reduction from baseline of the specified lesion count measure (computed as -100*(score - baseline score) / baseline score). The "12 PP" and "12 ITT" denote the Week 12 Per Protocol and Intent to Treat (using LOCF imputation) populations, respectively. At the bottom of each table are entries indicating non-inferiority comparisons. Since change from baseline would be zero, the entries under "Baseline" give the actual baseline summary lesion counts for that treatment group.

The 95% two-sided confidence interval about the difference in percent reduction in non-inflammatory lesions, (foam - gel), in the ITT population at Week 12 using LOCF imputation for dropouts, is given by (3.1,13.5). These come from estimated contrasts in an analysis of variance with terms for treatment, center, and interaction. Since the 3.1 lower bound is above -10%, we would accept the hypothesis that clindamycin foam is non-inferior to Clindagel in terms of percent reduction in non-inflammatory lesions. Since the entire interval is above 0, we would also accept the hypothesis that the foam is superior (actually the test of superiority has p≤ 0.0019).

Table 4. Study C003: Percent Reduction in Non-inflammatory Lesion Counts

		Week Baseline	3	6	9	12	12 PP	12 ITT	p-value
Clindamycin Foam	N	386	365	350	347	348	336	386	0.0014[1]
	Mean	45.7	13.7	24.5	33.2	40.8	41.2	38.3	
	Std Dev	25.6	33.3	33.1	33.4	31.3	31.2	31.7	
Clindagel	N	384	357	344	346	346	336	384	0.0185[1]
	Mean	48.0	11.5	19.9	28.2	33.1	32.8	30.2	
	Std Dev	26.9	32.2	34.5	36.6	39.0	39.3	38.8	
Vehicle Foam	N	127	118	116	110	115	110	127	
	Mean	46.9	11.3	19.3	23.8	29.2	29.1	27.1	
	Std Dev	28.8	37.0	33.9	40.6	39.5	39.9	38.4	
Vehicle Gel	N	128	123	113	113	115	108	128	
	Mean	45.8	8.3	13.7	18.4	21.7	20.3	20.8	
	Std Dev	24.7	32.2	33.7	43.9	47.5	48.1	45.8	

Week 12 LOCF, two-sided 95% confidence interval on (foam mean - gel mean) is (3.1,13.5). Corresponding test of superiority has p ≤ 0.0019.

[1] Superiority Test against appropriate vehicle from ANOVA contrast

Note that with this endpoint, in this study both the clindamycin foam and the vehicle foam seem to have trajectories over time dominating the corresponding gel formulations, with the clindagel foam dominating the other three treatment groups. At Week 12, in the ITT population, using LOCF imputation, both clindamycin foam and the Clindagel formulations were statistically significantly better than their corresponding vehicles ($p \leq 0.0014$ and $p \leq 0.0185$, respectively).

For inflammatory and total lesions we compute the following tables (sample sizes are the same. Again, the baseline values are from the actual lesion counts, where other values denote change from baseline.

A 95% two sided confidence about the difference in percent reduction (foam - gel) is given by (-0.6, 9.7). Since the -0.6 lower bound of the interval is above -10%, we would accept the hypothesis that the foam is non-inferior to the gel in terms of percent reduction in inflammatory lesions.

Table 5. Study C003: Percent Reduction in Inflammatory Lesion Counts

		Week: Baseline	3	6	9	12	12 PP	12 ITT	p-value
Clindamycin Foam	Mean	26.0	31.3	43.0	47.4	52.6	53.2	49.2	<0.0001[1]
	Std Dev	6.9	35.4	33.8	34.0	36.0	35.3	36.8	
Clindagel	Mean	26.1	27.9	39.3	42.5	49.0	49.1	45.2	0.0741[1,2]
	Std Dev	7.4	40.9	33.5	42.4	36.6	37.0	37.6	
Vehicle Foam	Mean	25.2	19.5	29.0	38.1	38.1	39.7	35.0	
	Std Dev	6.9	37.0	35.7	40.3	36.6	36.5	37.3	
Vehicle Gel	Mean	26.4	23.4	33.5	36.4	39.8	38.7	37.0	
	Std Dev	7.7	29.5	32.3	32.1	39.1	39.7	40.2	

Week 12 LOCF, two-sided 95% confidence interval on (foam mean - gel mean) is (-0.6,9.7). Test of superiority has $p \leq 0.0846$.

[1] Superiority Test against appropriate vehicle from ANOVA contrast

[2] Note that a more powerful test dropping the interaction term in the model had $p \leq 0.0351$.

Again the clindamycin foam treatment has a trajectory over time that seems to dominate the trajectories of the other treatment groups. However, even the vehicles seem to show considerable efficacy over time. Clindamycin foam was found to statistically significantly better than the corresponding foam vehicle ($p < 0.0001$). Clindagel was better than its vehicle, but the difference was only close to statistical significance ($p \leq 0.0741$). Note that in the model with no interaction, Clindagel was statistically significantly better than its vehicle ($p \leq 0.0351$), however the effect of the pre-test on the true significance level is not clear.

Results for percent change in total lesion count are similar to the results for non-inflammatory lesion counts. A 95% two sided confidence interval about the difference in percent reduction in total lesions (foam - gel) is given by (3.3, 11.7). Since the lower bound of the

interval is above 0, we would conclude that not only is the foam non-inferior to the gel in terms of percent reduction in total lesions, it is superior ($p \leq 0.0005$).

Table 6. Study C003: Percent Reduction in Total Counts

		Week: Baseline	3	6	9	12	12 PP	12 ITT	p-value
Clindamycin Foam	Mean	71.7	20.6	31.7	38.9	45.7	46.1	42.8	<0.0001[1]
	Std Dev	28.0	26.8	26.1	26.8	26.4	26.2	27.5	
Clindagel	Mean	74.1	17.8	27.4	33.7	39.0	38.8	35.7	0.0199[1]
	Std Dev	29.0	27.6	26.1	30.2	31.1	31.5	31.6	
Vehicle Foam	Mean	72.1	15.3	23.8	30.2	33.1	33.7	30.6	
	Std Dev	31.0	29.8	27.6	28.4	29.7	30.0	29.6	
Vehicle Gel	Mean	72.2	14.3	21.4	25.7	29.4	28.2	27.7	
	Std Dev	27.6	21.9	24.7	29.1	35.2	35.4	34.3	

Week 12 LOCF, two-sided 95% confidence interval on (foam mean - gel mean) is (3.3,11.7). Test of superiority has $p \leq 0.0005$.

[1] Superiority Test against appropriate vehicle from ANOVA contrast

Again, for reduction in total lesions, both the clindamycin foam and the vehicle foam seem to have trajectories over time dominating the corresponding gel formulations, with the clindagel foam dominating the other three treatment groups. At Week 12, in the ITT population, using LOCF imputation, both clindamycin foam and the Clindagel formulations were statistically significantly better than their corresponding vehicles ($p<0.0001$ and $p \leq 0.0199$, respectively).

As discussed in the section on Statistical issues and Appendix A.5, the "usual" approach to testing non-inferiority in "success" proportions seems to be based on a simple difference in binomial proportions, ignoring stratification. Using a normal approximation we compute that a 95% two-sided confidence about the difference in percentages in active success rates (foam - gel) is given by (-2.6,10.2). However, following Koch, et al (1995), this reviewer preferred an analysis that explicitly adjusts for the stratification. Using the pooled hypergeometric variance estimate of that adjusted estimator we compute that a 95% two-sided confidence about the difference in success rates (foam - gel) is given by (-2.3, 9.9). Using the pooled product binomial variance estimate resulted in the interval (-2.3,9.8) reported below. In all three cases, the lower confidence limits were all above the -10% non-inferiority limit, and in each case we would accept the hypothesis that Clindamycin Foam is non-inferior to Clindagel.

Table 7. Study C003 Success Rates in Investigator's Static Global Assessment

Treatment		Week 3	6	9	12	12 PP	12 ITT	p-value[1]
Clindamycin Foam	n	32/	59/	74/	118/	117/	120/	0.0025[1]
	N	365	350	347	348	336	386	
	%	8.8	16.9	21.3	33.9	34.8	31.1	
Clindagel	n	24/	50/	71/	104/	99/	105/	0.1118[1]
	N	357	345	347	347	336	385	
	%	6.7	14.5	20.5	30.0	29.5	27.3	
Vehicle Foam	n	1/	8/	16/	23/	23/	23/	
	N	118	116	110	115	110	127	
	%	0.8	6.9	14.5	20.0	20.9	18.1	
Vehicle Gel	n	3/	7/	15/	25/	23/	26/	
	N	122	113	113	115	108	128	
	%	2.5	6.2	13.2	21.9	21.3	20.3	

Week 12 ITT-LOCF population, two-sided 95% confidence interval on (foam mean - gel mean) is (-2.3, 9.8). Test of superiority has $p \leq 0.2253$.

[1]–Superiority Test against appropriate vehicle from CMH test

Once again, in terms of success rate in the ISGA, the clindamycin foam treatment has a trajectory over time that seems to dominate the trajectories of the other three treatment groups. At Week 12 in the ITT population clindamycin foam was found to statistically significantly better than the corresponding foam vehicle ($p \leq 0.0025$). Although Clindagel was better than its vehicle, the difference was not statistically significant ($p \leq 0.1118$).

An alternative analysis would be to define "success" as those subjects who had achieved at least a two step reduction in the ISGA AND achieved a final score of clear or minimal ("0" or "1"). Results from this analysis are given in Appendix 1.

The only secondary endpoints specified by the Sponsor that were considered to be of regulatory utility by the Medical team were the changes from baseline in the three lesion counts. The following table displays mean absolute change from baseline in these lesion counts. The Visit 1, Baseline, measures are the actual baseline mean scores for each lesion count. Values after baseline correspond to the mean change from baseline in that particular measure. The per protocol group is denoted "PP", the intent-to-treat group (using LOCF) is denoted "ITT". Other groups are completers.

The protocol specified that the secondary endpoints should be analyzed using ANOVA followed by a Fisher protected LSD on mean differences. However, there are two problems with such a procedure: 1) Note that the effect on type I error of the Sponsor's pretest for interaction followed by possible model modification is not clear, but the result is certainly not the nominal p-value. 2) Since we can expect overall treatment differences from vehicle, the Fisher protected LSD provides very little family-wise type I error protection. A conceptually similar method of analysis that does control type I error within each endpoint is to perform a Tukey-Kramer test of

difference on least squares means from the original analysis. However, that would involve six comparisons. Only the comparisons between clindamycin foam and its vehicle, clindagel and its vehicle, and clindamycin foam and clindagel and its vehicle are of interest. Thus, for significance levels of interest we would expect a Bonferroni correction for three comparisons to have more power than a Tukey-Kramer adjustment. So, for the comparisons within each response variable, the Bonferroni adjustment is used below.

Table 8. Study C003 Profiles of Changes in Absolute Lesion Counts

			Week					
		Baseline	3	6	9	12	12 PP	12 ITT	p-value
Change in Non-inflammatory Lesion Count									
Clindamycin Foam	Mean	45.7	-5.9	-10.7	-14.7	-18.0	-18.1	-17.0	0.0186[1]
	Std dev	25.6	14.8	17.1	18.4	17.1	17.2	17.1	
Clindagel	Mean	48.0	-5.4	-9.1	-13.6	-15.6	-15.5	-14.3	0.1512[1]
	Std dev	26.9	15.5	17.0	18.6	20.7	20.9	20.2	
Vehicle Foam	Mean	46.9	-6.6	-9.9	-12.1	-13.0	-13.1	-12.1	
	Std dev	28.8	16.5	16.0	18.8	17.7	18.0	17.3	
Vehicle Gel	Mean	45.8	-4.5	-7.5	-9.4	-11.1	-9.7	-10.4	
	Std dev	24.7	12.3	17.2	19.9	21.5	20.2	20.8	
Test superiority of clindamycin foam over clindagel									0.0954
Change in Inflammatory Lesion Count									
Clindamycin Foam	Mean	26.0	-7.9	-10.7	-11.9	-13.2	-13.3	-12.3	<0.0003[1]
	Std dev	6.9	9.0	9.0	9.7	10.1	9.8	10.2	
Clindagel	Mean	26.1	-7.3	-10.0	-11.0	-12.5	-12.5	-11.6	0.4452[1]
	Std dev	7.4	9.6	9.1	10.6	9.9	9.9	10.1	
Vehicle Foam	Mean	25.2	-4.9	-7.3	-9.3	-9.3	-9.7	-8.5	
	Std dev	6.9	8.8	8.5	10.1	9.0	8.9	9.3	
Vehicle Gel	Mean	26.4	-5.9	-8.8	-9.4	-10.4	-10.0	-9.8	
	Std dev	7.7	7.8	9.5	9.0	10.9	10.9	10.9	
Test superiority of clindamycin foam over clindagel									0.6309
Change in Total Lesion Count									
Clindamycin Foam	Mean	71.7	-13.8	-21.4	-26.6	-31.2	-31.4	-29.2	<0.0003[1]
	Std dev	28.0	18.3	20.4	21.9	21.2	21.2	21.6	
Clindagel	Mean	74.1	-12.6	-19.0	-24.6	-28.2	-28.0	-25.9	0.0843[1]
	Std dev	29.0	19.3	19.9	22.3	24.7	24.9	24.7	
Vehicle Foam	Mean	72.1	-11.5	-17.1	-21.3	-22.3	-22.8	-20.7	
	Std dev	31.0	20.6	19.9	20.7	21.9	22.2	21.6	
Vehicle Gel	Mean	72.2	-10.3	-16.3	-18.8	-21.5	-19.7	-20.2	
	Std dev	27.6	14.4	20.9	24.4	27.9	26.4	27.1	
Test superiority of clindamycin foam over clindagel									0.0687

[1] Test against corresponding vehicle (adjusted for multiplicity within each variable).

