

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



US Department of Health and Human Services
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Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION
NEW DRUG APPLICATION
CLINICAL STUDIES

NDA/Serial Number: 50-802/SN000
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Indication(s): Acne
Applicant: Dow Pharmaceutical Sciences, Inc.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The initial NDA was submitted on February 6, 2004 and in response to this application a Not Approvable (NA) letter was issued to the sponsor on 12/07/2004 citing, "The contribution to efficacy of each component of your combination product was not adequately demonstrated. Specifically the contribution of tretinoin to efficacy was not adequately demonstrated." In response to the NA letter the sponsor also appealed the decision via formal dispute resolutions to the Office of Drug Evaluation V (ODE V) and later to the Office on New Drugs (OND) based upon the denial of the sponsor's request from ODE V. On 11/03/2005 Dr. John Jenkins, Director of OND, denied the sponsor's request and concurred with the Division of Dermatology and Dental Products that the sponsor failed to establish the contribution of tretinoin in their combination product.

In May of 2005 the sponsor submitted a special protocol assessment (SPA) proposing to conduct an additional Phase 3 study with two arms; Ziana™ Gel and Clindamycin Gel. In response to this SPA the Agency agreed to allow the sponsor to conduct an additional two arm study to establish the contribution of tretinoin to the combination product (i.e. a two arm study with Ziana™ Gel and Clindamycin Gel).

The resubmission submitted on 05/06/2006 contains the results of the Phase 3 study with two arms enrolling approximately 1000 subjects on each arm. Efficacy was based upon the co-primary endpoints; percent reduction in two out of three lesions counts (inflammatory, non-inflammatory, and total) and dichotomized success (two grade improvement) on an investigator global assessment scale. For each endpoint, Ziana™ Gel was statistically superior to Clindamycin Gel, (all $p < 0.001$) establishing the contribution of tretinoin to the combination product.

1.2 Brief Overview of Clinical Studies

The original NDA submission contained two Phase 3 trials with the objective of showing that the combination product was superior to each component and vehicle when applied once daily. As both of these trials failed to establish the contribution of tretinoin, the resubmission now contains data from an additional Phase 3 trial, Study MPI-02, with two arm: Ziana™ Gel and Clindamycin Gel both applied once daily. This trial enrolled a total of 2010 subjects, 1008 randomized to Ziana™ Gel and 1002 randomized to Clindamycin Gel. The objective of Study MPI-02 was to show Ziana™ Gel to be superior to Clindamycin Gel on the basis of two out of three lesion counts and an investigator's global assessment.

1.3 Statistical Issues and Findings

As the Not Approvable (NA) letter specified that the clinical trials failed to establish the contribution of tretinoin to the combination product, the sponsor proposed to conduct a two arm trial including treatments arm Ziana™ Gel and Clindamycin Gel. The Agency stated that the above two arm study should be acceptable to establish the contribution of tretinoin to the combination drug product.

Study MPI-02 enrolled subjects with moderate to severe acne (IGA=3 or 4) on a six point IGA scale (0=clear to 5-very severe), 20-50 inflammatory lesions, and 20-100 non-inflammatory lesions. The sponsor's success criteria for the IGA is defined as clear, almost clear, or a two grade improvement. It should be noted that with enrollment of subjects with an IGA of 3 or 4 such a definition reduces to a two grade improvement which is consistent with the draft Acne Guidance.

Study MPI-02 enrolled 2010 subjects and efficacy results demonstrate that Ziana™ Gel is superior to Clindamycin Gel for both co-primary endpoints. Efficacy results are shown in Table 1 for IGA success, inflammatory lesions, and non-inflammatory lesions; total lesions is excluded since both inflammatory and non-inflammatory lesion counts are significant which implies total lesions is also significant. The safety profiles of Ziana™ Gel and Clindamycin Gel are similar with a slightly higher percentage of subjects receiving Ziana™ Gel reporting adverse events related to skin and subcutaneous tissue disorders.

Table 1: Primary Efficacy Results for Study MPI-02 (ITT)

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)
Investigator's Global Assessment		
Success (%)	415 (41.2)	345 (34.4)
p-value ¹	-	< .001
Non-inflammatory Lesions		
Mean (SD)	49.8 (37.1)	41.3 (38.6)
p-value ²	-	< .001
Inflammatory Lesions		
Mean (SD)	60.9 (35.8)	54.8 (38.0)
p-value ²	-	< .001

¹ CMH stratified by center.

² ANOVA with terms for treatment and pooled site.

Source: Reviewer's analysis.

2 INTRODUCTION

Note that in the initial NDA submission the sponsor proposed the tradename ClinRA Gel but this was not accepted by the Division of Medication Errors and Technical Support (DMETS). In the resubmission the sponsor now proposes the tradename Ziana™ Gel.

2.1 Overview

Ziana™ Gel is a combination product consisting of the two active moieties, clindamycin and tretinoin, both of which have been approved by the FDA for the treatment of acne vulgaris. The current trial, Study MPI-02, is a two-arm trial comparing Ziana™ Gel to Clindamycin Gel. This trial was conducted after the two previous Phase 3 trials failed to establish the contribution of tretinoin to the combination product. A listing of the three pivotal Phase 3 trials is provided in Table 2 on the following page. A couple of notes about the differences in the initial four-arm Phase 3 trials from the two-arm trial are as follows.

- Neither of the initial Phase 3 trials listed a baseline IGA score as an enrollment criteria. Study MPI-02 has an enrollment criteria of moderate to severe according to the IGA.
- The definition of success on the IGA is now two grade improvement, whereas the previous trial was clear or almost clear.
- Study MPI-02 has a balanced randomization scheme to Ziana™ Gel and Clindamycin Gel with much larger sample sizes than the previous trials. The previous trials randomized subjects in a 2:1:2:1 ratio to Ziana™ Gel, Clindamycin Gel, Tretinoin gel, and vehicle, respectively.

Note that prior to the initial Phase 3 trials being conducted, the Agency cautioned the sponsor against under powering the Phase 3 trials by not powering the trials for the IGA endpoint. The sponsor acknowledged this risk and choose to conduct the studies as planned with randomization of half as many subjects to the clindamycin arm as the combination arm. Upon completion, response rates (based upon the IGA) were slightly higher in the clindamycin arm than the tretinoin arm which in effect resulted in the combination product failing to reach statistical significance.

2.2 Data Sources

The original efficacy analysis data set (AD_OPV) submitted for Study MPI-02 is provided in //Cdsesub1/n50802/N_000/2006-05-05/N050802/crt/datasets/mp-1501-02. Based upon AD_OPV, the efficacy results in the study report for Study MPI-02 could not be reproduced.

Table 2: Pivotal Phase 3 Trials

Study	Dates	Inclusion Criteria	Arms (N)
7001-G2HP-06-02	Start: 02/11/03 End: 10/21/03	IGA: NA ⁱ	Ziana TM (420)
		Non-IFL: 20-100	clindamycin (208)
		IFL: 20-50 nodules: ≤ 2	tretinoin (417) vehicle (207)
7001-G2HP-07-02	Start: 01/30/03 End: 10/20/03	IGA: NA ⁱ	Ziana TM (425)
		Non-IFL: 20-100	clindamycin (218)
		IFL: 20-50 nodules: ≤ 2	tretinoin (429) vehicle (216)
MPI-1501-02	Start: 09/09/05 End: 03/01/06	IGA: moderate or severe	Ziana TM (1008)
		Non-IFL: 20-100	clindamycin (1002)
		IFL: 20-50 nodules: ≤ 2	

ⁱ Studies did not incorporate IGA into inclusion criteria.

Therefore the Agency requested the sponsor to resubmit the efficacy data in a pre-specified format. As provided by the sponsor on July 14, 2006, the reconstructed data set used for the efficacy analysis is listed in //Cdsesub1/n50802/N_000/2006-07-14/crt/datasets/mp-1501-02.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

In the evaluation of efficacy, the review focuses on data collected in Study MPI-02 and not on the previous Phase 3 studies, Study 7001-G2HP-06-02 (Study 06) and Study 7001-G2HP-07-02 (Study 07). A brief summary of efficacy for Study 06 and Study 07 is provided in the Appendix Section A.1 on page 23. For a more extensive review of efficacy for Study 06 and Study 07 refer to the statistical review signed in DFS on October 14, 2004 by Dr. Shiowjen Lee.

3.1.1 Study Design

Study MPI-02 is a randomized, double-blind, multi-center, two-arm trial to compare the safety and efficacy of ZianaTM Gel and Clindamycin Gel in the treatment of acne vulgaris when applied once daily. Randomization to ZianaTM Gel and Clindamycin Gel was in a 1:1 ratio with the randomization being stratified on Fitzpatrick Skin Type (FST) and baseline IGA. 2010 subjects were enrolled in 47 centers in the United States. Treatment duration was 12 weeks with the

primary time point for efficacy evaluation occurring on week 12. The objective of the trial is to demonstrate ZianaTM Gel is superior to Clindamycin Gel which in turn establishes the contribution of tretinoin to the combination drug product, ZianaTM Gel.

At enrollment subjects were at least 12 years of age, assigned an IGA score of moderate or severe, and had 20-50 inflammatory lesions and 20-100 non-inflammatory lesions. The treatment period consisted of 12 weeks with 5 visits occurring at baseline, week 2, week 4, week 8, and week 12. The last visit was planned to occur within -3 or + 5 days from day 84.

3.1.2 Endpoints

As agreed upon with the Division and as used in Study 06 and Study 07, the protocol defined co-primary endpoints for Study MPI-02 are as follows.

- Two out three lesions counts (inflammatory, non-inflammatory, total). Analysis will be based upon the percent change from baseline.
- IGA success defined as clear or almost clear or a two grade improvement. Note this is equivalent to defining a success as a two grade improvement with IGA entry criteria of moderate to severe. For this reason, IGA success is defined as a two grade improvement.

For ZianaTM Gel to be declared superior to Clindamycin Gel, all co-primary endpoints must reach statistical significance at the $\alpha = 0.05$ level.

3.1.3 Patient Disposition and Baseline Characteristics

3.1.3.1 Patient Disposition A total of 313 out of 2010 (15.5%) subjects withdrew from the study prior to week 12. Table 3 lists the reason subjects did not complete the study. A large portion of the dropouts for both treatment arms is due to being lost to follow-up. Overall, the proportion of dropouts is quite similar between the treatment arms.

The protocol defined primary analysis population is defined as the intent to treat (ITT) population. The ITT population was defined in the protocol as all subjects randomized and dispensed drug product. The per protocol population (PP) is defined as all subjects who complete 12 weeks of treatment and who do not have any noteworthy protocol violations. Table 4 displays the two analysis populations used for the efficacy assessment of ZianaTM Gel.

After the study was completed the SAP stated, "...a subject presenting data for a visit later than the allowed visit window will be considered to have missing data for that visit. The latest data reported during or before the visit window will be used in the analysis of the visit. Data reported after Day 89 of treatment are therefore not included in any efficacy analysis." As such a 'windowed' type of analysis was not agreed upon or provided in the protocol prior to the study conduct, the primary analysis considered in the review is based upon the ITT population defined as all subjects randomized and dispensed drug product regardless if treatment occurred

Table 3: Disposition for Study MP-1501-02

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)
Subject Request	17 (1.7)	28 (2.8)
Adverse Event	6 (0.6)	2 (0.2)
Protocol Violation	1 (0.1)	0 (0)
Lost to Follow-up	92 (9.1)	108 (10.8)
Non-compliance	1 (0.1)	3 (0.3)
Withdrew Consent	27 (2.7)	20 (2)
Pregnancy	0 (0)	0 (0)
Enrollment Violation	0 (0)	0 (0)
Other	5 (0.5)	3 (0.3)
Total	149 (14.8)	164 (16.4)

Source: Reproduction of study report Table 9.1.1

Table 4: Analysis Populations for Study MP-1501-02

	Clin-RA Gel	Clindamycin Gel
ITT	1008	1002
PP	727 (72.1%)	718 (71.7%)

Source: Reproduction of study report Table 9.1.1

in the specified visit window. The windowed analysis is considered as a supportive analysis to the primary analysis.

3.1.3.2 Baseline Characteristics

3.1.3.2.1 Demographics The demographic comparison considered age, Fitzpatrick Skin Type (FST), gender, and race. As randomization was stratified by FST and as expected, the distribution across FST was nearly identical between the treatments. The only factor that was significantly different the treatments was gender with a higher percentage of females receiving Clindamycin Gel than Ziana™ Gel; 55% and 49%, respectively. Tabled results are provided in the Appendix Section A.2 on page 25.

3.1.3.2.2 Baseline Prognostic Factors Each of the baseline lesion counts and baseline IGA were compared; Table 5 depicts the results. This table and the subsequent tests show the two treatment arms are not significantly different for any of the lesion counts or the baseline

IGA.

Table 5: Baseline Primary Endpoints by Treatment

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)	Test Statistic
Inflammatory	24 29 35	24 29 37	$F_{1,2008} = 0.3, P = 0.584^1$
Non-inflammatory	33 44 61	33 44 60	$F_{1,2008} = 0.11, P = 0.742^1$
Total	62 75 96	61 76 94	$F_{1,2008} = 0, P = 0.947^1$
IGA : 4 (severe)	25% (255)	25% (255)	$\chi_1^2 = 0.01, P = 0.938^2$

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used:

¹Wilcoxon test; ²Pearson test

3.1.4 Statistical Methodology

Following the NA action, two submissions were reviewed by the biostatistics team for designing a future trial to resolve the deficiency of not establishing the contribution of tretinoin to the combination product in the two previous trials. Highlights from each of these reviews is provided below.

- SPA submitted in SN033 on 05/24/2005.
 - Agreed to two-arm trial.
 - Minor modifications to the Statistical Analysis Plan (SAP).
- Phase 3 protocol submitted in SN035 on 09/13/2005.
 - SAP was a departure from SAP submitted in the SPA. Issues remaining were the following.
 - * Sensitivity analyses for the method of data imputation should be based on assuming favorable outcomes and also unfavorable outcome.
 - * Test for treatment by center interaction was not included.
 - * No justification for performing the primary analysis of the lesions counts on ranks.
 - Review and comments were entered into DFS, but comments were not conveyed to the sponsor.

As there was not agreement in the analysis of the co-primary endpoints and Agency comments were not conveyed to the sponsor, the following describes the analysis plan of the review with

clarifications of what is protocol defined and what is not. Note that while such issues are important, with the large sample sizes the efficacy claims are robust to modifications of the analysis plan.

As specified in the protocol the primary analysis will be based on the ITT population with supportive analysis on the PP population (see Section 3.1.3.1 for definitions of the populations). The primary method of imputation defined in the protocol is LOCF with sensitivity analysis imputing all missing IGA as failures. In addition to imputing all missing IGA as failures, the review also examines imputing all missing IGA as successes.

As outlined in Section 3.1.3.1, prior to database lock the statistical analysis plan was modified such that subjects that did not attend the visit within the protocol defined treatment window were treated as missing. In this case results are provided treating these subjects as missing (define this as the 'windowed' analysis). While this strategy is reasonable, it was not pre-specified in the protocol. Thus an analysis is conducted retaining the values recorded despite the fact the subject visit is outside the treatment window (define this as the 'as recorded' analysis). Note that the sponsor includes such a strategy in the analysis of the IGA only and not in the analysis of lesion counts. Further, the proposed label reports results based on the 'as recorded' analysis.

In the analysis of the dichotomized IGA the protocol defines CMH stratified by investigative site which was in agreement with the Agency. For the analysis of the percent change in lesion counts the SPA listed ANOVA with terms for treatment and investigative center which was in agreement with the Agency. However, the revised protocol, which the Agency's comments were not sent, lists the analysis of percent change in lesion counts using Cochran-Mantel-Haenszel Row Mean Score Statistic. Results from both analyses are provided.

3.1.5 Primary Endpoint Results (ITT)

3.1.5.1 Investigator's Global Assessment The protocol dichotomizes the 6 point IGA to success for subjects that have an IGA of clear (IGA=0), almost clear (IGA=1), or two grade improvement at week 12. As enrollment criteria restrict enrollment to subjects with IGA's of moderate (IGA=3) or severe (IGA=4), success can be simplified to two grade improvement. Defining treatment success as two grade improvement will be used throughout as it is consistent with the draft Acne Guidance.

Results for both the 'as recorded' and 'windowed' analyses are provided in Table 6. The treatment effect for the 'as recorded' analysis ($\delta = 6.8$) is slightly higher than for the 'window' analysis ($\delta = 6.1$). However, both analyses show highly significant results demonstrating the superiority of Ziana™ Gel to Clindamycin Gel.

3.1.5.2 Lesion Counts While the objective of Study MPI-02 is to establish the efficacy of Ziana™ Gel on the co-primary endpoints two out of three lesions counts and the IGA, the

Table 6: IGA Efficacy Results for ZianaTM Gel (ITT)

	As Recorded [†]		Windowed*	
	Ziana TM Gel (N = 1008)	Clindamycin Gel (N = 1002)	Ziana TM Gel (N = 1008)	Clindamycin Gel (N = 1002)
Success (%)	415 (41.2)	345 (34.4)	381 (37.8)	318 (31.7)
p-value	-	< .001	-	0.0018

[†] Source: Reviewer's Analysis using CMH stratified by pooled site.

* Source: Sponsor's Table 10.3.1.1 using CMH stratified by pooled site.

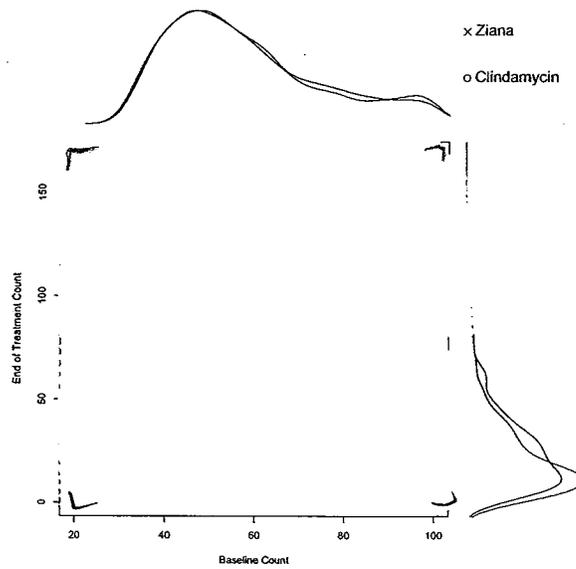
reporting of efficacy results for percent change in lesion counts will only include inflammatory and non-inflammatory lesions counts and not total lesion counts as the former are both highly significant.

Figure 1 depicts a scatter plot of the non-inflammatory lesions at baseline and end of treatment along with univariate density estimates of the distributions. As one would expect due to randomization the baseline distributions of non-inflammatory lesion counts is nearly identical, whereas a higher percentage of subjects treated with ZianaTM Gel have low end of treatment non-inflammatory lesion counts compared to subjects treated with Clindamycin Gel. The smoothed regression line using loess is also depicted showing roughly parallel lines between the two treatment arms implying a constant treatment effect throughout the range of baseline non-inflammatory lesion counts.

Figure 2 depicts a scatter plot of the inflammatory lesions at baseline and end of treatment along with univariate density estimates of the distributions. As with the non-inflammatory lesions the baseline distributions of inflammatory lesion counts are very similar, whereas a higher percentage of subjects treated with ZianaTM Gel have low inflammatory lesion counts at end of treatment compared to subjects treated with Clindamycin Gel. The smoothed regression line using loess is also depicted showing slightly diverging lines between the two treatment arms implying a possibly slightly higher treatment effect in subjects with higher baseline inflammatory lesion counts.

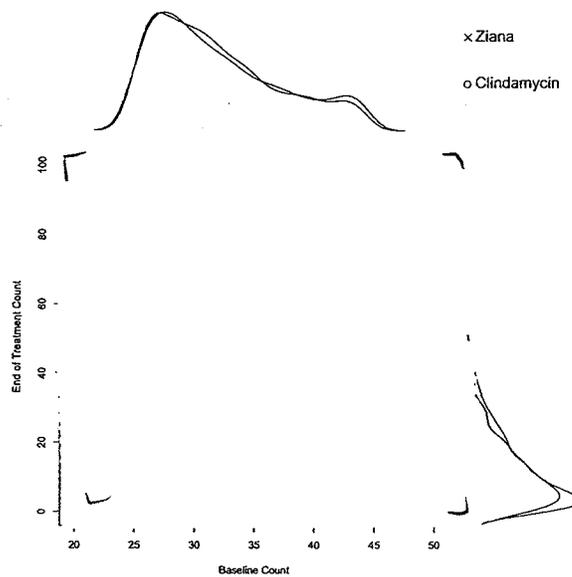
The efficacy results for percent change in non-inflammatory and inflammatory lesion counts is presented in Table 7. Based on ANOVA with terms for treatment and pooled site the table shows convincing statistical evidence that ZianaTM Gel is superior to Clindamycin Gel for both inflammatory and non-inflammatory lesion counts. Note that while Table 7 reports only the p-value from ANOVA the p-value for the Cochran-Mantel-Haenszel Row Mean Score Statistic is also < 0.001 (sponsor's results).

Figure 1: Non-Inflammatory Lesions



b(4)

Figure 2: Inflammatory Lesions



b(4)

Table 7: Percent Change in Lesion Counts (ITT)

	Ziana TM Gel (N = 1008)	Clindamycin Gel (N = 1002)
Non-inflammatory Lesions		
Mean (SD)	49.8 (37.1)	41.3 (38.6)
p-value [†]	-	< .001
Inflammatory Lesions		
Mean (SD)	60.9 (35.8)	54.8 (38.0)
p-value [†]	-	< .001

[†] Source: Reviewer's analysis using ANOVA with terms for treatment and pooled site

3.1.6 Primary Endpoint Results (PP)

The per protocol population (PP) is defined as all subjects who complete 12 weeks of treatment and who do not have any noteworthy protocol violations. The SAP states that subjects excluded from the PP population were identified prior to database lock. A summary of the sponsor's efficacy results for the PP population can be found in Table 14.2.1.2 of the study report which are consistent with those reported below.

3.1.6.1 Investigator's Global Assessment Note that one of the exclusion criteria from the PP population was if the visit occurred outside the treatment window. Consequently one does not have to distinguish between a 'as recorded' and 'windowed' analysis as was done with the ITT population. Table 8 depicts the IGA efficacy results for the PP population. In the PP population a larger treatment effect can be seen than in the ITT population, $\delta = 8.3$ and $\delta = 6.8$, respectively. The CMH analysis stratified by pooled investigative site shows a highly significant result demonstrating the superiority of ZianaTM Gel to Clindamycin Gel on the basis of the IGA.

3.1.6.2 Lesion Counts Table 9 depicts the efficacy results for the percent change in inflammatory and non-inflammatory lesion counts. Consistent with results seen in the ITT population, ZianaTM Gel is superior to Clindamycin Gel on the basis of the percent change in lesion counts.

Table 8: IGA Efficacy Results for Ziana™ Gel (PP)

	Ziana™ Gel (N = 727)	Clindamycin Gel (N = 718)
Success (%)	357 (49.1)	293 (40.8)
p-value†	-	< .001

† Source: Reviewer's Analysis using CMH stratified by pooled site.

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Table 9: Percent Change in Lesion Counts (PP)

	Ziana™ Gel (N = 727)	Clindamycin Gel (N = 718)
Non-inflammatory Lesions		
Mean (SD)	55.8 (34.8)	48.0 (36.7)
p-value†	-	< .001
Inflammatory Lesions		
Mean (SD)	67.0 (31.4)	61.2 (34.0)
p-value†	-	< .001

† Source: Reviewer's analysis using ANOVA with terms for treatment and pooled site

3.1.7 Sensitivity Analysis of IGA

Efficacy assessments based on the ITT and PP result in statistically convincing evidence that Ziana™ Gel is superior to Clindamycin Gel for both co-primary endpoints. As the results are so convincing the only sensitivity analysis reported and included in the review is to examine the method of data imputation for the IGA only.

As pre-specified in the protocol, as a sensitivity analysis, all subjects with a missing IGA at week 12 are imputed as failures. In review of the SPA the Agency also requested to impute all missing IGA at week 12 as successes to ensure efficacy results are not driven by the method of imputation. Results for each of the imputation strategies is provided in Table 10. Note that the sensitivity analysis of imputing as all failures is equivalent to the ITT 'windowed' analysis. Both of the sensitivity analyses are consistent with the primary and supportive analyses demonstrating the superiority of Ziana™ Gel to Clindamycin Gel.

Table 10: IGA Efficacy Results for Ziana™ Gel (Sensitivity)

	Failures [†]		Successes [†]	
	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)
Success (%)	381 (37.8)	318 (31.7)	548 (54.4)	481 (48.0)
p-value [†]	-	0.0018	-	< .001

[†] Missing IGA imputed as either failure or success.

Source: Reviewer's Analysis using CMH stratified by pooled site.

3.1.8 Secondary Endpoint Results

No secondary endpoints were listed in the protocol for the resubmission to the NA letter received. Further, the proposed label does not contain any efficacy claims for any secondary endpoints.

3.2 Evaluation of Safety

3.2.1 Adverse Events

Adverse events listed according to system organ classification (SOC) and preferred term are provided in Table 11 for AE's which fall under an SOC in at least 0.5% of subjects and in which the AE is listed by the investigator as at least possibly related to treatment by the investigator. The most common AE's occur for the skin and subcutaneous tissue disorders class. Within this class the most reported AE is dry skin. In general Ziana™ Gel has a higher incidence of

AE's reported for the two SOC's listed in Table 11, and specifically a higher number of subjects reporting dry skin.