For all three changes in lesion counts, the clindamycin foam has a trajectory that seems to dominate the Clindagel formulation. Clindagel, in turn, tends to dominate the vehicles. Even adjusting for the multiple comparisons for each endpoint, for all three endpoints the difference between the clindamycin foam and its vehicle were statistically significant (all $p \leq 0.0186$). Other relevant pairwise comparisons were not statistically significant.

3.1.4 Sponsor's Results for Study C.003

The following tables summarize the Sponsor's results and the corresponding FDA analyses. For the percent change from baseline measures both the mean and the standard

deviation (sd) are presented. For the Investigator Static Global Assessment the number of successes and the corresponding percentages are also presented. The p-values for the test of superiority correspond to testing clindamycin foam versus vehicle foam. The confidence limits for the assessment of non-inferiority of clindamycin foam to Clindagel are provided in the column labeled "Equivalence bounds". We would accept non-inferiority provided the lower bound of the interval is above -10.

Table 9 gives a summary of the Sponsor's results. Table 10 provides the corresponding values in the FDA analysis.

Table 9. Study C003 Summary of Sponsor's Results

	Clindamy-cin Foam	Clinda-gel	Vehicle Foam	Vehicle Gel	p-value superiority	Equivalence bounds
N	386	384	127	128		
% Change in Non-inflam-matory Lesions Mean/(sd)	38.3 (31.7)	30.2 (38.8)	27.1 (38.4)	20.8 (45.8)	0.0018	3.2, 13.0
% Change in Inflammatory Lesions Mean/(sd)	49.0 (37.1)	45.0 (37.6)	34.7 (37.5)	36.6 (40.5)	0.0001	-1.0, 9.2
% Change in Total Lesions Mean/(sd)	42.8 (27.5)	35.7 (31.6)	30.5 (29.6)	27.6 (34.4)	< 0.0001	3.0, 11.2
N success / % success in ISGA	120 (31%)	105 (27%)	23 (18%)	26 (20%)	0.0025	-2.6, 10.2

Table 10. Study C003 Summary of FDA Results

	Clindamy-cin Foam	Clinda-gel	Vehicle Foam	Vehicle Gel	p-value superiority	Equivalence bounds
N	386	384	127	128		
% Change in Non-inflam-matory Lesions Mean/(sd)	38.3 (31.7)	30.2 (38.8)	27.1 (38.4)	20.8 (45.8)	0.0014	3.1, 13.5
% Change in Inflammatory Lesions Mean/(sd)	49.2 (36.8)	45.2 (37.6)	35.0 (37.3)	37.0 (40.2)	< 0.0001	-0.6, 9.7
% Change in Total Lesions Mean/(sd)	42.8 (27.5)	35.7 (31.6)	30.6 (29.6)	27.7 (34.3)	< 0.0001	3.3, 11.7
N success / % success in ISGA	120 (31%)	105 (27%)	23 (18%)	26 (20%)	0.0025	-2.3, 9.8

Observed means and proportions in the 12 week ITT population for the percent change in non-inflammatory lesions and the success rate in the IGSA agree exactly. Means and standard deviations for the percent change from baseline in inflammatory and total lesion counts are close. The differences in significance levels and in equivalence bounds are due to slightly different models as discussed in sections on statistical issues and in Appendix A.5. In both the Sponsor's analyses and the FDA analyses each endpoint was statistically significantly better than its vehicle (all $p \leq 0.0025$ in both analyses). Since the lower bound of the equivalence region was, in each case above 10%, for each endpoint we would accept the hypothesis of non-inferiority of clindamycin foam to Clindagel.

3.2 Evaluation of Safety

A review of adverse events in this submission is provided in the Medical Officer's review. Note that the incidence of adverse events was lower in the clindamycin foam group than in the vehicle group. However no formal statistical analysis was done.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following tables provide summaries of the primary endpoints by demographic subgroup. In each case N denotes the number of subjects in that subgroup by treatment combination. Of course, total lesion counts are the sum of non-inflammatory and inflammatory lesion counts, and, for the sake of brevity, are not tabulated here. For simplicity baseline counts are not included. For readability only standard deviation of the Week 12 ITT group is included.

Tables 11.1-11.3, below, provide breakdowns by gender of the percent reduction in non-inflammatory and inflammatory lesions, plus the success rate on the Investigator's Static Global Assessment.

Table 11.1 Breakdown of Percent Reduction in Non-Inflammatory Lesions by Gender

% Reduction in Non-Inflammatory Lesions		Week					
		3	6	9	12	12 PP	12 ITT
Male Clindamycin Foam	N	170	167	165	167	163	180
	Mean	13.5	21.8	27.2	36.6	36.9	34.9
	Std dev						30.9
Clindagel	N	166	162	164	165	161	175
	Mean	8.8	17.6	24.1	31.5	31.1	29.7
	Std dev						42.5
Vehicle Foam	N	55	53	51	53	50	59
	Mean	14.1	20.8	17.2	26.9	26.1	25.3
	Std dev						47.6
Vehicle Gel	N	59	57	59	58	55	62
	Mean	4.3	10.5	14.9	14.5	12.6	13.7
	Std dev						47.3
Female Clindamycin Foam	N	195	183	182	181	173	206
	Mean	13.8	27.0	38.6	44.7	45.2	41.3
	Std dev						32.2
Clindagel	N	191	182	182	181	175	209
	Mean	13.8	22.1	31.9	34.6	34.4	30.5
	Std dev						35.4
Vehicle Foam	N	63	63	59	62	60	68
	Mean	9.0	17.9	29.5	31.2	31.6	28.7
	Std dev						28.4
Vehicle Gel	N	64	56	54	57	53	66
	Mean	12.1	17.0	22.4	29.0	28.2	27.4
	Std dev						43.6

Studying the trajectories over time above in per cent reduction from baseline in non-inflammatory lesions and comparing across genders there seems to be evidence of greater

effectiveness among females than among males in each of the clindamycin foam, Clindagel, and vehicle gel treatment groups. Further, for both genders clindamycin foam seems to be associated with a greater percent decrease in non-inflammatory lesions than its active comparator, Clindagel. Also, the superiority of clindamycin foam over its vehicle seems to be generally higher in females than among males. However, the study was not planned or powered for these comparisons and thus results based on these comparisons should not be considered conclusive.

Table 11.2 Breakdown of Percent Reduction in Inflammatory Lesions by Gender

			Week					
% Reduction in Inflammatory Lesions			3	6	9	12	12 PP	12 ITT
Male	Clindamycin Foam	N	170	167	165	167	163	180
		Mean	31.8	36.5	42.7	47.1	47.2	45.0
		Std dev						37.6
	Clindagel	N	166	162	164	165	161	175
		Mean	28.1	38.0	41.4	44.5	44.7	42.2
		Std dev						40.1
	Vehicle Foam	N	55	53	51	53	50	59
		Mean	13.8	23.4	34.2	29.1	31.5	26.6
		Std dev						35.3
	Vehicle Gel	N	59	57	59	58	55	62
		Mean	19.6	31.2	31.4	32.0	30.4	29.9
		Std dev						41.6
Female	Clindamycin Foam	N	194	182	181	180	173	205
		Mean	30.8	48.9	51.7	57.8	58.9	53.0
		Std dev						35.8
	Clindagel	N	191	182	182	181	175	209
		Mean	27.7	40.4	43.5	53.1	53.1	47.7
		Std dev						35.3
	Vehicle Foam	N	63	63	59	62	60	68
		Mean	24.5	33.8	41.4	45.8	46.5	42.3
		Std dev						37.8
	Vehicle Gel	N	64	56	54	57	53	66
		Mean	26.9	35.8	41.9	47.7	47.4	43.7
		Std dev						38.0

Again, with percent reduction in inflammatory lesions there seems to a trend toward greater effectiveness among females than among males in each of the four treatment groups. Further, there seems to be a trend for Clindamycin foam to be associated with a greater percent decrease in inflammatory lesions than Clindagel, particularly among females.

The breakdown by gender of the success rate on the ISGA is given in table 11.3 below.

Table 11.3 Breakdown of Success Rate by Gender

Success			Week 3	6	9	12	12 PP	12 ITT
Male	Clindamycin Foam	N	170	167	165	167	163	180
		%	8.8	12.6	14.5	25.1	25.8	23.3
	Clindagel	N	165	162	164	165	161	175
		%	7.9	11.7	17.1	26.7	26.7	25.1
	Vehicle Foam	N	55	53	51	53	50	59
		%	.	3.8	11.8	15.1	16.0	13.6
	Vehicle Gel	N	59	57	59	58	55	62
		%	.	1.8	6.8	20.7	20.0	19.4
Female	Clindamycin	N	195	183	182	181	173	206
		%	8.7	20.8	27.5	42.0	43.4	37.9
	Clindagel	N	192	183	183	182	175	210
		%	5.7	16.9	23.5	33.0	32.0	29.0
	Vehicle Foam	N	63	63	59	62	60	68
		%	1.6	9.5	16.9	24.2	25.0	22.1
	Vehicle Gel	N	63	56	54	57	53	66
		%	4.8	10.7	20.4	22.8	22.6	21.2

As with the percent reductions in lesion counts, by Week 6 there seems to be a trend for the success rate among females to be higher than the corresponding rate among males in each of the four treatment groups. Further, the success rate for clindamycin foam seems be generally equivalent to the success rate for Clindagel in males, but in females seems much higher than the corresponding rate with Clindagel.

Tables 12.1-12.3, below, provide breakdowns by race (Caucasian versus Other).

Table 12.1 Breakdown of Percent Reduction in Non-inflammatory Lesions by Race

	Week:		Week 3	6	9	12	12 PP	12 ITT
Caucasian	Clindamycin Foam	N	236	229	229	231	225	252
		Mean	15.9	26.7	35.6	42.0	42.5	39.7
		Std dev						32.8
	Clindagel	N	225	219	220	220	216	241
		Mean	16.4	25.0	32.1	35.6	35.1	33.3
		Std dev						38.3
	Vehicle Foam	N	79	75	74	75	71	84
		Mean	12.5	19.8	27.3	25.9	26.1	24.3
		Std dev						42.6
	Vehicle Gel	N	76	69	69	71	66	79
		Mean	11.9	14.4	20.5	22.6	22.0	21.8
		Std dev						45.1
Other	Clindamycin Foam	N	129	121	118	117	111	134
		Mean	9.6	20.5	28.4	38.4	38.6	35.7
		Std dev						29.5
	Clindagel	N	132	125	126	126	120	143
		Mean	3.1	11.1	21.4	28.9	28.6	25.0
		Std dev						39.1
	Vehicle Foam	N	39	41	36	40	39	43
		Mean	9.0	18.4	16.6	35.4	34.6	32.5
		Std dev						28.1
	Vehicle Gel	N	47	44	44	44	42	49
		Mean	2.5	12.7	15.3	20.1	17.5	19.1
		Std dev						47.3

For non-inflammatory lesions, there is some evidence of greater effectiveness among Caucasian subjects than among non-Caucasians (i.e., "Other") in each of the clindamycin foam, Clindagel, and vehicle gel treatment groups (but not necessarily with the vehicle foam treatment group). There is an apparent trend for vehicle foam to be better than vehicle gel in both race groups. Further, among the non-Caucasians at the end of the study the vehicle foam seems to actually have a larger decrease than the decrease associated with the Clindagel group.