Table 11: All AEs listed by System Organ Class

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)
Skin and subcutaneous tissue disorders	34 (3.4)	14 (1.4)
Dry Skin	23 (2.3)	6 (0.6)
Rash scaly	7 (0.7)	1 (0.1)
Skin burning sensation	4 (0.4)	1 (0.1)
Erythema	4 (0.4)	0 (0.0)
Pruritus	3 (0.3)	1 (0.1)
Skin exfoliation	3 (0.3)	0 (0.0)
Rash	2 (0.2)	0 (0.0)
Skin tightness	0 (0.0)	2 (0.2)
General disorders and administration site conditions	7 (0.7)	0 (0.0)
Application site reaction	3 (0.3)	0 (0.0)
Pain	2 (0.2)	0 (0.0)
Application site swelling	1 (0.1)	0 (0.0)
Feeling hot	1 (0.1)	0 (0.0)

Source: Reviewer's Analysis. Subjects are counted only once per row.

3.2.2 Serious Adverse events

Five serious adverse events were reported in the 2010 subjects. Table 12 depicts the five subjects and the serious AE by preferred term. Note that none of the investigators recorded the serious AE's as being related to study drug.

Table 12: Serious AEs by Preferred Term

ID	Preferred Term	Treatment	Severity	Related
12030	Intentional self-injury	Ziana™ Gel	Moderate	Unrelated
13013	Abdominoplasty	Clindamycin Gel	Severe	Unrelated
35028	Dermoid cyst	Clindamycin Gel	Severe	Unlikely
45023	Depression	Ziana™ Gel	Severe	Unrelated
53025	Tonsillitis	Clindamycin Gel	Severe	Unrelated

Source: Reviewer's Analysis.

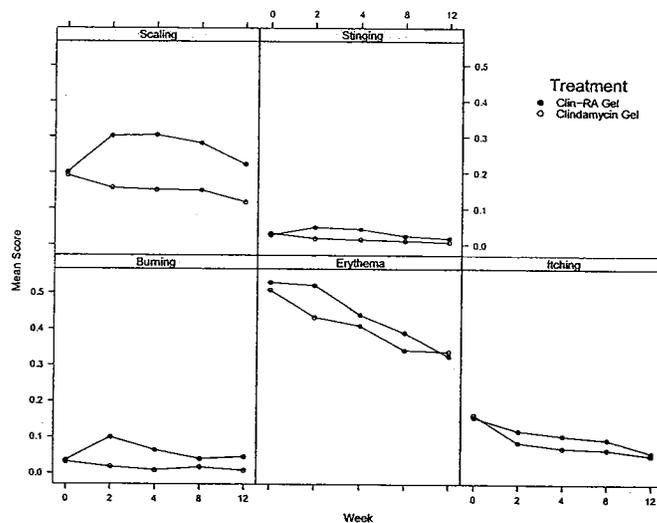
3.2.3 Local Skin Safety

Five local skin parameters: burning, erythema, itching, scaling, and stinging were recorded at each visit by the site investigator using the four-point scale shown below.

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

For each investigator recorded parameter the mean was calculated at each of the visits and shown in Figure 3. The figure shows that subjects tended to have some erythema at the start of the trial and this decreased during the treatment portion of the trial for both Ziana™ Gel and Clindamycin Gel. The only parameter that shows some worsening during the trial is scaling for subjects applying Ziana™ Gel. Otherwise the ratings on the local skin parameters tended to stay the same for the start of the trial through to the end of treatment for both Ziana™ Gel and Clindamycin Gel.

Figure 3: Local Skin Symptoms Over Time



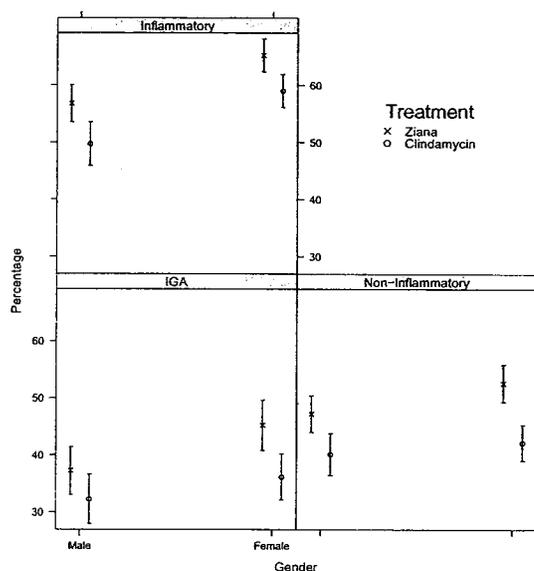
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The following section contains graphics of the efficacy by subgroups. Tabular results are provided in the Appendix Section A.3 on page 26. Each of the figures use percentage as a label for the y-axis which corresponds to percent change for the lesion counts and percent success for IGA.

4.1 Gender, Race, and Age

Figure 4 depicts efficacy results by gender along with unadjusted 95% confidence intervals for the mean. For all endpoints Ziana™ Gel showed an increase in efficacy over Clindamycin Gel. For each of the endpoints, the response rates were higher in female subjects than in male subjects for both treatment arms. Further, the treatment effects for the dichotomized IGA and percent change in inflammatory lesion appears to be slightly higher in females than in males.

Figure 4: Efficacy Results by Gender



Rather than look at efficacy by race, Figure 5 on the following page depicts efficacy by Fitzpatrick Skin Type (FST). FST classifies skin according to pigment where I = lightest and VI = darkest skin type. FST was also used to stratify the enrollment as the sponsor stated in the dispute resolution that darker skin types would be harder to establish efficacy. Response rates for each of the treatment arms is quite consistent across all values of FST for each endpoint which shows higher efficacy in Ziana™ Gel than Clindamycin Gel.

The quartiles of age were calculated and Figure 6 on the following page depicts efficacy results by age quartile. Response rates for Ziana™ Gel and Clindamycin Gel are quite similar across age quartile for all endpoints with Ziana™ Gel showing increased response rates over Clindamycin Gel.

4.2 Other Special/Subgroup Populations

No other special subgroups were examined.

Figure 5: Efficacy Results by Fitzpatrick Skin Type

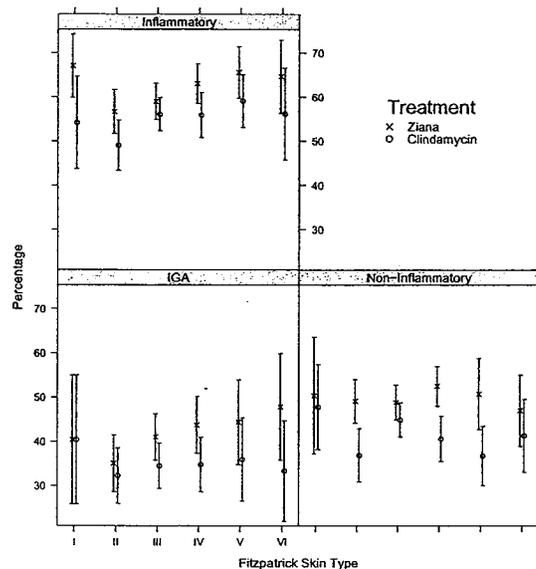
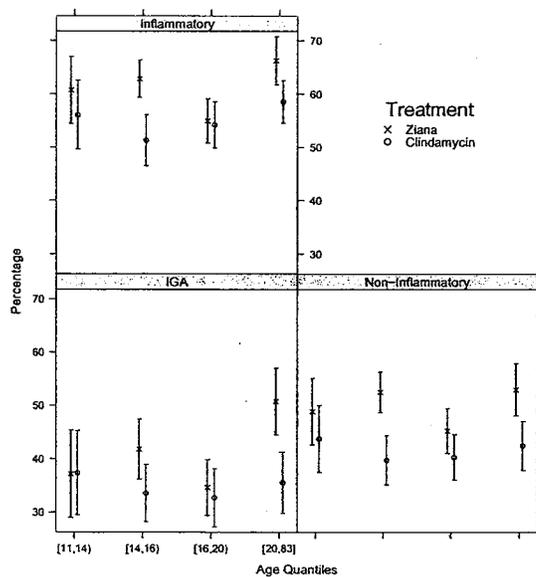


Figure 6: Efficacy Results by Age Quartiles



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As the Not Approvable (NA) letter specified that the clinical trials failed to establish the contribution of tretinoin to the combination product, the sponsor proposed to conduct a two arm trial including treatments arm Ziana™ Gel and Clindamycin Gel. The Agency stated that the above two arm study should be acceptable to establish the contribution of tretinoin to the combination drug product.

Study MPI-02 enrolled subjects with moderate to severe acne (IGA=3 or 4) on a six point IGA scale (0=clear to 5-very severe), 20-50 inflammatory lesions, and 20-100 non-inflammatory lesions. The sponsor's success criteria for the IGA is defined as clear, almost clear, or a two grade improvement. It should be noted that with enrollment of subjects with an IGA of 3 or 4 such a definition reduces to a two grade improvement which is consistent with the draft Acne Guidance.

Study MPI-02 enrolled 2010 subjects and efficacy results demonstrate that Ziana™ Gel is superior to Clindamycin Gel for both co-primary endpoints. Efficacy results are shown in Table 13 for IGA success, inflammatory lesions, and non-inflammatory lesions; total lesions is excluded since both inflammatory and non-inflammatory lesion counts are significant which implies total lesions is also significant. The safety profiles of Ziana™ Gel and Clindamycin Gel are similar with a slightly higher percentage of subjects receiving Ziana™ Gel reporting adverse events related to skin and subcutaneous tissue disorders.

5.2 Conclusions and Recommendations

The initial NDA was submitted on February 6, 2004 and in response to this application a Not Approvable (NA) letter was issued to the sponsor on 12/07/2004 citing, "The contribution to efficacy of each component of your combination product was not adequately demonstrated. Specifically the contribution of tretinoin to efficacy was not adequately demonstrated." In response to the NA letter the sponsor also appealed the decision via formal dispute resolutions to the Office of Drug Evaluation V (ODE V) and later to the Office on New Drugs (OND) based upon the denial of the sponsor's request from ODE V. On 11/03/2005 Dr. John Jenkins, Director of OND, denied the sponsor's request and concurred with the Division of Dermatology and Dental Products that the sponsor failed to establish the contribution of tretinoin in their combination product.

In May of 2005 the sponsor submitted a special protocol assessment (SPA) proposing to conduct an additional Phase 3 study with two arms; Ziana™ Gel and Clindamycin Gel. In response to this SPA the Agency agreed to allow the sponsor to conduct an additional two arm study to establish the contribution of tretinoin to the combination product (i.e. a two arm study

Table 13: Primary Efficacy Results for Study MPI-02 (ITT)

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)
Investigator's Global Assessment		
Success (%)	415 (41.2)	345 (34.4)
p-value ¹	-	< .001
Non-inflammatory Lesions		
Mean (SD)	49.8 (37.1)	41.3 (38.6)
p-value ²	-	< .001
Inflammatory Lesions		
Mean (SD)	60.9 (35.8)	54.8 (38.0)
p-value ²	-	< .001

¹ CMH stratified by center.

² ANOVA with terms for treatment and pooled site.

Source: Reviewer's analysis.

with Ziana™ Gel and Clindamycin Gel).

The resubmission submitted on 05/06/2006 contains the results of the Phase 3 study with two arms enrolling approximately 1000 subjects on each arm. Efficacy was based upon the co-primary endpoints; percent reduction in two out of three lesions counts (inflammatory, non-inflammatory, and total) and dichotomized success (two grade improvement) on an investigator global assessment scale. For each endpoint, Ziana™ Gel was statistically superior to Clindamycin Gel, (all $p < 0.001$) establishing the contribution of tretinoin to the combination product.

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APPENDIX

A.1 Summary of Previous Clinical Trials

The results reported in this section are obtained from the statistical review of the initial NDA submission performed by Dr. Shiojwen Lee and signed in DFS on October 14, 2004. Note that in Dr. Lee's review the combination drug uses the tradename ClinRA Gel whereas the current tradename is ZianaTM Gel.

A.1.1 Study Design

ZianaTM Gel was assessed in two 12-week prospective, multi-center, randomized, double-blind, Phase 3 trials (Studies 06 and 07) in subjects 12 years and older which compared ZianaTM Gel to clindamycin in the vehicle gel, tretinoin in the vehicle gel, and the vehicle gel alone. These Phase 3 trials enrolled a total of 2540 subjects with mild, moderate, and severe acne according to the Investigator Global Assessment (IGA). The co-primary endpoints were:

1. Mean percent change from baseline at week 12 in two out of three lesion counts.
 - Inflammatory
 - Non-inflammatory
 - Total
2. Percent of subjects with an IGA rating of clear or almost at week.

A.1.2 Results

A.1.2.1 Investigator's Global Assessment In the two Phase 3 trials conducted for the initial NDA submission, treatment success was defined as being either clear (IGA=0) or almost clear (IGA=1). Results from the primary analysis are shown in Table 14. Both Study 06 and Study 07 failed to show that ZianaTM Gel is statistically superior to Clindamycin Gel on the basis of the IGA at the $\alpha = 0.05$ level.

A.1.2.2 Lesion Counts Tables 15 and 16 depict the percent reduction in lesion counts from the two Phase 3 trials in the initial NDA submission. The percent reduction is defined as

$$100 \times \frac{\text{base} - \text{eot}}{\text{base}}, \text{ where}$$

base=baseline lesion count and eot=end of treatment lesion count. Thus, positive values of the percent reduction correspond to a reduction in lesions. Neither Clindamycin Gel or tretinoin Gel were statistically superior to Clindamycin Gel for non-inflammatory lesions in study 07, however both did win on two of three lesion counts.

Table 14: Efficacy based on Investigator Global Assessment (ITT)

Study 06				
	Ziana™ (N = 420)	Clindamycin (N = 208)	Tretinoin (N = 417)	Vehicle (N = 207)
Success ¹ (%)	88 (21%)	34 (16%)	64 (15%)	18 (9%)
P-value ²	-	0.172	0.032	< 0.001
Study 07				
	Ziana™ (N = 425)	Clindamycin (N = 218)	Tretinoin (N = 429)	Vehicle (N = 216)
Success ¹ (%)	97 (23%)	38 (17%)	63 (15%)	17 (8%)
P-value ²	-	0.094	0.002	< 0.001

¹ Success is defined as IGA = 0 (clear) or 1 (almost clear).

² P-values are based on Cochran-Mantel-Haenszel test stratified on center.

Table 15: Efficacy based on Lesion Counts (ITT) Study 06

	Ziana™ (N = 420)	Clindamycin (N = 208)	Tretinoin (N = 417)	Vehicle (N = 207)
Non-Inflammatory Lesions				
Mean	37.6	24.1	31.9	13.5
P-value ¹	-	< 0.001	0.018	< 0.001
Inflammatory Lesions				
Mean	46.0	39.7	37.5	19.6
P-value ¹	-	0.028	< 0.001	< 0.001
Total Lesions				
Mean	41.4	31.3	34.7	16.5
P-value ¹	-	< 0.001	0.001	< 0.001

¹ P-values are based on ANOVA with terms for treatment, center, and treatment by center interaction.

Table 16: Efficacy based on Lesion Counts (ITT) Study 07

	Ziana TM (N = 425)	Clindamycin (N = 218)	Tretinoin (N = 429)	Vehicle (N = 216)
Non-Inflammatory Lesions				
Mean	35.7	30.1	29.9	18.5
P-value ¹	-	0.088	0.110	< 0.001
Inflammatory Lesions				
Mean	50.6	43.6	40.1	31.7
P-value ¹	-	0.020	< 0.001	< 0.001
Total Lesions				
Mean	41.8	35.9	34.2	23.2
P-value ¹	-	0.018	0.002	< 0.001

¹ P-values are based on ANOVA with terms for treatment, center, and treatment by center interaction.

A.2 Demographic Table

Table 17 provides results of the demographic comparisons of ZianaTM Gel and Clindamycin Gel. Note that FST corresponds to Fitzpatrick Skin Type which classifies skin according to its pigment: I being the lightest and VI being the darkest.

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Table 17: Demographic Factors by Treatment

	Ziana™ Gel (N = 1008)	Clindamycin Gel (N = 1002)	Test Statistic
Age	14 16 19	14 16 20	$F_{1,2008} = 0, P = 0.949^1$
FST : Phototype I	5% (47)	5% (47)	$\chi_5^2 = 0.03, P = 1^2$
Phototype II	21% (214)	21% (214)	
Phototype III	34% (341)	34% (339)	
Phototype IV	23% (231)	23% (230)	
Phototype V	11% (106)	10% (103)	
Phototype VI	7% (69)	7% (69)	
Gender : Female	49% (493)	55% (547)	$\chi_1^2 = 6.5, P = 0.0108^2$
Race : Caucasian	76% (765)	76% (758)	$\chi_4^2 = 0.35, P = 0.986^2$
African-American	10% (102)	10% (97)	
Asian	2% (25)	3% (28)	
Hispanic	10% (100)	10% (103)	
Other	2% (16)	2% (16)	

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies. Tests used:

¹Wilcoxon test; ²Pearson test

A.3 Efficacy by Subgroup Tables

The following tables supplement the figures in Section 4.1.

Table 18: Efficacy Results by Gender

	Investigator Global		Non-Inflammatory		Inflammatory	
	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel
Male	37.3% $\frac{192}{515}$	32.3% $\frac{147}{455}$	27.0 (23.3)	30.5 (23.9)	13.7 (12.4)	16.7 (14.8)
Female	45.2% $\frac{223}{493}$	36.2% $\frac{198}{547}$	22.6 (19.5)	27.4 (21.2)	10.1 (9.6)	12 (10.9)

Results for the IGA are percent success (2 grade improvement) followed by the fraction of the number of successes. Results for lesion counts are means followed by standard deviations in parentheses.

Source: Reviewer's Analysis

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Table 19: Efficacy Results by Fitzpatrick Skin Type

	Investigator Global		Non-Inflammatory		Inflammatory	
	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel
I	40.4% $\frac{19}{47}$	40.4% $\frac{19}{47}$	20.6 (20.7)	20.4 (15.6)	10.5 (7.7)	15.8 (14.4)
II	35.0% $\frac{75}{214}$	32.2% $\frac{69}{214}$	24.3 (20.2)	30.3 (23.3)	13.8 (12.5)	16.5 (14.4)
III	41.1% $\frac{140}{341}$	34.5% $\frac{117}{339}$	25.0 (22.1)	28.4 (23.6)	12.7 (12.3)	13.8 (12.2)
IV	43.7% $\frac{101}{231}$	34.8% $\frac{80}{230}$	24.2 (21.4)	28.0 (21.7)	11.1 (10.4)	13.6 (13.6)
V	44.3% $\frac{47}{106}$	35.9% $\frac{37}{103}$	24.8 (22.3)	31.6 (22.3)	9.7 (8.5)	11.7 (8.8)
VI	47.8% $\frac{33}{69}$	33.3% $\frac{23}{69}$	31.1 (23.3)	30.6 (21.2)	9.7 (10.1)	13.3 (14.0)

Results for the IGA are percent success (2 grade improvement) followed by the fraction of the number of successes. Results for lesion counts are means followed by standard deviations in parentheses.

Source: Reviewer's Analysis

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Table 20: Efficacy Results by Age Quartiles

	Investigator Global		Non-Inflammatory		Inflammatory	
	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel	Ziana™ Gel	Clindamycin Gel
[11,14)	37.2% $\frac{51}{137}$	37.4% $\frac{55}{147}$	25.9 (20.9)	31.6 (26.2)	11.6 (11.4)	14.2 (14.3)
[14,16)	41.9% $\frac{126}{301}$	33.6% $\frac{100}{298}$	26.8 (24.1)	32.3 (24.3)	12.0 (10.6)	15.9 (14.5)
[16,20)	34.7% $\frac{111}{320}$	32.8% $\frac{94}{287}$	27.0 (22.0)	28.2 (21.0)	13.8 (11.9)	14.7 (13.2)
[20,83]	50.8% $\frac{127}{250}$	35.6% $\frac{96}{270}$	19.3 (17.1)	24.1 (18.9)	9.5 (10.7)	11.6 (9.7)

Results for the IGA are percent success (2 grade improvement) followed by the fraction of the number of successes. Results for lesion counts are means followed by standard deviations in parentheses.

Source: Reviewer's Analysis

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: October 5, 2006

Statistical Team Leader: Mohamed Alesh, Ph.D.

cc:

Archival NDA

DDDP/Walker

DDDP/Luke

DDDP/Carr

DDDP/Jain

OBIO/O'Neill

OBIO/Patrician

DB3/Wilson

DB3/Alesh

DB3/Soukup

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/s/

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Mohamed Alesh
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Concur with review

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STATISTICAL REVIEW AND EVALUATION FILEABILITY REVIEW

NDA Number: 50-802
Drug Name: Clin RA Gel
Applicant: Dow Pharmaceutical Sciences, Inc.
Indication: Acne
Filing Date: 07/20/2006
Fileability Meeting Date: 06/06/2006
User Fee Date: 11/06/2006
Received for Stat Review: 05/10/2006
Statistical Reviewer: Mat Soukup, Ph.D., DBIII
Medical Officer: Brenda Carr, M.D., DERM-DENTAL
Project Manager: Shalini Jain, DERM-DENTAL

1 ORGANIZATION AND DATA REPRESENTATION

1. Is there a comprehensive table of contents with adequate indexing and pagination?
Yes, table of contents is listed in amendtoc.pdf
2. Are the original protocols, protocol amendments, and proposed label provided?
Yes, protocols and amendments are submitted (Section 16.1). It doesn't appear a new label is submitted or whether the sponsor plans to use the label submitted in the original submission.
3. Are the following tables/listings provided in each study report?
 - (a) Patient profile listings by center for all enrolled subjects.
Results by center can be ascertained by electronic data sets.
 - (b) Discontinued subject tables by center (includes reason and time of loss).
The table is not provided by center, however, this is possible with the electronic data.
 - (c) Subgroup analysis summary tables (gender, race, age, etc.).
Yes this is provided for baseline IGA, gender, race, age, and skin type.
 - (d) Adverse event listings by center and time of occurrence.
No adverse events by center or time of occurrence. However, such assessments can be made using AE.XPT.
4. Have the data been submitted electronically?
 - (a) Has adequate documentation of the data sets been provided?
Yes.

- (b) Do the data appear to accurately represent the data described in the study reports?
At this time, results in the study reports cannot be verified; requesting resubmission of the data.
- (c) Can the data be easily merged across studies and indications?
For the most part, the variable PTID is the unique patient ID which can be used to merge data sets.

2 STATISTICAL METHODOLOGY

1. Are all primary efficacy studies of appropriate design to meet basic approvability requirements within current Division policy or to the extent agreed upon previously with the sponsor by the Division?
Yes, the design is consistent with the Agency's comments on the protocol submitted for Special Protocol Assessment.
2. For each study, is there a comprehensive statistical summary of the efficacy which covers the intent-to-treat population and per protocol population?
The single study contains such information.
3. Based on the summary analyses of each study:
- (a) Are the analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims)?
Analysis of the percent change in lesion counts is presented using the Cochran-Mantel-Haenszel Mean Score statistic. This differs from the SPA in which the analysis of percent change was to be performed using ANOVA.
- (b) Are the intent-to-treat and per protocol patient analyses properly performed?
The definitions of ITT and PP appear to be consistent with the protocol definitions submitted to the SPA.
- (c) Has missing data been appropriately handled?
Primary analysis methods states the ITT population will be used and missing data will be imputed using LOCF. Yet, it appears the sponsor is defining the primary analysis method of Evaluator Global Static Scale (EGSS) imputing all missing week 12 data (end of treatment) as failures if no data were recorded at week 12.
- (d) Have multiplicity issues (regarding endpoints, timepoints, or dose groups) been adequately addressed?
NA
- (e) If interim analyses were performed, were they planned in the protocol and appropriate significance level adjustments made?
NA

4. Were sufficient and appropriate references included for novel statistical approaches?

NA

5. Are all pivotal studies complete?

Yes.

6. Has the safety data been comprehensively and adequately summarized?

Yes.

3 FILEABILITY CONCLUSIONS

From a statistical perspective this submission, or indications therein, *is* reviewable with moderate further input from the sponsor.

4 74-DAY LETTER COMMENTS

Filing Issues

1. Based upon the primary analysis data set (AD_OPV.XPT) submitted, the reviewer was not able to reproduce the sponsor's results as reported in the study report for Study 1501-02.
2. Per the SPA, analysis of the percent change in lesion counts was planned to use ANOVA with terms for treatment and pooled center. In addition a sensitivity analysis was planned to ensure efficacy results were not driven by extreme centers. However, the current submission states analysis of the percent change in lesion counts will be based on the Cochran-Mantel-Haenszel Mean Score statistic. Further, the study report does not include a sensitivity analysis to examine the effect of any influential center(s).
3. The SPA defined the primary analysis of the multiple endpoints to be based on the ITT population imputing missing data by the LOCF approach which the Agency concurred. However, the study reports define the primary analysis of dichotomized EGSS to be based upon treating all subjects with no week 12 data as EGSS failures.
4. The protocol submitted to the SPA provided an algorithm to pool small centers, defined as centers that fail to recruit at least 8 subjects per treatment arm. However, the data sets do not appear to provide a variable corresponding to pooled sites.
5. A proposed label was not found in the submission.

To address the above filing issues and to facilitate the review, the Agency requests the following information.