Table 12.2, below, provides a breakdown of inflammatory lesions by race (Caucasian versus Other).

Table 12.2 Breakdown of Percent Reduction in Inflammatory Lesions by Race

		Week:	3	6	9	12	12 PP	12 ITT
Caucasian	Clindamycin Foam	N	235	228	228	230	225	251
		Mean	32.7	42.0	46.0	51.6	51.5	48.9
		Std dev						35.8
	Clindagel	N	225	219	220	220	216	241
		Mean	27.3	38.0	40.6	47.0	47.1	43.3
		Std dev						38.4
	Vehicle Foam	N	79	75	74	75	71	84
		Mean	16.7	29.2	38.2	35.5	37.2	32.5
		Std dev						38.2
	Vehicle Grl	N	76	69	69	71	66	79
		Mean	23.4	31.3	31.3	33.2	32.2	31.8
		Std dev						41.5
Other	Clindamycin Foam	N	129	121	118	117	111	134
		Mean	28.7	44.7	50.1	54.6	56.7	49.9
		Std dev						38.8
	Clindagel	N	132	125	126	126	120	143
		Mean	29.0	41.5	45.8	52.5	52.6	48.4
		Std dev						36.2
	Vehicle Foam	N	39	41	36	40	39	43
		Mean	25.1	28.6	37.9	43.0	44.4	40.0
		Std dev						35.5
	Vehicle Gel	N	47	44	44	44	42	49
		Mean	23.4	36.9	44.4	50.4	49.0	45.5
		Std dev						37.0

A partial reverse of the case with non-inflammatory lesions, for inflammatory lesions there is some evidence of greater effectiveness in terms of percent reduction from baseline among the non-Caucasian group than among the Caucasians in each of the clindamycin foam and clindagel treatment groups.

A breakdown by race of the success rate on the ISGA is given in table 12.3 below.

Table 12.3 Breakdown of Success Rate by Race

			Week: 3	6	9	12	12 PP	12 ITT
Caucasian	Clindamycin Foam	N	236	229	229	231	225	252
		%	10.2	17.5	19.2	32.0	32.4	29.8
	Clindagel	N	225	220	221	221	216	242
		%	8.4	16.8	22.6	32.1	31.9	29.3
	Vehicle Foam	N	79	75	74	75	71	84
		%	1.3	6.7	18.9	20.0	21.1	17.9
	Vehicle Gel	N	75	69	69	71	66	79
		%	2.7	7.2	14.5	16.9	18.2	15.2
Other	Clindamycin Foam	N	129	121	118	117	111	134
		%	6.2	15.7	25.4	37.6	39.6	33.6
	Clindagel	N	132	125	126	126	120	143
		%	3.8	10.4	16.7	26.2	25.0	23.8
	Vehicle Foam	N	39	41	36	40	39	43
		%	.	7.3	5.6	20.0	20.5	18.6
	Vehicle Gel	N	47	44	44	44	42	49
		%	2.1	4.5	11.4	29.5	26.2	28.6

For the ISGA, the success rates associated with Caucasian patients are roughly the same in the clindamycin foam group and in Clindagel group. Among non-Caucasian patients, the clindamycin foam seems to have a higher success rate than the success rate in the Clindagel group. In fact, at week 12, among non-Caucasians the vehicle gel seems to be roughly as effective as the Clindagel treatment.

Table 13.1, below, provides treatment group profiles of non-inflammatory lesions by age group (12-16 versus 17+).

Table 13.1 Breakdown of Percent Reduction in Non-inflammatory Lesions by Age Group

			Week 3	6	9	12	12 PP	12 ITT
Age Group								
% Reduction in Non-Inflammatory Lesions								
12-16	Clindamycin Foam	N	177	175	174	177	173	186
		Mean	9.6	20.4	29.7	36.8	37.2	35.8
		Std dev						32.2
	Clindagel	N	184	178	180	180	176	190
		Mean	11.8	19.0	26.9	31.4	31.1	30.2
		Std dev						41.3
	Vehicle Foam	N	64	62	61	63	62	67
		Mean	6.6	13.6	18.3	19.2	18.4	18.8
		Std dev						45.4
	Vehicle Gel	N	65	60	63	63	61	67
		Mean	5.3	7.5	8.6	11.0	10.6	10.1
		Std dev						54.8
17+	Clindamycin Foam	N	188	175	173	171	163	200
		Mean	17.5	28.6	36.7	45.0	45.4	40.7
		Std dev						31.1
	Clindagel	N	173	166	166	166	160	194
		Mean	11.2	20.9	29.6	35.0	34.7	30.1
		Std dev						36.2
	Vehicle Foam	N	54	54	49	52	48	60
		Mean	17.0	25.7	30.7	41.4	42.9	36.4
		Std dev						26.1
	Vehicle Gel	N	58	53	50	52	47	61
		Mean	11.8	20.8	30.9	34.6	32.7	32.5
		Std dev						29.5

Thus, for non-inflammatory lesions, over the course of the study both clindamycin foam and Clindagel seem to have roughly equal mean percent reductions from baseline in the 12-16 age group. However, in the population of older patients, 17-40+ years, the mean percent decreases from baseline seem to be larger in the clindamycin foam treatment group than in the Clindagel group. By comparison, among the younger patients, vehicle foam seems to have a larger mean decrease than that associated with the vehicle gel.

A breakdown by age group of percent reduction in inflammatory lesions is presented in table 13.2 below.

Table 13.2 Breakdown of Percent Reduction in Inflammatory Lesions by Age Group

			Week					
Age Group			3	6	9	12	12 PP	12 ITT
% Reduction in Inflammatory Lesions								
12-16	Clindamycin Foam	N	176	174	173	176	173	185
		Mean	27.2	34.7	40.0	44.3	44.4	43.0
		Std dev						37.8
	Clindagel	N	184	178	180	180	176	190
		Mean	28.8	38.2	40.7	46.0	46.1	44.4
		Std dev						39.9
	Vehicle Foam	N	64	62	61	63	62	67
		Mean	17.1	23.6	31.8	27.5	28.1	25.6
		Std dev						38.9
	Vehicle Gel	N	65	60	63	63	61	67
		Mean	22.2	29.9	30.0	29.4	29.4	28.9
17+	Clindamycin Foam	N	188	175	173	171	163	200
		Mean	35.1	51.2	54.9	61.2	62.5	54.9
		Std dev						35.0
	Clindagel	N	173	166	166	166	160	194
		Mean	27.0	40.5	44.5	52.3	52.4	46.0
		Std dev						35.3
	Vehicle Foam	N	54	54	49	52	48	60
		Mean	22.4	35.3	45.9	50.9	54.7	45.5
		Std dev						32.8
	Vehicle Gel	N	58	53	50	52	47	61
		Mean	24.8	37.5	44.5	52.3	50.9	45.9
		Std dev						33.9

For inflammatory lesions, the pattern among younger patients is similar to that with the non-inflammatory lesions. That is, over the course of the study both the clindamycin foam and Clindagel treatment groups seem to have roughly equal mean percent reductions from baseline. However, in the population of older patients in the study the mean percent decreases from baseline seem to be larger in the clindamycin foam treatment group than in the Clindagel group.

A breakdown age group of the success rate on the ISGA is given in table 13.3 below.

Table 13.3 Breakdown of Success Rate by Age Group

			Week					
			3	6	9	12	12 PP	12 ITT
12-16	Clindamycin Foam	N	177	175	174	177	173	186
		%	5.6	11.4	13.2	22.0	22.5	21.0
	Clindagel	N	183	178	180	180	176	190
		%	7.7	13.5	17.8	24.4	25.0	23.7
	Vehicle Foam	N	64	62	61	63	62	67
		%	.	3.2	9.8	11.1	11.3	10.4
	Vehicle Gel	N	65	60	63	63	61	67
		%	3.1	6.7	9.5	17.5	18.0	17.9
17+	Clindamycin Foam	N	188	175	173	171	163	200
		%	11.7	22.3	29.5	46.2	47.9	40.5
	Clindagel	N	174	167	167	167	160	195
		%	5.7	15.6	23.4	35.9	34.4	30.8
	Vehicle Foam	N	54	54	49	52	48	60
		%	1.9	11.1	20.4	30.8	33.3	26.7
	Vehicle Gel	N	57	53	50	52	47	61
		%	1.8	5.7	18.0	26.9	25.5	23.0

By Weeks 6-9 there seems to be trend for greater effectiveness among older patients than among the 12-16 year old subjects. Observe that at all weeks, among younger subjects, Clindagel tends to have a slightly higher mean success rates than the corresponding clindamycin foam success rates. However, the situation seems to be reversed among older patients. That is, among older subjects the clindamycin foam tends to have higher success rates than among the corresponding Clindagel patients.

Again, note that these observations are only rough descriptions of apparent patterns. The studies were not designed to investigate these patterns. Hence the observed results can not be considered conclusive, only possibly suggestive.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Sponsor indicated that this submission was intended to demonstrate, using acne lesion count measures and an Investigator's Static Global Assessment, the non-inferiority of clindamycin phosphate foam, 1% (Clindamycin Foam), versus Clindagel® (clindamycin phosphate gel) Topical Gel, and the superiority of Clindamycin Foam versus vehicle foam.

5.1.1 Statistical Issues

There were some issues in the analysis:

1. Note that at the Pre-IND meeting on April 10, 2002, the Sponsor was told that a non-inferiority bound of 11% would be acceptable. This was implicitly confirmed in the Special

Protocol Assessment submitted 7 May 2002. However, current practice is to generally maintain at least a 10% bound. The latter value was used in this report. Note that this does not Reduction any conclusions.

2. Residuals from the linear models for the lesion count measures were clearly not normal. The protocol specified a Shapiro-Wilk test of normality, though it is not clear if this is to be applied to the residuals or the original observations. However, the distributions of the residuals tended to be strongly unimodal, thin tailed, and only moderately skewed to the right. So with these large sample sizes analysis of variance on these measures should be appropriate. While not reviewed here, normit transformed ranks seemed to give much the same test results as the original responses, confirming this observation.

3. The non-inferiority analysis in the percent reduction from baseline in the various lesion count measures use confidence intervals based on contrasts in an analysis of variance with factors for center and treatment. In these ANOVA's center by treatment interaction was never statistically significant. The protocol specified that under such circumstances the interaction term should be dropped from the model. However, there are two problems with such an approach:
1) The confidence intervals are then conditional confidence intervals and the true unconditional confidence level is not clear.
2) When estimating contrasts in the center by treatment layouts, effectively this means that in the full space associated with the factorial design, the basis for the contrast terms are effectively orthogonalized to the subspace spanned by the center by treatment interaction contrasts. This reviewer would prefer the simpler interpretation of the contrasts prior to this orthogonalization to the generally greater power associated with this transformation.
Hence, the contrasts used to define the non-inferiority comparisons in the FDA analysis include, and are balanced over these interactions, not orthogonalized to the interactions. For the non-inferiority comparisons this deviation from the protocol has no effect on conclusions.

4. As discussed in Appendix 5, when computing confidence intervals for the non-inferiority comparisons in binary responses like success on ISGA, there are a number of reasonable choices, including whether or not the analysis is stratified by center and the type of error variance used. For the FDA analysis three different intervals are displayed, but note that they are all close to each other, and all lead to the same conclusions.

5. To assess the sensitivity of results to differences over investigators profile plots of mean lesion counts and success proportions were computed over centers. Because of the bandwidth needed for these plots, they are not displayed here. Overall, results seemed consistent across centers. There were a small number of centers where one of the vehicles was superior to the other treatments, but for a strong majority of centers Clindagel, and especially the clindamycin foam seemed to behave fairly uniformly in lesion count means. Behavior appeared more erratic with the success proportions, but for these the test of homogeneity of odds ration was always accepted. So there is reasonable evidence that results are not driven by the outcomes in one or two centers.