1. The Agency requests the sponsor submit the data in the following format which is similar to that of AD_OPV.XPT.

- For each subject the following variables should always be recorded and never be recorded as missing:
 - PTID: patient ID; please use the nomenclature used in the EFFICACY.XPT and DEMO.XPT data sets.
 - site: investigator site number
 - visit: 1 through 6 corresponding to the screening visit through the visit at week 12.
 - * Note that if the screening visit (visit 1) and the baseline visit (visit 2) are the same, all data values for visit 1 and visit 2 should be the same (i.e. no missing should be recorded).
 - trtxt: treatment assigned; same values as included in AD_OPV.XPT
 - itt: 1 = ITT evaluable, 0 = not ITT evaluable
 - pp: 1 = PP evaluable, 0 = not PP evaluable
 - visitflag: 1 = visit was on time \pm protocol defined window, 0 = visit was not on time.
- The following variables should be recorded based on observed data and in the case a subject did not attend the visit or the variable was not recorded, the data should be recorded as missing. Note that the nomenclature is much the same as used in AD_OPV.XPT.
 - inf_bsl: inflammatory lesion count at baseline
 - inf_obs: observed inflammatory lesion count
 - inf_cbsl: change in inflammatory lesion counts from baseline
 - inf_pbsl: percent change in inflammatory lesion counts from baseline.
 - non_bsl: non-inflammatory lesion count at baseline
 - non_obs: observed non-inflammatory lesion count
 - non_cbsl: change in non-inflammatory lesion counts from baseline
 - non_pbsl: percent change in non-inflammatory lesion counts from baseline.
 - tot_bsl: total lesion count at baseline
 - tot_obs: observed total lesion count
 - tot_cbsl: change in total lesion counts from baseline
 - tot_pbsl: percent change in total lesion counts from baseline.
 - egss_bsl: EGSS at baseline
 - egss_obs: observed EGSS
 - egss_cbsl: change in EGSS from baseline
 - visitdt: date of visit

- trtdur: treatment duration= current visit - baseline visit + 1
- When imputing missing values, new variables may be recorded similarly to those used in AD_OPV.XPT. Please provide adequate documentation for how the imputation was carried out.
 - Example for LOCF: locf_inf, locf_non, locf_tot, and locf_egss
 - Sensitivity analysis 1: sens1_inf, sens1_non, sens1_tot, sens1_egss.
 - Sensitivity analysis 2: sens2_inf, sens2_non, sens2_tot, sens2_egss.
 - Note that variables for changes from baseline can also be provided that incorporate missing data.
 - * For example: locf_egss_cbsl
- 2. The sponsor should provide results of the percent change in lesion counts using ANOVA as agreed upon in the SPA along with the sensitivity analysis for examining the effect of influential sites as provided in the protocol submitted to the SPA.
- 3. Per the SPA and prior Agency concurrence, the primary efficacy analysis of dichotomized EGSS will be based upon the ITT population imputing missing data with the LOCF approach. Please submit such information to the NDA.
- 4. In addition to the variables requested above, the data set should also include a variable for pooled sites which follows the algorithm provided in the SPA. Analyses of the primary endpoints should be conducted which includes a term for pooled site.
- 5. Please provide a copy of the proposed label.

Mat Soukup, Ph.D.
Mathematical Statistician, Biometrics 3

Concur: Mohamed Alesh, Ph.D.
Team Leader, Biometrics 3

Cc:
Orig. NDA 50,802/SN000
DERM-DENTAL/Walker
DERM-DENTAL/Luke
DERM-DENTAL/Carr
DERM-DENTAL/Jain
OBIO/O'Neill
OBIO/Patrician
DBIII/Wilson

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Drug Name: Clin RA Gel
Indication: Acne Vulgaris
NDA: 50-802

DBIII/Alosh
DBIII/Soukup

June 7, 2006

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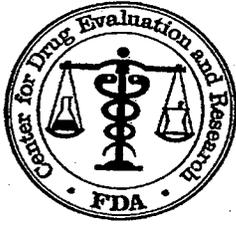
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Mohamed Alesh
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-739/N000

Drug Name: Clin-RA Gel (1.2% Clindamycin phosphate, 0.025% Tretinoin)

Indication(s): Acne vulgaris

Applicant: Dow Pharmaceutical Sciences

Dates:

Submitted:	February 6, 2004
Received:	February 9, 2004
User fee:	December 9, 2004
Review completion:	September 13, 2004

Review Status: Standard

Biometrics Division: Division of Biometrics III (HFD-725)

Statistics Reviewer: Shiohjen Lee, Ph.D.

Concurring Reviewers: Mohamed Alos, Ph.D.

Medical Division: Dermatologic and Dental Drug Products (HFD-540)

Clinical Team: Brenda Carr, M.D.

Project Manager: Jacquelyn Smith

Keywords: Combination drug, superiority, inflammatory, non-inflammatory and Evaluator's global severity score.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two pivotal trials (7001-G2HP-06-02 and 7001-G2HP-07-02, denoted as studies 06 and 07) were evaluated for the efficacy claim of Clin-RA Gel in the treatment of acne vulgaris. The overall superiority efficacy claim of Clin-RA Gel to Clindamycin, Tretinoin and its vehicle is supported for each of the trials in terms of lesion reduction from baseline to week 12. Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage of patients having an Evaluator's Global Severity score of 0 or 1 (clear or almost clear) at week 12. However, the superiority of Clin-RA Gel to Clindamycin is not established in both pivotal trials.

1.2 Brief Overview of Clinical Studies

The study drug product Clin-RA Gel is a combination drug of Clindamycin phosphate 1.2% and Tretinoin 0.025% for the indication of acne vulgaris. The dosing studied was once daily applied to the face before bedtime for 12 weeks. The drug dosage was based on currently approved labeling for products containing Clindamycin phosphate 1.2% (Clindagel™) and Tretinoin 0.025% (Retin-A® 0.025% Gel). No dose ranging studies were conducted for Clin-RA Gel during the sponsor's drug development stage.

For the efficacy claim of Clin-RA Gel, results of two pivotal trials 06 and 07 were submitted. The two studies were identically designed and were conducted in the U.S. during January 2003 and October 2003. Totals of 1,252 and 1,288 patients were enrolled from 28 and 32 sites for studies 06 and 07, respectively. The enrolled patients were randomized in an allocation ratio of 2:1:2:1 to receive Clin-RA Gel, Clindamycin, Tretinoin and gel vehicle. The randomization resulted in 420, 208, 417 and 207 patients in the respective group for study 06; while 425, 218, 429 and 216 patients for study 07. The treatment duration was 12-week. The time point for efficacy assessment was at week 12.

1.3 Statistical Issues and Findings

Statistical Issues

Per the Division's recommendation on the co-primary efficacy endpoint, the treatment success of EGS is defined as clear or almost clear in the EGS score at week 12.

The primary statistical issue for the sponsor's pivotal studies 06 and 07 is that the sponsor did not power the studies based on the treatment success rate of EGS score at the IND stage. The Division had made comments about this point at the EOP-2 Meeting (dated 12/16/02) and IND 65,531/SN-006. The sponsor was aware that it was their risk to proceed with their planned power calculations. This was documented in the Division's comments to the sponsor dated 3/27/03.

Sponsor's results of studies 06 and 07 demonstrate the efficacy of Clin-RA Gel in the lesion reduction; however, the superiority of Clin-RA Gel to Clindamycin is not established with respect to the treatment success rate of the EGS score in both pivotal trials (p-value = 0.172 and 0.094 for studies 06 and 07, respectively).

Statistical Findings

The sponsor in this submission presented results for two pivotal studies (06 and 07) in support of the efficacy and safety claim of Clin-RA Gel for the treatment of acne vulgaris. The dosing of Clin-RA Gel is once daily applied to the face before bedtime for 12 weeks. Results of the primary efficacy endpoints based on the ITT population with the last observation carried forward (LOCF) method for missing data are presented in Table E.1 for studies 06 and 07. In addition, results of the modified success rate are included in the table, where the modified success is defined as the percentage of patients with a score of 0 or 1 or had at least a 2-grade improvement in the EGS score.

Table E.1: Efficacy Results for Studies 06 and 07 (ITT)

Primary Endpoints	Study 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
Mean % Lesion Reduction Inflammatory	46.0%	39.7%	37.5%	19.6%
	NA	0.028	< 0.001	< 0.001
Non-inflammatory	37.6%	24.1%	31.9%	13.5%
	NA	< 0.001	0.018	< 0.001
Total	41.4%	31.3%	34.7%	16.5%
	NA	< 0.001	0.001	< 0.001
% of patients with EGS score of 0 or 1	88 (21%)	34 (16%)	64 (15%)	18 (9%)
	NA	0.172	0.032	< 0.001
Modified Success ¹ Rate	101 (24%)	38 (18%)	70 (17%)	20 (9.7%)
	NA	0.100	0.008	< 0.001
	Study 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
Mean % Lesion Reduction Inflammatory	50.6%	43.6%	40.1%	31.7%
	NA	0.020	< 0.001	< 0.001
Non-inflammatory	35.7%	30.1%	29.9%	18.5%
	NA	0.088	0.110	< 0.001
Total	41.8%	35.9%	34.2%	23.2%
	NA	0.018	0.002	< 0.001
% of patients with EGS score of 0 or 1	97 (23%)	38 (17%)	63 (15%)	17 (8%)
	NA	0.094	0.002	< 0.001
Modified Success ¹ Rate	118 (28%)	44 (20%)	83 (19%)	24 (11%)
	NA	0.030	0.003	< 0.001

¹ Modified success is defined as clear or almost clear or had at least a 2-grade improvement in the EGS score.
 For lesion reduction, p-value based on the ranked ANOVA analysis with terms of treatment, investigational group and treatment-by-investigational group interaction is reported. Success rates were analyzed based on Cochran-Mantel-Haenszel test adjusted for investigational group.

The following summarizes the efficacy results.

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Efficacy: (Studies 06 and 07)

- Study 06:
 - Clin-RA Gel is superior to Clindamycin, Tretinoin and vehicle in each type of lesion reduction from baseline to week 12.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA Gel to Clindamycin is not established (p-value = 0.172).
- Study 07:
 - Clin-RA Gel is superior to Clindamycin and to Tretinoin in inflammatory and total lesion reduction from baseline to week 12. The superiority is not established in the non-inflammatory lesion reduction. Clin-RA Gel is superior to its vehicle in each type of lesion reduction from baseline to week 12.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage of patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA to Clindamycin is not established (p-value = 0.094).
- The inclusion of patients with at least a 2-grade improvement in the EGS score to the success category warrants the superiority of Clin-RA to Clindamycin with respect to the modified success rate for study 07 (p-value = 0.030); however, not for study 06 (p-value = 0.100).
- Subgroup results suggest that
 - Female patients had higher responses than males (both lesion reduction and treatment success rate in the EGS score).
 - Patients older than 16 years of age had higher responses than younger patients (both lesion reduction and treatment success rate in the EGS score).

Safety:

With respect to the adverse event incidence, the safety profile of Clin-RA Gel is similar to that of Tretinoin based on studies 06 and 07 combined. The summary is:

- The overall adverse event incidence rate is comparable between Clin-RA and Tretinoin groups. They are slightly higher than those of Clindamycin and vehicle groups. The incidence rates were 27%, 24%, 27% and 22% for Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively. The treatment-related adverse event incidence rates were 4%, 1%, 4% and 2% in the respective group.
- A total of 20 patients had non-serious adverse events that resulted in a discontinuation from the trials. Thirteen of them had adverse events judged by investigators to be treatment-related (7, 1, 5 and 0 in Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively). Two patients had serious adverse events that resulted in study discontinuation (one each in Clin-RA and Tretinoin groups).
- The adverse event incidences occurred in at least 5% of patients were events related to respiratory, thoracic and mediastinal disorders (9%, 8%, 10% and 9% in the respective group), followed by skin and subcutaneous tissue disorders (7%, 4%, 8% and 4% in the respective group). For events related to skin and subcutaneous tissue disorders, Clin-RA and Tretinoin appear to have statistically higher incidence rates than Clindamycin (p-value = 0.052 and 0.024, respectively), and vehicle (p-value = 0.026 and 0.008, respectively).

In summary, Clin-RA Gel demonstrates the efficacy in the lesion reduction from baseline to week 12 in each of studies 06 and 07. Clin-RA Gel is superior to Tretinoin and vehicle with

respect to the Division's recommended co-primary efficacy endpoint, the treatment success rate which is defined as the percentage of patients with EGS score of 0 or 1 at week 12, for each of studies 06 and 07. However, the superiority of Clin-RA to Clindamycin with respect to treatment success according to EGS is not established. The inclusion of patients with at least a 2-grade improvement in the EGS score as successes warrants the superiority of Clin-RA to Clindamycin with respect to the modified success rate for study 07, but not for study 06. As the treatment success rates in Clindamycin and Tretinoin groups are similar, the ultimate problem that the superiority of Clin-RA to Clindamycin is not established statistically is the sample size/power calculations. The enrollment of Clindamycin arm was only about 50% of that of each of Clin-RA and Tretinoin groups for each study.

As safety profile of Clin-RA Gel was similar to that of Tretinoin and data in studies 06 and 07 did not suggest noteworthy safety concerns, it is the judgment of the reviewing medical division to decide whether the drug should be approved.

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2. INTRODUCTION

2.1 Overview

The proposed drug product Clin-RA Gel is a combination drug of Clindamycin phosphate 1.2% and Tretinoin 0.025% for the indication of acne vulgaris. Clindamycin phosphate 1.2% is expected to be effective in the treatment of inflammatory lesions, and Tretinoin 0.025% is thought to be effective in treating non-inflammatory lesions. Clin-RA Gel combines the two active ingredients that are expected to be effective in treating both the inflammatory and non-inflammatory lesions. The proposed dosing is topically once daily before bedtime for 12 weeks.

According to the sponsor, subject selection, selection of treatment duration, and dosages were based on the currently approved labeling for products containing Clindamycin phosphate 1.2% (ClindagelTM) and Tretinoin 0.025% (Retin-A[®] 0.025% Gel). Consequently, no dose ranging studies were conducted for Clin-RA Gel.

Two pivotal trials (7001-G2HP-06-02 and 7001-G2HP-07-02, denoted as studies 06 and 07 hereafter) were conducted to establish efficacy claims of Clin-RA Gel. The two studies were identically designed as multicenter, double blind, active- and vehicle-controlled and randomized. The treatment duration was 12-week. Since Clin-RA Gel is a combination drug, four treatment arms were included in each study to establish efficacy and to demonstrate the contribution of each active ingredient. The four treatment arms were Clin-RA Gel, Clindamycin 1.2%, Tretinoin 0.025%, and Clin-RA Gel vehicle. The efficacy objectives for each study were:

- Superiority of Clin-RA Gel to its vehicle with respect to the reduction from baseline in inflammatory and non-inflammatory lesion counts, and percentage of patients with clear or almost clear in Evaluator's Global Severity (EGS) score.
- Superiority of Clin-RA Gel to each of the monads (i.e., Clindamycin and Tretinoin) with respect to the reduction from baseline in two out of the three lesion counts (inflammatory, non-inflammatory and total); and percentage of patients with clear or almost clear in EGS score.

The overview of the two clinical studies is presented in Table 1.

Table 1: Overview of Pivotal Clinical Studies

Study	Study conducted Country (date)	Patients inclusion	Enrollment	Comments on treatments
06	U.S. (2/11/03 – 10/21/03)	Patients who were 12 years of age or older, with acne vulgaris, presenting 20-50 inflammatory lesions, 20-100 non-inflammatory lesions and ≤ 2 nodules.	Clin-RA: 420 Clindamycin: 208 Tretinoin: 417 Vehicle: 207	Once daily application to face for 12 weeks.
07	U.S. (1/30/03 – 10/20/03)	Patients who were 12 years of age or older, with acne vulgaris, presenting 20-50 inflammatory lesions, 20-100 non-inflammatory lesions and ≤ 2 nodules.	Clin-RA: 425 Clindamycin: 218 Tretinoin: 429 Vehicle: 216	Once daily application to face for 12 weeks.

2.2 Data Sources

The data analyzed in this review is based on the sponsor's electronic NDA submission dated 2/6/04 in the Electronic Document Room location of \\cdsesub1\n21739\n_000, and information request received on 4/19/04, 6/8/04 and 8/3/04.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Studies 06 and 07

Study Design

Studies 06 and 07 were identically designed as multicenter, double blind, active- and vehicle-controlled and randomized. The treatment duration was 12-week. The two studies were conducted in the U.S. during January 2003 and October 2003. Each study planned to enroll 1,200 patients from 32 study centers. The actual study enrollments were 1,252 and 1,288 patients from 28 and 32 sites in studies 06 and 07, respectively. The study entry criteria included 12 years of age or older, with acne vulgaris, presenting 20-50 inflammatory lesions, 20-100 non-inflammatory lesions and ≤ 2 nodules.

The enrolled patients were randomly assigned in an allocation ratio of 2:2:1:1 to Clin-RA, Tretinoin, Clindamycin and vehicle groups. The randomization resulted in 420, 417, 208 and 207 patients in the respective group for study 06; while 425, 429, 218 and 216 patients for study 07. Patients were instructed to apply assigned medication once daily to cleaned face prior to bedtime for 12 weeks. Clinical evaluation was assessed at baseline, weeks 2, 4, 8 and 12, with week 12 as the primary time point for efficacy assessment.

Randomization and Blinding

Sponsor's randomization procedure was computer-generated based on blocks of size 6. The lists were used for the labeling of study medication. Drug supplies were numbered sequentially in order. Blocks of drug supplies were shipped to study sites and were dispensed sequentially to the subjects entering the study within a study site.

A total of 1,200 randomization numbers were originally prepared as study planned on 10/14/02 for each study. The first patient was enrolled in studies 06 and 07, respectively, on 2/13/03 and 1/30/03. Due to a large enrollment, additional 288 randomization numbers were prepared in April 2003 for each study. The first patient using the additional generated randomization numbers was enrolled in the studies on 5/28/03. Following examining the sponsor's randomization lists, the treatment assignments of 6 (0.5%) and 11 (0.8%) patients in studies 06 and 07, respectively, were out of sequence. However, this is not expected to have a large impact on the efficacy results

The studies were conducted in a double blind way, as the study drugs were indistinguishable in appearance and packaged in 30-gram tubes. The packaging materials and labeling for all drug medications were identical. Neither investigator nor patients knew which drug they received.

Efficacy Endpoints Specified in the Protocol and Submission

For efficacy evaluation, the following endpoints were specified in the sponsor's protocols and submission.

- Primary:
 - Percent change from baseline to week 12 in inflammatory, non-inflammatory, and total lesion counts.
 - Percentage of patients with clear or almost clear in EGS score at week 12.
- Secondary efficacy endpoints included
 - Percent change from baseline to weeks 2, 4, and 8 in inflammatory, non-inflammatory, and total lesion counts.
 - Percentage of patients with clear or almost clear in EGS score at weeks 2, 4, and 8.

Each type of lesion number (inflammatory and non-inflammatory) was counted and recorded from the facial area. For the global evaluation of disease status, EGS scoring system based on the following 6-point scale was used for assessment at baseline, weeks 2, 4, 8 and 12.

0 = Clear; normal, clear skin with no evidence of acne vulgaris.

1 = Almost clear; rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red).

2 = Mild; some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions).

3 = Moderate; non-inflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion.

4 = Severe; inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions.

5 = Very severe; highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulo-cystic lesions.

In addition to the incidence of adverse events, severity and relationship of adverse events for safety evaluation, sponsor's safety parameters included cutaneous safety and tolerability evaluations. Cutaneous safety evaluation included scaling and erythema. The tolerability evaluation assessed itching, burning and stinging. Each of the parameters was evaluated based on a 4-point scale. The scoring systems for cutaneous safety evaluation as well as tolerability evaluation are described by the following tables.

Cutaneous safety evaluation			
Score	Severity	Scaling	Erythema
0	None	No scaling	No evidence of erythema present
1	Mild	Barely perceptible, fine scales present to limited areas of the face	Slight pink coloration
2	Moderate	Fine scale generalized to all areas of the face	Definite redness
3	Severe	Scaling and peeling of skin over all areas of the face	Marked erythema, bright red to dusky dark red in color

Tolerability Evaluation				
Score	Severity	Itching	Burning	Stinging
0	None	No itching	No burning	No stinging
1	Mild	Slight itching, not really bothersome	Slight burning sensation; not really bothersome	Slight stinging sensation, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome	Definite warm, burning sensation that is somewhat bothersome	Definite stinging sensation that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Population Analyzed in the Protocols and Submission

The intent-to-treat (ITT) and per-protocol (PP) populations were analyzed for efficacy, with the ITT analysis as the primary. Sponsor's ITT population included all randomized patients in the studies. Subjects were eligible for the PP analysis if they completed the 12-week evaluation without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).

Sponsor's safety population included all randomized patients who took at least 1 dose of study medication.

Statistical Analysis Plan in the Protocol and Submission

- For the lesion reduction from baseline (including inflammatory, non-inflammatory and total), percent change was the primary analysis and was based on the analysis of variance (ANOVA) with terms of treatment, investigational group, and treatment-by-investigational group interaction. The Zar's test was proposed at the Pre-NDA meeting (dated 10/1/03) and used in the NDA submission to examine the normality assumption of data. Sponsor performed both ANOVA and ranked ANOVA analyses.
- For the percentage of patients with clear or almost clear in the EGS score, the analysis was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigational group. The consistency of treatment response across investigational groups was investigated based on SAS PROC CATMOD procedure that fit a linear model to functions of response frequencies. The model included terms of treatment, investigational group, and treatment-by-investigational group interaction. The interaction was tested at a significance level of 0.10.
- The sponsor also submitted analyses of the percentage of patients who were clear or almost clear or showed at least a 2-grade improvement in the EGS score. The sponsor stated that patients who had severe or very severe EGS score at baseline should be considered as treatment success if they had at least a 2-grade improvement in the EGS score at week 12.
- The last observation carried forward (LOCF) method was proposed for imputing missing lesion counts. However, missing data in patients with clear or almost clear of EGS score were imputed as failures.

- The small-center pooling method pre-specified in the protocols was based on taking the investigator with the smallest enrollment and combining it with the investigator with the largest. If there was a further need to combine data, then the data of the investigator with the second smallest enrollment was combined with the investigator's data which had the second largest enrollment, and so on. The process continued for all investigators who did not have a minimum of 10 subjects per arm.

Based on this algorithm, study sites were pooled into 17 and 18 investigational groups for studies 06 and 07, respectively, which were used in the efficacy analyses. They are presented in the following:

Study 06		Study 07	
Group #: study site ID	Number of patients	Group #: study site ID	Number of patients
Group 1: 600	97	Group 1: 727	90
Group 2: 602	92	Group 2: 706	78
Group 3: 627	78	Group 3: 731	72
Group 4: 622	66	Group 4: 730	72
Group 5: 604	66	Group 5: 725	60
Group 6: 621	62	Group 6: 709, 728	58, 6
Group 7: 606	59	Group 7: 700, 713	55, 7
Group 8: 617, 624, 625	2, 55, 10	Group 8: 712, 720	54, 9
Group 9: 618, 619	54, 22	Group 9: 703, 707	52, 13
Group 10: 607, 610	26, 45	Group 10: 705, 718	51, 14
Group 11: 601, 614	47, 26	Group 11: 710, 723	21, 48
Group 12: 623, 628	46, 29	Group 12: 714, 715	48, 24
Group 13: 609, 630	29, 45	Group 13: 719, 729	46, 24
Group 14: 603, 616	45, 31	Group 14: 704, 722	27, 44
Group 15: 611, 629	33, 38	Group 15: 701, 717	47, 27
Group 16: 613, 626	35, 39	Group 16: 702, 716	29, 40
Group 17: 612, 620	36, 39	Group 17: 711, 721	39, 29
		Group 18: 708, 724, 726	39, 32, 33

- Fisher's exact test was used to compare the adverse event incidence rates between treatments.

Reviewer's Comments on Studies 06 and 07:

- In addition to the results of the percentage of patients with clear or almost clear in the EGS score at week 12, the sponsor submitted results for the percentage of patients with clear or almost clear or having at least a 2-grade improvement in the EGS score at week 12. In agreement with the clinical team, the co-primary endpoint is the percentage of patients with clear or almost clear in the EGS score at week 12.
- Per the Division's recommendation to the sponsor (dated 3/27/03), the last observation carried forward (LOCF) approach should be used for the extrapolation of missing data for the EGS score. Consequently, results based on the LOCF method for missing data are reported as the primary analyses in this review. The imputation of treatment failures is reviewed as a sensitivity analysis.
- It should be noted that the sponsor's sample size calculations did not power for the dichotomized EGS score. The Division had made comments about this point at EOP-2 Meeting (12/16/02) and IND 65,531/SN-006. The sponsor indicated in submission IND 65,531/SN-006 that they were unaware of previous studies using the EGS from which to base power calculations; and they were aware that it was their risk to proceed with the planned power calculations (Note: This comment was conveyed to the sponsor on 3/27/03).

4. Per IND 65,531/SN-005, SN-006, SN-008 and Pre-NDA meeting minutes (dated 10/1/03), a multiplicity adjustment would be required for the comparisons of treatment arms with respect to the secondary efficacy endpoints if they are intended to be included in the labeling. However, the sponsor's NDA submission did not provide inferential analyses for the endpoints, nor the endpoints were included in the proposed labeling. Therefore, only efficacy trend is explored in this review for the secondary efficacy endpoints.
5. As studies 06 and 07 were identically designed, this review reports the results of studies 06 and 07 simultaneously.

3.1.1.1 Patient Disposition and Baseline Characteristics

To evaluate the comparability between treatments for studies 06 and 07, Table 2 presents results of the patient disposition. The patient enrollment with respect to study site is in Table A.1 of the Appendix. Patient demographics and baseline characteristics are presented in Tables A.2-A.3 of the Appendix for each study.