5.1.2 Collective Evidence

In particular, in the Week 12 intent-to-treat (ITT) population, for each of the measures: percent reduction from baseline in non-inflammatory lesion counts, inflammatory lesion counts, and total lesion counts, plus the dichotomization of the six point Investigator's Static Global Assessment (ISGA) there were statistically significant differences between clindamycin foam and its vehicle ($p \leq 0.0014$, $p < 0.0001$, $p < 0.0001$, and $p \leq 0.0025$, respectively). Similarly, in each case clindamycin foam was found to be non-inferior to Clindagel. For the percent decrease in non-inflammatory lesion counts, a 95% confidence interval about the difference between clindamycin foam and Clindagel was computed as (3.1,13.5). Since the lower limit of this interval was greater than the non-inferiority bound of -10%, we would conclude that the hypothesis of non-inferiority was accepted. In fact, since the interval was uniformly greater than 0, we conclude that superiority is accepted (actual test of superiority has $p \leq 0.0019$). For percent reduction in inflammatory lesions, the interval about the difference is (-0.6, 9.7), again uniformly greater than -10%. For percent reduction in total lesions the confidence interval is (3.3, 11.7), once again uniformly greater than the -10% bound. As before, since the interval was greater than 0, we accept the hypothesis of superiority (test of superiority has $p \leq 0.0005$). Success on the ISGA was defined as a score of 0 or 1 on the six-point scale in the ITT population at 12 weeks. Success percentages were 31.1% in the clindamycin foam group versus 27.3% in the Clindagel group. The 95% confidence interval on the treatment difference was (-2.3,9.9), again greater than the -10% bound. Since all these intervals were above -10% bound, we accept the hypothesis of non-inferiority.

5.2 Conclusions and Recommendations

The Sponsor is submitting NDA 21-709 for clindamycin phosphate foam, 1%, for topical application in the treatment of acne vulgaris under the Food, Drug, and Cosmetic Act, Section 505 (b) (2). Clindamycin phosphate foam was developed as a change in dosage form for the reference listed drug, Clindagel® (clindamycin phosphate) Topical Gel, 1%. The results are based on a single four armed, Phase 3 study, with treatment groups: 1) clindamycin foam, 2) Clindagel, 3) vehicle foam, and 4) vehicle gel. The primary endpoints specified in the protocol were the percent change from baseline in each of the non-inflammatory lesion counts, the inflammatory lesion counts, and the total lesion counts, plus a dichotomization of a six point Investigator's Static Global Assessment (ISGA), all computed in the intent-to-treat population. For all lesion count measures and the ISGA, clindamycin foam was shown to be statistically significantly superior to its vehicle and non-inferior to the gel formulation. In fact, for the percent change from baseline in non-inflammatory and total lesions, the foam was shown to be statistically significantly better than the gel formulation. A preliminary Bayesian analysis of the non-inferiority comparisons was consistent with these results (Appendix 7). Although results from the intent to treat population are emphasized, results from the per protocol and simple completer populations are similar.

APPENDICES A.1-A.7

APPENDIX A.1. STUDY C.003: ALTERNATIVE ANALYSIS OF ISGA

The protocol specified that the Investigator's Static Global Assessment (ISGA) be analyzed so that a score of 0 or 1 was counted as a "success". This is the analysis provided in the main body of this report. An alternative analysis would be to define "success" as those subjects who had achieved at least a two step reduction in the ISGA AND achieved a final score of clear or minimal ("0" or "1"). In the following table n denotes the number of successes using this definition and N denotes the number of subjects at this time.

Using the normal approximation for the simple comparison of binomial proportions we compute that a two-sided 95% confidence interval about the difference in percentages in active success rates (foam - gel) is given by (-1.9,8.5). This analysis ignores the stratification on center. As discussed before (and in Appendix 5), using the pooled hypergeometric variance estimate with the Mantel-Haenszel adjusted difference in proportions we get the interval (-1.4,8.6), while using the pooled product binomial variance estimate we get (-1.3, 8.5), as reported above. In any case, the confidence limits are above the -10% non-inferiority "delta", and we would accept the hypothesis that Clindamycin Foam is non-inferior to Clindagel. For further discussion on non-inferiority issues, please see Appendix 5.

Table A.1.1. Study C003 Alternative Success Rates in Investigator's Static Global Assessment

		Week					
		3	6	9	12	12 PP	12 ITT
Clindamycin Foam	n	11	27	37	68	67	69
	N	364	349	347	348	336	386
	%	3.0	7.7	10.7	19.5	19.9	17.9
p-value[1]					0.0049	0.0070	0.0044
Clindagel	n	10	19	36	56	52	56
	N	357	344	347	347	335	385
	%	2.8	5.5	10.4	16.1	15.5	14.3
p-value[1]					0.1024	0.0962	0.1243
Vehicle Foam	n	.	4	8	10	10	10
	N	118	116	110	115	110	127
	%	.	3.4	7.3	8.7	9.1	7.9
Vehicle Gel	n	3	3	8	11	10	12
	N	122	113	113	115	108	128
	%	2.5	2.7	7.1	9.6	9.3	9.4

[1] Test of superiority over corresponding vehicle.

The Week 12 LOCF, two-sided 95% confidence interval on (foam % - gel %) is (-1.3,8.5). The test of superiority has $p \leq 0.1909$.

Success rates using this modified definition are roughly half those using the Sponsor's original definition (i.e., a grade of 0 or 1 at endpoint), slightly higher for the two actives, slightly less for the two vehicles. Still, the overall description of the profiles over time given there apply here as well. That is, in terms of success rate in the ISGA, the active treatments have trajectories over time that seem to dominate the trajectories of their vehicles. At Week 12 in the ITT population clindamycin foam was found to be statistically significantly better than the corresponding foam vehicle ($p \leq 0.0044$). Although Clindagel was better than its vehicle, the difference was not statistically significant ($p \leq 0.1243$).

APPENDIX A.2. STUDY C.003: CHANGE FROM BASELINE IN ISGA

Recall that the Investigator's Static Global Assessment (ISGA) scores fit the following summary table:

Table A.2.1. Summary of Investigator's Static Global Assessment

Score	Definition
0	Normal, clear skin with no evidence of acne vulgaris
1	Skin almost clear: rare non-inflammatory lesions present
2	Some non-inflammatory lesions are present
3	Non-inflammatory lesions predominate
4	Inflammatory lesions are more apparent
5	Highly inflammatory lesions predominate

The following table provides the baseline scores of the ISGA cross tabulated with the scores at later times. For example, in the following table of the 129 Clindamycin Foam patients with an ISGA score at baseline of 2, "Some non-inflammatory lesions are present", at visit 2 (Week 3) 21 subjects improved to a score of 1, 99 had a score of 2, and 9 deteriorated to a score of 3.

Table A.2.2 Change Table for Investigator's Static Global Assessment Score

		Week 3					Week 6					
Score		1	2	3	4	5	0	1	2	3	4	5
Clindamycin Foam												
2	n	21	99	9	.	.	.	32	83	10	.	.
	%	16.3	76.7	7.0	.	.	.	25.6	66.4	8.0	.	.
3	n	10	78	108	2	.	.	25	90	73	2	.
	%	5.1	39.4	54.5	1.0	.	.	13.2	47.4	38.4	1.1	.
4	n	1	8	14	14	1	.	2	11	13	8	1
	%	2.6	21.1	36.8	36.8	2.6	.	5.7	31.4	37.1	22.9	2.9
All	n	32	185	131	16	1	.	59	184	96	10	1
Clindagel												
2	n	14	106	10	2	.	.	31	88	9	.	.
	%	10.6	80.3	7.6	1.5	.	.	24.2	68.8	7.0	.	.
3	n	10	71	110	5	.	1	14	110	61	3	.
	%	5.1	36.2	56.1	2.6	.	0.5	7.4	58.2	32.3	1.6	.
4	n	.	6	14	8	.	.	3	5	12	7	.
	%	.	21.4	50.0	28.6	.	.	11.1	18.5	44.4	25.9	.
All	n	24	183	134	15	.	1	48	203	82	10	.

Table A.2.2 (cont.) Change Table for Investigator's Static Global Assessment Score

		Week 3								6		
		1	2	3	4	5	0	1	2	3	4	5
Vehicle Foam												
2	n	1	37	9	.	.	.	4	37	6	.	.
	%	2.1	78.7	19.1	.	.	.	8.5	78.7	12.8	.	.
3	n	.	26	35	.	.	.	4	27	29	.	.
	%	.	42.6	57.4	.	.	.	6.7	45.0	48.3	.	.
4	n	.	1	4	5	.	.	.	1	4	4	.
	%	.	10.0	40.0	50.0	.	.	.	11.1	44.4	44.4	.
All	n	1	64	48	5	.	.	8	65	39	4	.
Vehicle Gel												
2	n	.	45	10	.	.	.	4	39	10	.	.
	%	.	81.8	18.2	.	.	.	7.5	73.6	18.9	.	.
3	n	3	10	35	5	.	.	3	18	24	2	.
	%	5.7	18.9	66.0	9.4	.	.	6.4	38.3	51.1	4.3	.
4	n	.	1	5	8	.	.	.	2	9	2	.
	%	.	7.1	35.7	57.1	.	.	.	15.4	69.2	15.4	.
All	n	3	56	50	13	.	.	7	59	43	4	.

These tables are designed to display improvement over time, but are only descriptive. For example, note that these tables show that 11 Clindamycin foam patients got worse by Week 3, versus 132 who got better. Clindagel numbers were quite similar. However, interpreting this difference is problematical. First, because all patients had a score of 2 or more at baseline, there are certainly some regression effects and possibly secular trends. These are confounded with any possible treatment effects.

Table A.2.2 (cont.) Change Table for Investigator's Static Global Assessment Score

		Week 9								12		
		0	1	2	3	4	5	0	1	2	3	4	5
Clindamycin Foam													
2	n	2	37	73	11	.	.	3	50	57	9	.	.
	%	1.6	30.1	59.3	8.9	.	.	2.5	42.0	47.9	7.6	.	.
3	n	1	30	101	56	2	.	1	56	85	49	4	.
	%	0.5	15.8	53.2	29.5	1.1	.	0.5	28.7	43.6	25.1	2.1	.
4	n	.	4	12	11	6	1	.	8	13	8	4	1
	%	.	11.8	35.3	32.4	17.6	2.9	.	23.5	38.2	23.5	11.8	2.6
All	n	3	71	186	78	8	1	4	114	155	66	8	1
Clindagel													
2	n	1	35	78	12	1	.	2	48	68	8	1	.
	%	0.8	27.6	61.4	9.4	0.8	.	1.6	37.8	53.5	6.3	0.8	.
3	n	2	31	95	60	5	.	1	45	94	50	2	.
	%	1.0	16.1	49.2	31.1	2.6	.	0.5	23.4	49.0	26.0	1.0	.
4	n	.	2	12	10	2	.	1	6	11	7	2	.
	%	.	7.7	46.2	38.5	7.7	.	3.7	22.2	40.7	25.9	7.4	.
All	n	3	68	185	82	8	.	4	99	173	65	5	.

Table A.2.2 (cont.) Change Table for Investigator's Static Global Assessment Score

	Week	9					12					
Score		0	1	2	3	4	5	0	1	2	3	4	5
Vehicle Foam													
2	n	.	8	28	7	.	.	.	13	29	4	1	.
	%	.	18.6	65.1	16.3	.	.	.	27.7	61.7	8.5	2.1	.
3	n	1	7	26	21	2	.	.	10	26	19	3	.
	%	1.8	12.3	45.6	36.8	3.5	.	.	17.2	44.8	32.8	5.2	.
4	n	.	.	1	4	5	.	.	.	2	4	4	.
	%	.	.	10.0	40.0	50.0	.	.	.	20.0	40.0	40.0	.
All	n	1	15	55	32	7	.	.	23	57	27	8	.
Vehicle Gel													
2	n	.	7	37	8	.	.	.	14	32	8	.	.
	%	.	13.5	71.2	15.4	.	.	.	25.9	59.3	14.8	.	.
3	n	.	7	18	22	1	.	.	9	21	17	1	.
	%	.	14.6	37.5	45.8	2.1	.	.	18.8	43.8	35.4	2.1	.
4	n	.	1	1	8	3	.	1	1	4	3	4	.
	%	.	7.7	7.7	61.5	23.1	.	7.7	7.7	30.8	23.1	30.8	.
All	n	.	15	56	38	4	.	1	24	57	28	5	.

Note there seems to be a general trend to improve over time, though this trend is stronger in Clindamycin foam and Clindagel groups.

Table A.2.2 (cont.) Change Table for Investigator's Static Global Assessment Score

	Week	12 LOCF					
Score		0	1	2	3	4	5
Clindamycin Foam							
2	n	3	51	74	9	.	.
	%	2.2	37.2	54.0	6.6	.	.
3	n	1	57	86	62	4	.
	%	0.5	27.1	41.0	29.5	1.9	.
4	n	.	8	13	10	7	1
	%	.	20.5	33.3	25.6	17.9	2.6
All	n	4	116	173	81	11	1
Clindagel							
2	n	2	49	80	9	1	.
	%	1.4	34.8	56.7	6.4	0.7	.
3	n	1	45	99	67	3	.
	%	0.5	20.9	46.0	31.2	1.4	.
4	n	1	6	11	8	2	.
	%	3.6	21.4	39.3	28.6	7.1	.
All	n	4	100	190	84	6	.
Vehicle Foam							
2	n	.	13	33	4	1	.
	%	.	25.5	64.7	7.8	2.0	.
3	n	.	10	27	25	3	.
	%	.	15.4	41.5	38.5	4.6	.
4	n	.	.	2	4	5	.
	%	.	.	18.2	36.4	45.5	.
All	n	.	23	62	33	9	.
Vehicle Gel							
2	n	.	14	33	9	.	.
	%	.	25.0	58.9	16.1	.	.
3	n	.	10	22	24	2	.
	%	.	17.2	37.9	41.4	3.4	.
4	n	1	1	5	3	4	.
	%	7.1	7.1	35.7	21.4	28.6	.
All	n	1	25	60	36	6	.

Thus, in the ITT population, in the Clindamycin Foam treatment group, 54% of the patients with a score of 2 at baseline remained with a score of 2 at the end of the study, versus 7% that showed deterioration, and 39% that had improvement. In the corresponding Clindagel treatment group, 57% of the patients with a score of 2 at baseline remained with a score of 2 at the end of the study, versus 6% that showed deterioration, and 36% that had improvement. In the Clindamycin Foam group, 29% of the patients with a score of 3 at baseline remained with a score of 3 at the end of the study, versus 2% that showed deterioration, and 69% that had improvement. In the corresponding Clindagel treatment group, 31% of the patients with a score of 3 at baseline remained with a score of 3 at the end of the study, versus 67% that had improvement.

Overall, among those ITT patients with a score of 4 at baseline, 20% of the Clindamycin Foam group, 21% of the Clindagel group, 0 % of the vehicle foam group, and 14% of the vehicle gel group achieved a score of 0 or 1 by the end of treatment.

APPENDIX A.3. C.003: ANALYSIS OF SECONDARY/TERTIARY ENDPOINTS

The Protocol specified secondary endpoints were:

1. The absolute change in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12.
2. The proportion of subjects who had a Subject's Global Assessment score of 0 or 1 at Week 12 (end of treatment).
3. The change in the Subject's Global Assessment from Baseline to Week 12.

Results for the absolute change in lesion counts are given in Table 8 of the report. Results for the Subject's Global Assessment are given below. The immediately following table defines the Subject's Global Assessment Scale:

Table A.3.1 Subject's Global Assessment

Score	Definition
0	My face is basically free of acne, with only an occasional blackhead and/or whitehead
1	My face has several blackheads and/or whiteheads and small pimples, but there are no tender deep-seated bumps or cysts
2	My face has several to many blackheads and/or whiteheads and small to medium-sized pimples, and may have one deep-seated bump or cyst
3	My face has many blackheads and/or whiteheads, many medium to large-sized pimples, and perhaps a few deep-seated bumps or cysts
4	My face has blackheads and/or whiteheads, and several to many medium to large-sized pimples and deep-seated bumps or cysts dominate

The protocol specifies that a score of 0 or 1 defines a "success" on the Subject's Global Assessment. Note, however, that at the guidance meetings the Medical team expressed the opinion that the SGA would be of no regulatory utility, but since it was specified as a secondary

endpoint, it is summarized in this appendix, however, only descriptive results are provided. No statistical tests were performed.

Table A.3.2 Profiles Over Time of Sponsor's "Success" in Subject's Global Assessment

		Week						
Success		Baseline	3	6	9	12	12 PP	12 ITT
Clindamycin Foam	n	65	162	190	230	250	243	267
	N	384	364	349	347	348	336	386
	%	16.9	44.5	54.4	66.3	71.8	72.3	69.2
Clindagel	n	62	148	174	196	225	217	237
	N	383	358	344	347	346	335	385
	%	16.2	41.3	50.6	56.5	65.0	64.8	61.6
Vehicle Foam	n	23	41	51	62	72	72	73
	N	127	118	116	110	115	110	127
	%	18.1	34.7	44.0	56.4	62.6	65.5	57.5
Vehicle Gel	n	17	35	59	55	72	68	74
	N	127	123	113	112	115	108	128
	%	13.4	28.5	52.2	49.1	62.6	63.0	57.8

Note that by Week 3, the success rate for Clindamycin Foam seems to dominate the success rates associated with the other treatment groups. Other than the apparent fact that success rates seem quite high with this endpoint, there seems to be no other particular pattern in the response trajectories among the other three treatment groups.

However, as can be seen from Table A.3.4 below, using the dichotomization of the Subject's Global Assessment displayed above, at baseline 13%-18% of the subjects already had a score of 0 or 1, i.e., a "Success". A much more stringent dichotomization would be to require at least a two unit reduction, as well as a score of 0 or 1 at baseline. This defines a much smaller subset of the cases above.

Table A.3.3 Profiles Over Time of Alternative "Success" Variable

		Week					
Success	Baseline	3	6	9	12	12 PP	12 ITT
Clindamycin Foam	n	.	27	43	63	88	87	91
	%	.	7.4	12.3	18.2	25.3	25.9	23.6
Clindagel	n	.	27	42	58	75	71	77
	%	.	7.5	12.2	16.7	21.7	21.2	20.0
Vehicle Foam	n	.	8	16	21	28	28	29
	%	.	6.8	13.8	19.1	24.3	25.5	22.8
Vehicle Gel	n	.	3	8	13	20	19	20
	%	.	2.4	7.1	11.6	17.4	17.6	15.6

One problem with this definition is that subjects who are treatment successes at baseline can never be considered as successes later. Thus, a reasonable case can be made that they should be be dropped from this particular table. However to maintain comparability of population with the preceding table, they have been retained. In terms of the actual profiles over time, results appear to be consistent with those in the previous definition of "success".

The following table displays the profiles over time of the actual values of Subject's Global Assessment defined in Table A.3.2 above.

Table A.3.4 Profiles over time in the Subject's Global Assessment

		Week						
		Baseline	3	6	9	12	12 PP	12 ITT
Clindamycin Foam								
0	n	3	20	25	37	63	62	66
	%	0.8	5.5	7.2	10.7	18.1	18.5	17.1
1	n	62	142	165	193	187	181	201
	%	16.1	39.0	47.3	55.6	53.7	53.9	52.1
2	n	211	163	134	104	83	80	96
	%	54.9	44.8	38.4	30.0	23.9	23.8	24.9
3	n	98	33	20	11	14	13	19
	%	25.5	9.1	5.7	3.2	4.0	3.9	4.9
4	n	10	6	5	2	1	.	4
	%	2.6	1.6	1.4	0.6	0.3	.	1.0
All	n	384	364	349	347	348	336	386
Clindagel								
0	n	1	14	18	32	54	54	55
	%	0.3	3.9	5.2	9.2	15.6	16.1	14.3
1	n	61	134	156	164	171	163	182
	%	15.9	37.4	45.3	47.3	49.4	48.7	47.3
2	n	212	172	132	125	93	91	110
	%	55.4	48.0	38.4	36.0	26.9	27.2	28.6
3	n	89	36	33	21	25	24	32
	%	23.2	10.1	9.6	6.1	7.2	7.2	8.3
4	n	20	2	5	5	3	3	6
	%	5.2	0.6	1.5	1.4	0.9	0.9	1.6
All	n	383	358	344	347	346	335	385
Vehicle Foam								
0	n	1	4	5	8	17	17	17
	%	0.8	3.4	4.3	7.3	14.8	15.5	13.4
1	n	22	37	46	54	55	55	56
	%	17.3	31.4	39.7	49.1	47.8	50.0	44.1
2	n	61	56	52	39	34	33	40
	%	48.0	47.5	44.8	35.5	29.6	30.0	31.5
3	n	40	19	10	8	9	5	13
	%	31.5	16.1	8.6	7.3	7.8	4.5	10.2
4	n	3	2	3	1	.	.	1
	%	2.4	1.7	2.6	0.9	.	.	0.8
All	n	127	118	116	110	115	110	127
Vehicle Gel								
0	n	2	4	3	7	14	13	14
	%	1.6	3.3	2.7	6.3	12.2	12.0	10.9
1	n	15	31	56	48	58	55	60
	%	11.8	25.2	49.6	42.9	50.4	50.9	46.9
2	n	73	61	40	45	32	31	37
	%	57.5	49.6	35.4	40.2	27.8	28.7	28.9
3	n	34	22	13	10	8	6	12
	%	26.8	17.9	11.5	8.9	7.0	5.6	9.4
4	n	3	5	1	2	3	3	5
	%	2.4	4.1	0.9	1.8	2.6	2.8	3.9
All	n	127	123	113	112	115	108	128

In all four treatment groups the majority of subjects achieved "success" using the Sponsor's dichotomization. As can also be seen in this more detailed display than in Table A.3.3, by Week 3, the success rate for Clindamycin Foam seems to dominate the success rates associated with the other treatment groups. Otherwise, there seems to be no other particular pattern in the response trajectories among the other three treatment groups.

The profiles of the last secondary endpoint specified by the Sponsor are given in the table A.3.5 below:

Table A.3.5 Profiles over Time in Change from Baseline in Subject's Global Assessment

Week		3	6	9	12	12 PP	12 ITT
Clindamycin Foam							
-4	n	1	1	.	3	3	3
	%	0.3	0.3	.	0.9	0.9	0.8
-3	n	4	5	7	12	12	13
	%	1.1	1.4	2.0	3.5	3.6	3.4
-2	n	25	39	60	75	74	77
	%	6.9	11.2	17.4	21.7	22.2	20.1
-1	n	148	152	167	159	153	173
	%	40.9	43.8	48.4	46.0	45.8	45.1
0	n	157	125	94	79	76	96
	%	43.4	36.0	27.2	22.8	22.8	25.0
1	n	22	24	15	16	15	20
	%	6.1	6.9	4.3	4.6	4.5	5.2
2	n	5	1	2	2	1	2
	%	1.4	0.3	0.6	0.6	0.3	0.5
Clindagel							
-4	n	.	1	2	1	1	2
	%	.	0.3	0.6	0.3	0.3	0.5
-3	n	5	3	13	18	17	18
	%	1.4	0.9	3.8	5.2	5.1	4.7
-2	n	26	44	47	61	58	62
	%	7.3	12.9	13.6	17.7	17.4	16.2
-1	n	143	145	141	148	145	155
	%	40.2	42.4	40.9	43.0	43.4	40.5
0	n	158	115	118	91	88	120
	%	44.4	33.6	34.2	26.5	26.3	31.3
1	n	21	30	20	22	22	23
	%	5.9	8.8	5.8	6.4	6.6	6.0
2	n	3	4	4	3	3	3
	%	0.8	1.2	1.2	0.9	0.9	0.8

Table A.3.5 (cont.) Profiles over Time in Change from Baseline in Subject's Global Assessment

Week		3	6	9	12	12 PP	12 ITT
Vehicle Foam							
-3	n	.	.	4	3	3	3
	%	.	.	3.6	2.6	2.7	2.4
-2	n	8	18	17	25	25	26
	%	6.8	15.5	15.5	21.7	22.7	20.5
-1	n	38	37	42	47	46	48
	%	32.2	31.9	38.2	40.9	41.8	37.8
0	n	59	48	38	32	30	40
	%	50.0	41.4	34.5	27.8	27.3	31.5
1	n	12	10	7	7	5	9
	%	10.2	8.6	6.4	6.1	4.5	7.1
2	n	1	3	2	.	.	.
	%	0.8	2.6	1.8	.	.	.
3	n	.	.	.	1	1	1
	%	.	.	.	0.9	0.9	0.8
Vehicle Gel							
-3	n	.	.	.	2	2	2
	%	.	.	.	1.8	1.9	1.6
-2	n	3	10	15	19	18	19
	%	2.5	8.9	13.5	16.7	16.8	15.0
-1	n	40	56	44	51	49	53
	%	32.8	50.0	39.6	44.7	45.8	41.7
0	n	63	37	44	36	33	45
	%	51.6	33.0	39.6	31.6	30.8	35.4
1	n	14	9	8	6	5	7
	%	11.5	8.0	7.2	5.3	4.7	5.5
2	n	2	.	.	.	.	1
	%	1.6	.	.	.	.	0.8

Tertiary endpoints, were:

1. The proportion of subjects who had an Investigator's Static Global Assessment score of 0 or 1 at Weeks 3, 6, and 9. These are summarized in text Table 7.
2. The percent (%) change in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Weeks 3, 6, and 9. These are summarized in text Tables 4-6.
3. The absolute change in lesion counts (inflammatory, non-inflammatory, and total) from Baseline to Weeks 3, 6, and 9. These are summarized in text Table 8 above.
4. The proportion of subjects who have a Subject's Global Assessment score of 0 or 1 at Weeks 3, 6, and 9. These are summarized in Tables A.3.2 and A.3.3 above in this appendix.
5. The change in the Subject's Global Assessment from Baseline to Weeks 3, 6, and 9. These are summarized in Table A.3.5 above.
6. The change in quality of life as measured by the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from Baseline to Weeks 12. The Medical team expressed the opinion that these were of no regulatory utility and hence they were ignored in this report.