Table 2: Patient Disposition – Studies 06 and 07

STUDY 06	Clin-RA	Clindamycin	Tretinoin	Vehicle
Subject randomized	420	208	417	207
Completed study	366 (87%)	176 (85%)	363 (87%)	182 (88%)
ITT population	420 (100%)	208 (100%)	417 (100%)	207 (100%)
PP population	317 (75%)	155 (75%)	313 (75%)	163 (79%)
STUDY 07	Clin-RA	Clindamycin	Tretinoin	Vehicle
Subject randomized	425	218	429	216
Completed study	352 (83%)	183 (84%)	347 (81%)	173 (80%)
ITT/Safety population	425 (100%)	218 (100%)	429 (100%)	216 (100%)
PP population	293 (69%)	161 (74%)	306 (71%)	144 (67%)

Source: Sponsor's NDA submission (pages 61-62, Clinical Study Report 7001-G2HP-06-02; pages 59-60, Clinical Study Report 7001-G2HP-07-02).

Generally, treatment groups are comparable with respect to the ITT, patients completed 12-week treatment period, PP and safety populations within each study. For the treatment distribution by demographic and baseline characteristics, the results in Tables A.2-A.3 generally show non-significant differences among treatment groups within each study except the distribution of race in study 07 (p-value = 0.010, Table A.3). The distribution of race among treatments is significant even when the race is classified into White vs. non-White (p-value = 0.015 based on chi-square test). Clin-RA group appeared to have a higher rate of White patient enrollment as compared to other treatment groups. Subgroup results by race are examined in the section of efficacy results.

Note that about 69% and 66% of enrolled patients were 18 years or younger in studies 06 and 07, respectively. Patients who were older than 45 years of age accounted for only about 0.6% and 1.5% of the enrolled patients in the respective study. A total of 6 patients (0.2%, 4 and 2 patients in studies 06 and 07) were 11 years old at the time of enrollment which violated the inclusion criterion of 12 years of age or older. However, this is not expected to affect efficacy results.

It should be noted that the enrolled patients had at least a mild score in the EGS at baseline. At least 71% of patients had baseline EGS score of "moderate" (Tables A.2-A.3). About 11% and 18% of patients had "severe" EGS score in studies 06 and 07, respectively. It should be noted

that there were only 3 patients enrolled in the pivotal studies having EGS score of “very severe” at baseline and they were all in study 07.

3.1.1.2 Primary Efficacy Endpoints

The study objectives were:

- Superiority of Clin-RA to its vehicle with respect to the reduction in inflammatory and non-inflammatory lesion counts, and percentage of patients with clear or almost clear in the EGS Score;
- Superiority of Clin-RA to each of the monads (i.e., Clindamycin and Tretinoin) with respect to the reduction in two out of the three lesion counts (inflammatory, non-inflammatory and total); and percentage of patients with clear or almost clear in the EGS score.

Three paired comparisons were made to establish the effectiveness of Clin-RA Gel with respect to each primary efficacy endpoint. The three paired comparisons were Clin-RA vs. Clindamycin; Clin-RA vs. Tretinoin; and Clin-RA vs. vehicle.

Lesion Reduction

Table 3 presents the ITT results of lesion change from baseline to week 12 for the four treatments. The PP results are presented in Table A.4 of the Appendix. The LOCF approach was used for imputation. Note that this reviewer has performed Shapiro-Wilk test, instead of Zar’s test as proposed by the sponsor, to examine the normality assumption of lesion change data (both absolute number and percent change). The normality assumption of lesion change data is not met, as p -value < 0.001 . Consequently, p -values based on ranked ANOVA are reported in Table 3 and Table A.4. Results in Table 3 and Table A.4 can be summarized by the following:

- The magnitude of the lesion reduction generally is higher in the PP analyses as compared to the ITT analyses regardless of treatment groups. The efficacy conclusions are generally consistent except for the comparison of Clin-RA vs. Tretinoin in the number of total lesion reduction in study 07 (see Table 3 and Table A.4, p -value = 0.021 for the ITT analyses; and p -value = 0.213 for the PP analyses). The non-significant PP result compared to the ITT results could be attributed to:
 - The treatment difference is 4.3 for the PP results, as compared to 5.1 for the ITT results.
 - Sample sizes are reduced in the PP population.
- Study 06: The ITT analyses show that
 - Clin-RA Gel is superior to Clindamycin, Tretinoin and vehicle in each type of lesion reduction (p -value ≤ 0.014 for absolute lesions reduction and ≤ 0.028 for percent reduction).
- Study 07: The ITT analyses show that
 - Clin-RA Gel is superior to Clindamycin in percent reduction of inflammatory and total lesion counts (p -value ≤ 0.020), and is trend superior in the reduction of non-inflammatory lesion counts (p -value = 0.088). With respect to the absolute number lesion reduction, the superiority of Clin-RA to Clindamycin is confirmed for inflammatory lesion (p -value = 0.042). The superiority is marginal for the total lesion (p -value = 0.082), and the two treatments, however, are not significantly different in terms of non-inflammatory lesion number reduction (p -value = 0.328).
 - Clin-RA Gel is superior to Tretinoin in the reduction of inflammatory and total lesion counts (p -value ≤ 0.021 for absolute lesion reduction and ≤ 0.002 for percent reduction).

But the two treatments are not significantly different in the reduction of non-inflammatory lesion count (p-value = 0.333 and 0.110 for absolute and percent reduction, respectively).

- o The superiority of Clin-RA Gel to vehicle is established with respect to each type of lesion reduction (p-value < 0.001 for both absolute number and percent reduction).

**Table 3: Comparison of Lesion Reduction from Baseline to Week 12
 (ITT Analyses) Studies 06 and 07**

Lesion Type Mean (s.d.)	STUDY 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
Inflammatory				
Mean baseline count	30.10 (8.64)	29.30 (8.38)	29.44 (8.40)	30.15 (8.43)
Mean number reduction	13.6 (13.0)	11.4 (12.0)	10.7 (12.9)	5.3 (15.6)
Mean % reduction	46.0% (42.2%)	39.7% (42.6%)	37.5% (42.3%)	19.6% (53.0%)
p-value (ranked ANOVA) ¹	NA	0.014	< 0.001	< 0.001
p-value (ranked ANOVA) ²	NA	0.028	< 0.001	< 0.001
Non-inflammatory				
Mean baseline count	50.86 (22.21)	47.64 (20.77)	49.53 (21.13)	49.28 (22.00)
Mean number reduction	19.2 (21.7)	11.9 (19.4)	15.6 (20.6)	6.9 (23.1)
Mean % reduction	37.6% (37.8%)	24.1% (44.3%)	31.9% (40.0%)	13.5% (50.0%)
p-value (ranked ANOVA) ¹	NA	< 0.001	0.009	< 0.001
p-value (ranked ANOVA) ²	NA	< 0.001	0.018	< 0.001
Total				
Mean baseline count	80.96 (25.69)	76.94 (23.57)	78.97 (24.20)	79.43 (24.50)
Mean number reduction	32.8 (28.5)	23.3 (26.4)	26.3 (28.0)	12.2 (32.7)
Mean % reduction	41.4% (33.2%)	31.3% (33.9%)	34.7% (34.8%)	16.5% (42.5%)
p-value (ranked ANOVA) ¹	NA	< 0.001	0.001	< 0.001
p-value (ranked ANOVA) ²	NA	< 0.001	0.002	< 0.001
Lesion Type Mean (s.d.)	STUDY 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
Inflammatory				
Mean baseline count	28.84 (8.15)	29.44 (8.18)	29.02 (8.07)	29.91 (8.50)
Mean number reduction	14.6 (12.6)	12.2 (14.5)	11.6 (12.8)	8.6 (13.6)
Mean % reduction	50.6% (48.8%)	43.6% (47.4%)	40.1% (42.5%)	31.7% (43.9%)
p-value (ranked ANOVA) ¹	NA	0.042	< 0.001	< 0.001
p-value (ranked ANOVA) ²	NA	0.020	< 0.001	< 0.001
Non-inflammatory				
Mean baseline count	46.35 (21.0)	49.83 (22.39)	48.11 (21.55)	48.64 (21.84)
Mean number reduction	15.9 (21.9)	14.7 (21.7)	13.8 (27.9)	7.5 (26.0)
Mean % reduction	35.7% (43.5%)	30.1% (44.8%)	29.9% (48.2%)	18.5% (47.0%)
p-value (ranked ANOVA) ¹	NA	0.328	0.333	< 0.001
p-value (ranked ANOVA) ²	NA	0.088	0.110	< 0.001
Total				
Mean baseline count	75.19 (24.23)	79.27 (25.52)	77.14 (24.73)	78.56 (24.81)
Mean number reduction	30.6 (29.2)	26.9 (28.6)	25.5 (34.7)	16.1 (32.9)
Mean % reduction	41.8% (37.8%)	35.9% (36.3%)	34.2% (39.3%)	23.2% (39.5%)
p-value (ranked ANOVA) ¹	NA	0.082	0.021	< 0.001
p-value (ranked ANOVA) ²	NA	0.018	0.002	< 0.001
Source: Sponsor's NDA submission (pages 122-125, 149-160, 169-174, 178-190, Clinical Study Report 7001-G2HP-06-02; pages 113-116, 140-148, 160-165, 168-182, Clinical Study Report 7001-G2HP-07-02); and sponsor's response (dated 6/4/04) to information requests.				
¹ p-values listed are the comparisons of mean absolute lesion reduction for Clin-RA vs. each of other three treatments.				
² p-values listed are the comparisons of mean percent lesion reduction for Clin-RA vs. each of other three treatments.				

Evaluator's Global Severity Score

Table 4 presents the distribution of EGS score at week 12 and percentage of patients who achieved clear or almost clear in the EGS score based on the ITT population, where EGS score is based on a 6-point static grading scale. Results based on the PP population are presented in Table A.5 of the Appendix.

The following summarizes the results in Table 4 and Table A.5:

- The magnitude of the success rate generally is higher in the PP analyses as compared to the ITT analyses (see Table 4 and Table A.5). The efficacy conclusions are generally consistent except the comparison between Clin-RA and Clindamycin in study 06. Clin-RA is superior to Clindamycin based on the PP analyses (p-value = 0.037, Table A.5), but the two groups are not significantly different based on the ITT analyses (p-value = 0.172, Table 4). The reason is that a higher rate of success patients in Clindamycin group was excluded from the PP analyses as compared to Clin-RA group (i.e., 9 (4.3%) and 9 (2.1%) patients in Clindamycin and Clin-RA, respectively).
- The ITT analyses from studies 06 and 07 show that
 - Clin-RA Gel is **not** significantly different from Clindamycin (p-value = 0.172 and 0.094 in studies 06 and 07, respectively).
 - Clin-RA Gel is superior to Tretinoin and its vehicle (p-value ≤ 0.032 and < 0.001, respectively)

Table 4: EGS Score at Week 12 (ITT Analyses) – Studies 06 and 07

Distribution of EGS at wk 12 n (%)	STUDY 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
Clear	5 (1%)	2 (1%)	4 (1%)	2 (1%)
Almost Clear	83 (20%)	32 (15%)	60 (14%)	16 (8%)
Mild	161 (38%)	83 (40%)	154 (37%)	57 (28%)
Moderate	153 (36%)	83 (40%)	180 (43%)	110 (53%)
Severe	18 (4%)	7 (3%)	18 (4%)	20 (10%)
Very Severe	0	1 (< 1%)	1 (< 1%)	2 (1%)
Percentage of patients with Clear or Almost Clear Comparison (p-value) ¹	88 (21%) NA	34 (16%) 0.172	64 (15%) 0.032	18 (9%) < 0.001
Distribution of EGS at wk 12 n (%)	STUDY 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
Clear	9 (2%)	3 (1%)	3 (1%)	1 (< 1%)
Almost Clear	88 (21%)	35 (16%)	60 (14%)	16 (7%)
Mild	172 (40%)	72 (33%)	151 (35%)	68 (31%)
Moderate	134 (32%)	90 (41%)	184 (43%)	103 (48%)
Severe	22 (5%)	17 (8%)	30 (7%)	28 (13%)
Very Severe	0	0	0	0
Not Reported	0	1	1	0
Percentage of patients with Clear or Almost Clear Comparison (p-value) ¹	97 (23%) NA	38 (17%) 0.094	63 (15%) 0.002	17 (8%) < 0.001
Source: Sponsor's NDA submission (pages 145-146, 181, 187, and 193, Clinical Study Report 7001-G2HP-06-02; pages 136-137, 170, 175, and 180, Clinical Study Report 7001-G2HP-07-02).				
¹ p-value is the comparison between Clin-RA and each of other three treatments and is based on CMH test adjusting for investigational group.				

Summary of the Primary Efficacy Results

The ITT results show that

1. Study 06:
 - Clin-RA Gel is superior to Clindamycin, Tretinoin and vehicle in each type of lesion reduction from baseline to week 12.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage of patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA Gel to Clindamycin is not established (p-value = 0.172).
2. Study 07:
 - Clin-RA Gel is superior to Clindamycin and to Tretinoin in inflammatory and total lesion reduction from baseline to week 12. The superiority is not established for each pair comparison in the non-inflammatory lesion reduction.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage of patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA to Clindamycin is not established (p-value = 0.094).