APPENDIX A.4. SUBJECT DEMOGRAPHICS & DISPOSITION

Baseline demographic values for the Phase 3 Study C.003 and the Phase 2 Study C.002 are summarized below:

Table A.4.1 Demographics

	Study C.003				Study C.002		
	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel	Clindamycin Foam	Clindagel	Vehicle Foam
N of Subjects	386	385	127	128	53	50	27
Age Mean (Std)	19.1 (6.4)	18.7 (6.1)	18.8 (6.3)	18.9 (7.3)	17.9 (6.1)	18.2 (7.4)	18.3 (7.9)
Min, Max	12-48	12-47	12-44	12-55	12-37	12-50	12-46
Age Category							
12-16	186 (48 %)	190 (49 %)	67 (53 %)	67 (52 %)	32 (60 %)	27 (54 %)	17 (63 %)
17-65	200 (52 %)	195 (51 %)	60 (47 %)	61 (48 %)	21 (40 %)	23 (46 %)	10 (37 %)
Gender							
Male	180 (47 %)	175 (45 %)	59 (46 %)	62 (48 %)	30 (57 %)	25 (50 %)	18 (67 %)
Female	206 (53 %)	210 (55 %)	68 (54 %)	66 (52 %)	23 (43 %)	25 (50 %)	9 (33 %)
Race Asian	4 (1 %)	5 (1 %)	1 (1 %)	3 (2 %)	-	1 (2 %)	-
Caucasian	252 (65 %)	242 (63 %)	84 (66 %)	79 (62 %)	39 (74 %)	39 (78 %)	21 (78 %)
Black	68 (18 %)	69 (18 %)	25 (20 %)	22 (17 %)	9 (17 %)	5 (10 %)	3 (11 %)
Hispanic	56 (15%)	65 (17 %)	16 (13%)	22 (17%)	5 (9 %)	5 (10%)	3 (11 %)
Other	6 (2%)	4 (1%)	1 (1%)	2 (2%)	-	-	-

No explicit age variable was included in the data sets, only date of birth. For the FDA analysis age was defined as age to the nearest month at the first visit.

Table A.4.2: Disposition of Patients

	Study C.003				Study C.002		
	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel	Clindamycin Foam	Clindagel	Vehicle Foam
Randomized and Treated	386	385	127	128	53	50	27
Completed Treatment	344 (89%)	346 (90%)	112 (88%)	113 (88%)	47 (89%)	46 (92%)	22 (81%)
Discontinued	42 (11%)	39 (10%)	15 (12%)	15 (12%)	6 (11%)	4 (8%)	5 (19%)
Reasons for Discontinuation:							
Adverse Events	2	0	1	0	0	1	1
Subject non-compliance	3	2	0	3	0	2	0
Disease Progression	0	0	1	0	0	0	0
Subject request to withdraw	15	15	6	6	2	1	3
Other	22	22	7	6	4	0	1

In Study C.003, of the 57 subjects in the "other" category, 51 subjects were lost to follow-up.

APPENDIX A.5. TESTING NON-INFERIORITY

Confidence intervals for the percent change from baseline in the various lesion count measures are based on contrasts in an analysis of variance. In these ANOVA's center by treatment interaction was never statistically significant. The protocol specified that under such circumstances the interaction term should be dropped from the model. However, when estimating contrasts in the center by treatment layouts, effectively this means that in the full space associated with the factorial design the basis for the contrast terms are effectively orthogonalized to the subspace spanned by the interaction contrasts. This reviewer would prefer the simpler interpretation of the contrasts prior to this orthogonalization to the generally greater power associated with the transformation. Hence, the contrasts used to define the non-inferiority comparisons in the FDA analysis include, and are balanced over interactions, not orthogonalized to the interactions. This does have some impact. But in terms of non-inferiority comparisons this convention has no effect.

For testing non-inferiority in proportions between a test drug and a reference drug the usual convention seems to be the use of simple binomial/normal approximations. That is, with n_1 subjects and an observed proportion p_1 of "successes" in the reference drug, and the corresponding n_2 subjects and observed proportion p_1 in the test drug, for a specified bound on the difference δ, we conclude non-inferiority if

$$-\delta < p_2 - p_1 - z_{\alpha/2} \sqrt{ (p_1 (1 - p_1)/n_1 + p_2 (1 - p_2)/n_2).}$$

This seems to be applied even in cases where the corresponding superiority analyses are stratified by center. That is, suppose that for each center k the data follow a table similar to the following, including marginal totals:

	Success	Failure	
Reference	n_{11k}	n_{12k}	n_{1+k}
Test drug	n_{21k}	n_{22k}	n_{2+k}
	n_{+1k}	n_{+2k}	n_{++k}

where $p_{jk} = n_{j1k} / (n_{j1k} + n_{j2k})$ is the observed proportion of successes.

The Mantel-Haenszel estimate of success rates is given by

$$d_{MH} = \sum_k w_k (p_{2k} - p_{jk})$$

where $w_k = (n_{1+k} n_{2+k}) / (n_{++k} \sum_k w_k)$. That is, the individual weights are normalized to sum to one.

The statistic d_{MH} is the square root of the numerator of the usual Mantel-Haenszel statistic. As discussed in Koch et al (1989) this adjusts for additive center effects. By comparison, the simple difference in proportions, i.e., the $p_2 - p_1$ above, confounds treatment differences with these additive center differences.

Using confidence intervals around d_{MH} to assess non-inferiority, we would first construct the interval and then see if this interval is within the specified δ bounds. Even with the Mantel-Haenszel numerator, there are a number of alternative variance estimates. To test superiority we

would generally use a Mantel-Haenszel statistic derived by conditioning on the marginals of each table for each center. This naturally leads to the pooled hypergeometric variance estimate:

$$\text{Var}\,(d_{MH}) = \Sigma_k\, w_k\, [n_{+1k}\, n_{+2k} / n_{++k}\, (n_{++k} - 1)]$$

These conditionings assume the totals are fixed, i.e., are ancillary. Conditioning on treatment totals is clearly appropriate for most designs where treatment allocation is reasonably fixed before data collection. However, conditioning upon response totals is clearly more debatable, since before collecting the data we would not know the response totals. An appropriate probability model for responses when response totals are not fixed in advance would be a product binomial model (with stochastically independent centers). Then we would estimate the variance of d_{MH} as:

$$\text{Var}\,(d_{MH}) = \Sigma_k\, w_k^2\, [p_{2k}\,(1 - p_{2k})/\, n_{2+k} + p_{1k}\,(1 - p_{1k})/\, n_{1+k}]$$

Other modifications are possible. For example, one could use so-called continuity corrected values. However these were not used here.

It does seem to this reviewer that a non-inferiority analysis should be consistent with the corresponding superiority analysis. In particular, in those cases where we use a Cochrane-Mantel-Haenszel test to assess treatment differences in superiority comparisons, a similar analysis should be used for the non-inferiority comparisons. This would argue for the use of the d_{MH} with the variance derived from a hypergeometric probability model. However, this reviewer would accept a slight inconsistency, and, for the reasons cited above, would prefer the d_{MH} with the product binomial variance. In the report, when computing confidence intervals for differences in success proportions both versions of the confidence intervals using d_{MH} are presented, along with the usual binomial/normal interval estimate of $p_2 - p_1$ as described above. Note the Sponsor used the binomial/normal estimate.

Neither the protocol nor the documentation of statistical methods specified non-inferiority comparisons among the secondary endpoints. However, note that differences in success rates (success is "0" or "1") could be analyzed by methods similar to those above. A reasonably complicated but possible approach to a non-inferiority comparisons using the absolute change would be to model the covariances over time, possibly using a robust sandwich covariance estimate after some initial proposal covariance matrix. This would be followed by the use of the delta method to estimate the variance of the difference relative to baseline. However, such an analysis was not specified in the protocol and was not done here.

Reference:

Koch, G.G., Carr, C.J., Amara, I.A., Stokes, M.E., & Unryniak, T.J. (1989) Categorical Data Analysis. In *Statistical Methodology in the Pharmaceutical Sciences*, D.A. Berry (ed.), Marcel Dekker, New York, NY, 391-475.

APPENDIX A.6. STUDY C.002: ANALYSIS OF THE PHASE 2 STUDY

CLN.C.002 A Phase II Multicenter, Randomized, Investigator-blinded Study to Evaluate the Safety and Efficacy of Once Daily Clindamycin Phosphate 1% in a Foam Formulation versus Vehicle Foam or Clindamycin Phosphate 1% Topical Gel in subjects with Acne Vulgaris

This was designed as a Phase 2, three-arm study comparing clindamycin phosphate foam, clindagel, and vehicle foam, with treatment applied once a day for 12 weeks. Entry criteria and endpoints were similar to the Phase 3 study, Study C.003. Demographic information on patients is given in Appendix 4. Entry criteria and endpoints were similar to Study C.003. One exception is with the Investigator's Static Global Assessment score described below.

A 95% two sided confidence about the difference in percent reduction in non-inflammatory lesions (foam - gel) is given by (-10.6, 21.2). Since the -10.6 lower is below -10, strictly speaking, one can not conclude that foam has been shown to be non-inferior to the gel.

Table A.6.1 Study C.002 Percent Reductions in Non-inflammatory Lesion Counts

Treatment		Week Baseline	3	6	9	12	12 PP	12 LOCF	p-value
Clindamycin Foam	N	53	50	49	47	47	45	53	
	Mean	38.1	13.8	18.5	22.7	38.9	38.4	35.8	0.7043*
	Std Dev	15.6	30.5	46.7	46.9	33.5	34.0	35.7	
Clindagel	N	50	48	47	45	46	46	50	
	Mean	35.8	10.1	18.9	25.5	32.5	32.5	30.9	
	Std Dev	14.2	31.6	40.7	50.0	45.9	45.9	44.4	
Vehicle Foam	N	27	26	25	25	22	21	27	
	Mean	37.7	18.6	25.1	23.7	39.1	39.4	31.5	
	Std Dev	14.5	32.6	29.3	40.8	32.9	33.7	40.2	

* Superiority test against appropriate vehicle foam from ANOVA contrast

In this study, with this relatively small sample size, there seems to be no particularly clear pattern among the trajectories of the three treatment groups.

The following table, Table A.6.2, displays the profiles of the percent reduction in inflammatory lesion counts. A two sided 95% confidence interval about the difference in percent reduction in inflammatory lesions (foam - gel) is given by (-24.6, 4.3). Since the -24.6 lower bound is below -10, one can not conclude that foam has been shown to be non-inferior to the gel.

Table A.6.2 Study C.002 Percent Reductions in Inflammatory Lesion Counts

Treatment		Week Baseline	3	6	9	12	12 PP	12 LOCF	p-value
Clindamycin Foam	Mean	26.5	27.8	39.5	41.4	50.4	57.2	45.6	0.6794*
	Std Dev	8.1	30.7	30.4	35.6	39.1	37.0	39.4	
Clindagel	Mean	26.7	35.9	37.4	47.1	51.5	51.5	49.5	
	Std Dev	7.2	28.9	32.8	36.3	38.3	38.3	38.1	
Vehicle Foam	Mean	26.3	17.7	16.5	35.2	46.1	46.0	41.2	
	Std Dev	7.1	37.7	39.1	38.3	35.1	36.0	34.2	

* Superiority test against appropriate vehicle foam from ANOVA contrast

Over the course of the study, both active treatment groups seem to be better than vehicle, but seem to be essentially equivalent.

Table A.6.3 shows the scores over time in the percent reduction in total lesions. A two-sided 95% confidence interval about the difference in percent reduction in total lesions (foam - gel) is given by (-13.0,13.3). Since the -13.0 lower bound is below -10, again, we would conclude that the foam has not been shown to be non-inferior to the gel in terms of percent reduction in total lesions.

Table A.6.3 Study C.002 Percent Reductions in Total Lesion Counts

Treatment		Week Baseline	3	6	9	12	12 PP	12 LOCF	p-value
Clindamycin Foam	Mean	64.6	20.5	27.5	32.3	43.9	44.0	39.8	0.6863*
	Std Dev	16.8	24.2	30.6	32.5	31.0	31.4	32.7	
Clindagel	Mean	62.5	21.5	27.2	34.3	40.0	40.0	38.3	
	Std Dev	16.6	24.5	28.3	36.6	37.2	37.2	36.5	
Vehicle Foam	Mean	64.0	18.6	22.0	28.7	42.6	42.7	36.0	
	Std Dev	18.6	27.1	22.7	31.1	26.1	26.7	29.6	

* Superiority test against appropriate vehicle foam from ANOVA contrast

Prior to Week 12 the active treatments seem to dominate the vehicle. By Week 12 this apparent superiority seems to vanish.

Study C.002 used a five-point Investigator's Static Global Assessment scale (ISGA) described below. For analysis this was dichotomized into a score of 0 or 1, i.e., "Clear" or "Minimal".

Table A.6.4 Five-point Investigator's Static Global Assessment

Score	Definition
0	Clear - No evidence of acne vulgaris requiring treatment
1	Minimal - Few non-inflammatory lesions may be present, with rare small papules/pustules, and no nodulo-cystic lesions
2	Mild - Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and perhaps one small nodulo-cystic lesions
3	Moderate - Inflammatory lesions are more apparent: many comedones and papules/pustules, perhaps a few nodulo-cystic lesions
4	Severe - Highly inflammatory lesions predominate: variable number of comedones, several to many papules/pustules and several to many nodulo-cystic lesions

Tables of success rate using the "0 or 1" versus "greater than 1" dichotomization are given in Table A.6.5 below. Using the usual binomial/normal approximation without stratification on center we compute that the 95% confidence interval on the difference in percentages between clindamycin foam and Clindagel is (-26.2,11.4). Using the Mantel-Haenszel weighted difference and a hypergeometric variance estimate we compute that a two-sided 95% confidence about the difference in success rates (foam - gel) is given by (-26.1, 9.9). Using the product binomial estimate of variance we get (-25.0, 8,8). In no case are the confidence limits are above the -10.0 non-inferiority limit, so we can not accept the hypothesis of non-inferiority between clindamycin foam and Clindagel.

Table A.6.5 Study C.002 Success Rates on Five Point Scale

		Week 3	6	9	12	12 PP	12 LOCF	p-value
Treatment								
Clindamycin Foam	n	16/	23/	21/	30/	29/	30/	0.0093*
	N	50	49	47	47	45	53	
	%	32.0	46.9	44.7	63.8	64.4	56.6	
Clindagel	n	12/	19/	30/	31/	31/	32/	
	N	48	47	45	46	46	50	
	%	25.0	40.4	66.7	67.4	67.4	64.0	
Vehicle Foam	n	6/	5/	6/	7/	7/	7/	
	N	26	25	25	22	21	27	
	%	23.1	20.0	24.0	31.8	33.3	25.9	

* CMH test of superiority test against vehicle foam.

Somewhat surprisingly considering the results on percent change in lesion counts, both treatment profiles clearly dominate the profile of the vehicle foam treatment group. The test of superiority of clindamycin foam over its vehicle is statistically significant ($p \leq 0.0093$).

According to the Sponsor, "After subject enrollment was complete, Connetics was involved in discussions with the FDA regarding further modification of the Protocol. Specifically, discussions centered on the Amendment 1 version of the 5-point Investigator's Static Global Assessment scale cited above. Per the FDA's recommendation, a 6-point scale was devised and added to the final Week 12/Study Termination visit efficacy assessments. Protocol Amendment 2 (26 August 2002) incorporates the implementation of the 6-point Investigator's Static Global Assessment scale." The five point scale is described be in Table A.6.4 above. The six-point scale was used in the C.003 Study and is described in the main body of the report.

Table A.6.6 Study C002 Success Rates on Six-Point Scale

	Clindamycin Foam	Clindagel	Vehicle Foam	p-value
n/N	15 / 48	18 / 48	5 / 25	0.2845[1]
%	31.3	37.5	20.0	

[1] CMH test of superiority test against vehicle foam.

Note the population used above was essentially the group of completers at week 12, since this evaluation was done once at the end of the study. In particular, it is slightly different population than that used with the five-point scale.

It is interesting to note that in this much smaller study for all endpoints, completely contrary to the results in the larger Study C.003, the success rates of the gel formulation are higher than in the foam formulation.

APPENDIX A.7. STUDY C.003: PRELIMINARY BAYESIAN ANALYSIS

The primary endpoints specified in the protocol included the percent change from baseline in each of the non-inflammatory lesion counts, the inflammatory lesion counts, and a dichotomization of a six point Investigator's Static Global Assessment (ISGA), all computed in the intent-to-treat population. A score of 0 or 1, i.e., clear or minimal, on the ISGA was defined as a treatment success. A simple Bayesian analysis of these non-inferiority comparisons using these endpoints was initiated. The logit of the success probability on the IGSA was modeled with a treatment effect and a random center effect. There are at least two reasonable models:

1) reduced data model with only clindamycin foam and Clindagel as factors,
2) full data model with all four treatment groups.

Thus for the binary response y_{ki}, we have the full data model:

$E(y_{ki}) = p_{ki}$ with $\text{logit}(p_{ki}) = a_k + b_{k1}\,\delta_{1i} + b_{k2}\,\delta_{2i} + b_{k3}\,\delta_{3i}$,

where k=1,...,C indicates the center and i=1,...,N denotes the subject. Assume $a_k \sim N(\mu, \sigma^2)$ and δ_{1i}, δ_{2i}, and δ_{3i} are 0-1 indicators of clindamycin foam, Clindagel, and vehicle gel, respectively. We assume priors $b_{kj} \sim N(\mu, \sigma^2)$, j=1,2,3, where $\mu \sim N(0.0,1000.0)$ and $1/\sigma^2 \sim \text{Gamma}(0.01, 0.0001)$.

The reduced data model, with data only from the clindamycin foam and Clindagel groups, has $\text{logit}(p_{ki}) = a_k + b_{k1}\,\delta_{1i}$.

Note that models with varying b_{kj} have treatment by center interaction, while models with constant b_{kj}, i.e., $b_{1j} = b_{2j} = \ldots = b_{Cj}$, correspond to a no interaction, main effects only, model.

One approach to model selection in Bayesian models is to use the Deviance Information Criterion (DIC). Effectively, for $D(\theta)$ denoting the usual deviance, $DIC \approx E(D(\theta)) + 1/2\,(\text{Var}(D(\theta))$. For a given data set the model with the smallest DIC would be preferred.

Deviance Information Criterion	Reduced Data Model (clindamycin foam & Clindagel only)	Full Data Model (all four treatment groups)
Model with treatment effects Constant across centers	868.689	1087.55
Model with treatment effects Varying across centers	885.687	1115.52

Thus for both the full data set and the reduced data set the no-interaction model with the b_{kj} constant across centers j, would be preferred to the model with interaction terms.

One of the strengths of the Bayesian approach with current MCMC techniques is that, in general, it is quite trivial to compute the distribution of any well defined functional of the parameters. There are a number of different reasonable approaches to assessing non-inferiority,

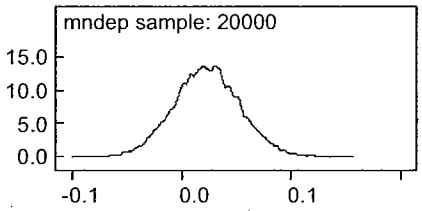
however most of these are based on pooled success probability. If we define $p_{k,foam}$ and $p_{k,gel}$ as the probability of success in the foam and gel groups respectively, we model $logit(p_{k,foam}) = a_k + b_{k1}$ and $logit(p_{k,gel}) = a_k$, in the reduced data set. It makes sense to define the mean effect of clindamycin foam versus its comparator as mean diff = $\Sigma p_{k,foam}/C - \Sigma p_{k,gel}/C$, where k=1,..,C.

Program 1 below gives the following edited output:

Parameter Estimates for Success Probability in Reduced Data Model

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
b	0.1251	0.1613	0.002243	-0.1827	0.1228	0.4504	5001	20000
Prob(mean diff ≥ 0.0)	0.7819	0.413	0.004263	0.0	1.0	1.0	5001	20000
Prob(mean diff ≥ -0.05)]	0.9932	0.08188	6.854E-4	1.0	1.0	1.0	5001	20000
Prob(mean diff ≥ -0.10)	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000
Mean diff	0.02314	0.02984	4.095E-4	-0.03412	0.02281	0.08284	5001	20000

Thus we would estimate $Pr(\Sigma p_{k,foam}/C - \Sigma p_{k,gel}/C \geq 0.0) = 0.78$
and $Pr(\Sigma p_{k,foam}/C - \Sigma p_{k,gel}/C \geq -0.05) = 0.99$.
These would seem to be sufficient to conclude non-inferiority. Note the fact that the estimated credible interval for b contains 0 is at least consistent with the notion of no treatment difference between the foam and the gel. The estima ted posterior distribution of the difference is plotted as follows:



The distribution is clearly well above the -0.1 (-10%) bound, again indicating noninferiority in success rates.

Another approach to assessing non-inferiority involves comparing the superiority of foam over its vehicle (or placebo) to the superiority of the gel formulation to its vehicle (or placebo). The ratio of these terms can be used as a measure of the proportion of improvement of the foam formulation relative to the improvement in the gel formulation. One way to compute such an expression using the full data set would be as follows:

Ratio = num / denom = $(\Sigma p_{k,foam} - \Sigma p_{k,foam\ veh}) / (\Sigma p_{k,gel} - \Sigma p_{k,gel\ veh})$.

To assess the superiority of the foam to its vehicle and the gel to its vehicle one possible approach would be to analyze the mean of the numerator (i.e., the sum divided by C) and the mean of the denominator in the expression separately.

Program 2 below gives the following edited output:

Parameter Estimates for Success Probability in Full Data Model

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
b[1]	0.3616	0.2353	0.005732	-0.07597	0.3558	0.8423	5001	20000
b[2]	0.1589	0.235	0.00558	-0.2754	0.1503	0.6443	5001	20000
b[3]	-0.2915	0.2979	0.005734	-0.8663	-0.2945	0.3033	5001	20000
num	0.0628	0.03968	9.349E-4	-0.01385	0.06269	0.1403	5001	20000
denom	0.07062	0.03935	2.76E-4	-0.008725	0.07095	0.1453	5001	20000
ratio	0.5931	140.4	0.9902	-3.106	0.81476.363	5001	20000	
Prob(mean diff ≥ 0.0)	0.9081	0.289	0.003215	0.0	1.0	1.0	5001	20000
Prob(mean diff ≥ -0.1)	0.9257	0.2623	0.002644	0.0	1.0	1.0	5001	20000
Prob(mean diff ≥ -0.2)	0.9372	0.2426	0.002221	0.0	1.0	1.0	5001	20000
Prob(mean diff ≥ -0.5)	0.9535	0.2106	0.00162	0.0	1.0	1.0	5001	20000

So the posterior probability that the superiority of foam to vehicle is greater than than the superiority of gel to vehicle is 0.91. The probability that the foam achieves at least 50% of the relative efficacy of the gel is at least 0.95. Note that b[1] is the estimated effect of clindamycin foam relative to its vehicle. The estimated posterior probability that this parameter is greater than zero is 0.9441, but the two-sided 0.95 credible interval includes zero.

For the ANOVA models, effects are strictly additive. For simplicity we use the reduced model (clindamycin foam and Clindagel treatment groups only). Following the protocol the percent change from baseline in inflammatory and non-inflammatory lesions is modeled as follows. For the binary response y_{ki}, we have the overall model:

$$E(y_{ki}) = a_k + b_{k1}\,\delta_{1i},$$

where k=1,…,C indicates the center and i=1,…,N denotes the subject (within center). $a_k \sim N(\mu, \sigma^2)$ and δ_{1i} are 0-1 indicators of clindamycin foam versus Clindagel. We assume priors $b_{kj} \sim N(\mu, \sigma^2)$, j=1,2,3, where $\mu \sim N(0.0,1000.0)$ and $1/\sigma^2 \sim$ Gamma(0.01, 0.0001). Using the DIC for model selection gives the following:

Deviance Information Criterion	Non-inflammatory Lesions	Inflammatory Lesions
Model with treatment effects Constant across centers	7641.76	7707.00
Model with treatment effects Varying across centers	7644.35	7709.79

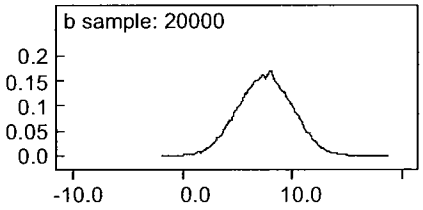
So again, using the DIC, the models without interaction are better than the models incorporating interaction terms. Note that in this case, for all centers k, $E(y_{k,foam}) - E(y_{k,gel}) = b$, so a suitable non-inferiority interval can be based on b.

WinBUGS programs similar to program 3 give the following parameter estimates. Note that mnb[1]-mnb[3] provide estimates of the probability that b, i.e. the differential effect of clindamycin foam over gel, is greater than 0%, -5%, and -10% respectively.

Parameter estimates for Percent Change in Non-inflammatory Lesions

node	mean	sd	MC error2.5%	median	97.5%	start	sample	
b	9.517	2.401	0.03104	4.789	9.519	14.2	5001	20000
mnb[1]	1.0	0.007071	4.98E-5	1.0	1.0	1.0	5001	20000
mnb[2]	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000
mnb[3]	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000

Thus, the posterior probability that b is greater than 0 is 1.0, so we conclude that there is clear evidence that in terms of percent change in non-inflammatory lesions, clindamycin foam is not inferior to Clindagel. In fact, the posterior probability that clindamycin foam is superior rounds to 1.0. The estimated posterior distribution of b is as follows:

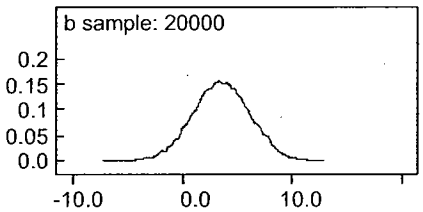


Results from a similar analysis of percent change in inflammatory lesions follow:

Parameter estimates for Percent Change in Inflammatory Lesions

node	mean	sd	MC error2.5%	median	97.5%	start	sample	
b	5.874	2.57	0.0343	0.8249	5.853	10.91	5001	20000
mnb[1]	0.9888	0.1055	9.22E-4	1.0	1.0	1.0	5001	20000
mnb[2]	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000
mnb[3]	1.0	0.0	7.071E-13	1.0	1.0	1.0	5001	20000

The posterior probability that b is greater than 0 is 0.99, and again we conclude that there is evidence that in terms of percent change in non-inflammatory lesions, clindamycin foam is not inferior to Clindagel. Here, the posterior probability that clindamycin foam is superior rounds to 0.99. The estimated posterior distribution of b is as follows:



So both plots are consistent with non-inferiority in the percent change from baseline in lesion counts.

Note that a descriptive residual analysis did suggest that the ANOVA mixed models above were appropriate. All WinBUGS analyses were performed with a burn-in of 5000

iterations. Formal Gelman-Rubin analysis of convergence was only conducted for a couple of the models, but history plots showed good mixing and autocorrelations tended to drop off relatively quickly. So the fit of the models and the convergence of estimates do not seem to have been an issue.

Similar models could be used to assess superiority, but due to time limitations and the fact that this was a secondary analysis, they were not analyzed.

Program 1:

```
model{
   for (i in 1:N){
       succ[i]~dbern(p[i])
       logit(p[i])<- a[ctr[i]] + b*trt[i]
   for (j in 1:nc) {
       a[j]~dnorm(mx,tau)
       dep[j]<- exp(a[j]+b)/(1+ exp(a[j]+ b)) - exp(a[j])/(1+exp(a[j]))
                        }
    b ~ dnorm(mx,tau)
    mndep<- mean(dep[ ])
    mdep[1]<- step(mndep)
    mdep[2]<- step(mndep + 0.05)
    mdep[3]<- step(mndep + 0.10)
    mx~dnorm(0.0,0.001)
    tau~dgamma(0.01,0.001)I(0.0001,)
  }
inits
list(a=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0))

data
list(N=771,nc=18)
ctr[ ]  trt[ ]   succ[ ]
   1    1    0
   1    1    1
   ~ data -
  18    0    0
  18    0    0
END
```

Program 2:

```
model{
   for (i in 1:N){
       trt1[i]<- equals(trt[i],1)
       trt2[i]<- equals(trt[i],2)
       trt3[i]<- equals(trt[i],4)
       succ[i]~dbern(p[i])
       logit(p[i])<- a[ctr[i]] + b[1]*trt1[i] +  b[2]*trt2[i] + b[3]*trt3[i]
                    }
    for (j in 1:nc) {
       a[j]~dnorm(mx,tau)
       pfoam[j] <- exp(a[j]+b[1])/(1+ exp(a[j]+ b[1]))
       pgel[j]    <- exp(a[j]+b[2])/(1+ exp(a[j]+ b[2]))
       pvfoam[j]<- exp(a[j])/(1+ exp(a[j]))
       pvgel[j]   <- exp(a[j]+b[3])/(1+ exp(a[j]+ b[3]))
                         }
    for (k in 1:3){
         b[k]  ~ dnorm(mx,tau)
                    }
    prob <- step(b[1])
    num    <-  mean(pfoam[ ]) - mean(pvfoam[ ])
    denom <- mean(pgel[ ]) - mean(pvgel[ ])
```

```
    ratio      <- num / denom
    mrat[1]<- step(ratio)
    mrat[2]<- step(ratio + 0.1)
    mrat[3]<- step(ratio + 0.2)
    mrat[4]<- step(ratio + 0.5)
    mx~dnorm(0.0,0.001)
    tau~dgamma(0.01,0.0001)I(0.00001,)
  }
inits
list(a=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0))

data
list(N=1025,nc=18)
ctr[ ]  trt[ ]   succ[ ]
   1    1    0
   1    1    1
   1    1    0
  -data-
  18    4    0
  18    4    0
END
```

Program 3:

```
model{
   for (i in 1:N){
       inf[i]~dnorm(mu[i],tau)
       mu[i]<- a[ctr[i]] + b*trt[i]
                    }
    for (j in 1:nc) {
       a[j]~dnorm(mx,tau.a)
                       }
    b~dnorm(mx,tau.a)
    mnb[1]<- 1-step(b)
    mnb[2]<- 1-step(b - 5)
    mnb[3]<- 1-step(b - 10)
    mx~dnorm(0.0,0.001)
    tau~dgamma(0.01,0.001)I(0.0001,)
    tau.a~dgamma(0.01,0.001)I(0.0001,)
  }

inits
list(a=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0))

data
list(N=771,nc=18)
ctr[ ]  trt[ ]   inf[ ]
   1    1     44.4
   1    1     80.8
   1    1     81.3
  - data -
  18    0     57.9
  18    0    -50.0
END
```

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Steve Thomson
Date: September 12, 2004

Concurring Reviewer:

Statistical Team Leader: Mohamed Alosh, Ph.D., HFD-725

cc:
HFD-540/J. Lindstrom, M.D..
HFD-540/M. Harris.
HFD-540/M. Luke, M.D., Ph.D.
HFD-540/J. Wilkin, M.D.
HFD-725/S. Thomson
HFD-725/M. Alosh, Ph.D.
HFD-725/J. Zalkikar, Ph.D.
HFD-725/M. Huque, Ph.D.,
HFD-725/C.. Anello, Ph.D.
HFD-725/S. Dubey, Ph.D.

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/s/

Steven Thomson
9/14/04 03:22:52 PM
BIOMETRICS

Mohamed Alosh
9/14/04 03:34:32 PM
BIOMETRICS
Concur with review

STATISTICAL REVIEW AND EVALUATION: 45 DAY FORWARD PLANNING MEETING REVIEW

(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21-709/ 3S-000
NAME OF DRUG: ——— (clindamycin phosphate foam) 1%
APPLICANT: Connectics Corporation

FILING DATE: Stamp Date: 12/24/03
INDICATION(S): Topical treatment of acne vulgaris.
NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES: Reports and data for one phase 3 study and one supporting phase 2 study, plus a study of cumulative irritation and an open label absorption study.
STATISTICAL REVIEWER: S. Thomson
CLINICAL REVIEWER: J. Lindstrom
PROJECT MANAGER: M. Harris.

FORWARD PLANNING MEETING DATE: 02/19/04
WAS THE NDA FILED: YES
USER FEE DATE: 10/24/04

I. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
*A. Is there a comprehensive table of contents with adequate indexing and pagination?	√		
@B. Are the original protocols, protocol amendments, and proposed label provided?	√		
˙C. Are the following tables/listings provided in each study report?			
1. Patient profile listings by center(includes all enrolled patients).	√		
2. Lost subject tables by center which includes reason and time of loss.	√		
3. Intermediate analysis summary tables(gender, age, race/ethnic, etc.).	√		
4. Pathogen listings.			√

*D.	Adverse event listings by center and time of occurrence relative to enrollment date.	√		
*1.	Are adverse events from cited sources(foreign and domestic) provided?			√
*E.	Is a CANDAR or an electronic submission of the data necessary?	√		
*F.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?	√		
G.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	√		
*H.	Are there discrepancies between CRF information and CANDAR/Jacket data?			√
I.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?	√		

II. STATISTICAL METHODOLOGY		YES	NO	N/A
*A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	√		

Sponsor provides an investigator global and lesion counts for inflammatory, non-inflammatory, and total lesions. The non-inflammatory counts exclude nasal lesions. The protocol specified analysis are based on percent change from baseline in lesion counts.

*B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	√		
C.	Based on the summary analyses of each study, do you believe:			
*1.	The analyses are appropriate for the type data collected, the study design, and the study objectives(based on protocol and proposed label claims)?	√		
*2.	Intent-to-treat (ITT and MITT) analyses are properly performed?	√		
3.	Sufficient and appropriate references were included for novel statistical approaches?			√

*D. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?	____	____	__√__
*E. Are there studies which are incomplete or ongoing?	____	___√_	____
*F. Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	__√__	____	____

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes.

Steve Thomson
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 2147019452 Serial 019/020
HFD-590
HFD-540/Dr. B. Vaughan
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HFD-540/Mr. F. Cross
HFD-725/Dr. M. Alosh
HFD-725/Dr. M. Huque
HFD-725/Mr. S. Thomson
HFD-725/Dr. Anello
Chron.

* These items, if not included or if incorrect, are justifiable reasons for not filing the NDA.
@ These items, if not acceptable, are reason to consider not filing.
# It is the Agency's intent that all submissions be CANDARs or electronic in format in 1995. Clearly, we do not need CANDARs for every submission, but, just as clearly, we need data on disks if we are to do an expeditious review. Since the company, in all likelihood, used computers to do their evaluations, all data should be readily available to us on disk, at least, for our use in the review action.
^ At this point of time, not applicable.

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/s/

Steven Thomson
2/19/04 02:29:04 PM
BIOMETRICS

Mohamed Alosh
2/21/04 04:01:12 PM
BIOMETRICS