3.1.1.3 Sensitivity Analyses of the Primary Efficacy Endpoints

Based on the efficacy results presented in the previous section, the pair comparison of Clin-RA vs. Clindamycin won the lesion reduction; however, failed the treatment success rate of EGS score for both pivotal trials, where treatment success was defined as clear or almost clear in the EGS score. The following analyses are carried out to examine the results of the comparison Clin-RA Gel vs. Clindamycin:

1. Analyses of lesion reduction by baseline severity for patients with success in the EGS score as compared to patients with failure in the EGS score. Lesion reduction for patients who achieved success in EGS score, and identification of possible outliers that affect the overall results.
2. Analyses of percent lesion reduction and the distribution of success in the EGS score by 10 categories of baseline lesion count to investigate any efficacy trend over categories of baseline lesion count.
3. Analysis of modified success rates, where modified success is defined as EGS score of 0 or 1 (i.e., clear or almost clear) or having at least a 2-grade improvement from baseline. The objective is to examine the impact of patients with severe disease at baseline to the overall efficacy results, where these patients did not achieve EGS score of 0 or 1, but had at least a 2-grade improvement from baseline.

Results are presented in Tables A.6 – A.10 and Figures 1 – 4 of the Appendix. The summary is:

1. (Tables A.6 – A.7 and Figures 1 – 2):
 - a. For patients who had baseline disease of moderate to severe, and were failures in the EGS score, Clin-RA is numerically better than Clindamycin in the percent reduction of each type of lesion count for the two studies. Clindamycin is numerically better than Clin-RA for patients with mild acne. On the other hand, for patients who were successes in the EGS score, Clin-RA is mostly numerically better than or approximately similar to Clindamycin in the percent reduction of each type of lesion count regardless of baseline disease (Table A.6).
 - b. Totals of 3 and 5 patients in studies 06 and 07 had decreasing inflammatory lesion counts and increasing non-inflammatory lesion counts. They achieved success in the EGS score

- at week 12 (Table A.7). As there were few such patients in Clin-RA and Clindamycin groups, efficacy conclusion is not expected to be affected.
- c. Outliers were examined with respect to the percent reduction from baseline in each type of lesion count for the four treatment arms (Figures 1 – 2, where treatment group of 1 = Clin-RA, 2 = Clindamycin, 3 = Tretinoin, and 4 = Vehicle). The magnitude of all outliers is negative which represents increasing lesion counts. Among patients with outlier data, only one patient treated with Clindamycin in study 06 (patient ID 130) achieved success in the EGS score at week 12. The patient's percent non-inflammatory lesion reduction –100% (from 27 counts at baseline to 54 counts at week 12) is an outlier with respect to the patients who were treated with Clindamycin in study 06. This is not expected to affect the overall efficacy results.
2. To investigate any efficacy trend over category of baseline lesion count, analyses by baseline lesion count are performed. Ten categories are considered with respect to each type of lesion count at baseline. The descriptive summary of the category of baseline lesion count is presented in Table A.8 of the Appendix. The percent lesion reduction and success rate in the EGS score by 10 categories of baseline lesion count for Clin-RA and Clindamycin groups are presented in Figures 3 – 4 for studies 06 and 07, respectively. The findings are:
 - a. Lesion reduction (Figures 3 – 4):
 - The efficacy trend of lesion reduction for Clin-RA and Clindamycin groups is generally constant over baseline lesion category in both studies.
 - For inflammatory lesion reduction, the efficacy lines for Clin-RA and Clindamycin groups generally across to each other over baseline lesion category with Clin-RA lines slightly higher for both studies. This suggests that Clin-RA and Clindamycin have similar effect, with Clin-RA slightly higher, in reducing inflammatory lesions.
 - For non-inflammatory lesion reduction, the efficacy line of Clin-RA arm is clearly above that of Clindamycin arm in study 06. Such a behavior generally holds in study 07. This indicates that Clindamycin has less effect in reducing the non-inflammatory lesions, as compared to Clin-RA Gel.
 - For total lesion reduction, the efficacy trend of Clin-RA Gel is generally above that of Clindamycin group for both studies.
 - b. Success in the EGS score (Figures 3 – 4):
 - The efficacy trend of success rate in the EGS score is generally constant over baseline inflammatory lesion category for Clin-RA and Clindamycin groups. The trend is slightly descending over baseline non-inflammatory lesion category; and more apparent over baseline total lesion category. The higher number of total lesion counts a patient had, the smaller chance the patient had to achieve success in the EGS score.
 - With respect to the baseline total lesion category, the efficacy trend of success rate in the EGS score for Clin-RA and Clindamycin groups generally across to each other with Clin-RA trend line slightly higher than that of Clindamycin. This might explain that the two groups are not statistically different with respect to the overall success rate in the EGS score for each of the two studies.
 3. To examine the impact of patients with severe or very severe disease at baseline, measured in terms of EGS, on the overall efficacy results, analyses of modified success rate in the EGS score at week 12 are performed. Modified success is defined as EGS score of 0 or 1 or at least a 2-grade improvement from baseline. The ITT and PP results are presented in Tables A.9 – A.10 of the Appendix. The summary is

- a. Clin-RA is superior to Tretinoin and vehicle with respect to the modified success rate in the EGS score for each study, regardless of the ITT and PP analyses.
- b. Clin-RA is superior to Clindamycin in study 07 based on both the ITT and PP analyses (p-value = 0.030 and 0.031, respectively).
- c. Clin-RA is superior to Clindamycin in study 06 based on the PP analysis (p-value = 0.020); however, such a comparison is not significant using the ITT analysis, as p-value = 0.100.

A comparison of treatment success rates and modified success rates for Clin-RA and Clindamycin groups is presented in Table 5 below. The summary is:

1. For study 06, Clin-RA is superior to Clindamycin based on the PP analyses with respect to each of the treatment success and modified success rates (p-value = 0.037, and 0.020, respectively). However, the ITT analyses did not show the superiority conclusion (p-value = 0.172 and 0.100).
2. On the other hand in study 07, Clin-RA is superior to Clindamycin with respect to modified success rate regardless of analysis populations (p-value = 0.030 and 0.031 for the ITT and PP analysis, respectively). However, the superiority conclusion is not shown statistically with respect to the treatment success rate (p-value = 0.094 and 0.130 for the ITT and PP analysis, respectively).

Table 5: Treatment Success and Modified Success Rates in the EGS Score at Week 12

Analysis	Variable	Study 06			Study 07		
		Clin-RA (n = 420)	Clindamycin (n = 208)	p-value ³	Clin-RA (n = 425)	Clindamycin (n = 218)	p-value ³
ITT	Treatment						
	Treatment Success ¹ rate	88 (21%)	34 (16%)	0.172	97 (23%)	38 (17%)	0.094
	Modified Success ² rate	101 (24%)	38 (18%)	0.100	118 (28%)	44 (20%)	0.030
PP	Treatment						
	Treatment success ¹ rate	79 (25%)	25 (16%)	0.037	81 (28%)	34 (21%)	0.130
	Modified Success ² rate	90 (28%)	28 (18%)	0.020	100 (34%)	40 (25%)	0.031

¹ Treatment success is the Division's recommended co-primary efficacy endpoint, defined as clear or almost clear in the EGS score at week 12.
² Modified success is defined as clear or almost clear or at least a 2-grade improvement from baseline in the EGS score at week 12.
³ p-value is based on CMH test adjusting for investigational group.

Data were examined further to find the differences in conclusions due to different definitions of success in the EGS score and patient populations analyzed for each study. The following summarizes the findings:

1. Study 06 –
 - Totals of 13 (3.1%) and 4 (1.9%) patients who had severe/very severe EGS score at baseline in Clin-RA and Clindamycin groups, respectively, and who did not reach a score of 0 or 1 at week 12, achieved at least a 2-grade improvement. As the ITT analysis of treatment success rate had a greater degree of insignificance (p-value = 0.172), ITT analyses of the modified success rate is not significant (p-value = 0.100) by adding these patients to the success category.
 - Nine patients in each of Clin-RA and Clindamycin groups who had treatment success in the EGS score were excluded from the PP analysis. The significant results in the PP analysis with respect to the treatment success rate in the EGS score could be attributed to:

- The PP population excluded a relatively higher rate of success patients in Clindamycin group of 4.3% as compared to Clin-RA arm of 2.1%.
 - The resulted treatment difference is 9% in the PP population following the exclusion of patients, as compared to 5% in the ITT population.
 - The inclusion of 11 (2.6%) and 3 (1.4%) patients to the success category in the PP population resulted in the superiority of Clin-RA to Clindamycin with respect to the modified success rate. These patients did not reach an EGS score of 0 or 1; however, had at least a 2-grade improvement from baseline in the EGS score.
2. Study 07 –
- The difference between the treatment success rate and modified success rate based on the ITT population is the totals of 21 (5%) and 6 (2.8%) patients in Clin-RA and Clindamycin groups, respectively. These patients did not reach an EGS score of 0 or 1 at week 12, but achieved at least a 2-grade improvement from baseline. By adding these patients to the success category, Clin-RA is superior to Clindamycin with respect to the modified success rate (p-value = 0.030). The resulted treatment difference (δ) is 6-7% for the treatment success rate, as compared to 8-9% for the modified success rate.
 - For treatment success rate, totals of 16 (3.8%) and 4 (1.8%) success patients in Clin-RA and Clindamycin groups, respectively, were excluded from the PP analyses. Consequently, the p-value for the comparison of Clin-RA vs. Clindamycin is relatively larger in the PP analysis as compared to that of the ITT analysis (i.e., 0.130 vs. 0.094 for the PP and ITT analyses, respectively).

The overall efficacy findings for the comparison of Clin-RA vs. Clindamycin show that,

- a. Generally, Clin-RA is numerically better than Clindamycin for moderate to severe acne vulgaris in terms of lesion reduction, regardless of achieving success or failure in the EGS score at week 12. For patients who achieved success in the EGS score at week 12, Clin-RA is better than Clindamycin for also patients with mild disease.
- b. No outlier that has an impact on the overall efficacy results is noted.
- c. The efficacy trend of treatment success rate in the EGS score decreases as the baseline total lesion count increases.
- d. Totals of 13 (3.1%) and 4 (1.9%) patients who had severe/very severe EGS score at baseline in Clin-RA and Clindamycin groups, respectively, and who did not reach an EGS score of 0 or 1 at week 12, achieved at least a 2-grade improvement at week 12 in study 06; while 21 (4.9%) and 6 (2.8%) patients in the respective group in study 07. The inclusion of these patients to the success category warrants a statistical superiority of Clin-RA to Clindamycin for study 07 (p-value = 0.030); but not for study 06 (p-value = 0.100).

In summary, the treatment success rates for Clindamycin and Tretinoin groups are similar in the two pivotal trials. Clin-RA is shown statistically superior to Tretinoin; however, the superiority of Clin-RA to Clindamycin is not established. As Clindamycin has similar efficacy results to those of Tretinoin group, the fact that Clin-RA is not superior to Clindamycin statistically should be attributed to the lower patient enrollment in Clindamycin arm as compared to Tretinoin group. The enrollment of Clindamycin group was only about 50% of that of each of Clin-RA and Tretinoin groups for each study.

3.1.1.4 Secondary Efficacy Endpoints

Sponsor's secondary efficacy endpoints included

- a. Percent reduction from baseline to weeks 2, 4, and 8 in inflammatory, non-inflammatory, and total lesion counts.
- b. Percentage of patients with clear or almost clear in the EGS score at weeks 2, 4, and 8.

As these endpoints were not included in the proposed labeling, efficacy trend of the secondary endpoints is explored using plots in this review.

The plots of percent lesion reduction (including inflammatory, non-inflammatory and total) over assessment week for studies 06 and 07 are presented in Figures 5-6 of the Appendix, respectively. Plots of percentage of patients with clear or almost clear in the EGS score over time are presented in Figure 7 of the Appendix. The plots generally suggest upward efficacy trend over time for Clin-RA Gel, as compared to other treatments.

3.1.1.5 Discussion on Missing Data Handling

The last observation carried forward (LOCF) was the pre-specified imputation method for lesion count. The sponsor specified the method of "treatment failure" for imputing missing data in the dichotomized EGS score. To examine the robustness of the methods on the primary efficacy results, missing data rate over time is examined. They are presented in Table 6.

Table 6: Missing Efficacy Data Rate Over Time – Studies 06 and 07

Study	Clin-RA	Clindamycin	Tretinoin	Vehicle	Comparison ¹
06					
Wk 2	22/420 (5.2%)	6/208 (2.9%)	18/417 (4.3%)	7/207 (3.4%)	0.502
Wk 4	30/420 (7.1%)	18/208 (8.7%)	29/417 (7.0%)	8/207 (3.9%)	0.257
Wk 8	50/420 (11.9%)	25/208 (12.0%)	51/417 (12.2%)	22/207 (10.6%)	0.948
Wk 12	29/420 (6.9%)	15/208 (7.2%)	26/417 (6.2%)	12/207 (5.8%)	0.920
07					
Wk 2	28/425 (6.6%)	13/218 (6.0%)	30/429 (7.0%)	15/216 (6.9%)	0.964
Wk 4	46/425 (10.8%)	19/218 (8.7%)	41/429 (9.6%)	23/216 (10.6%)	0.822
Wk 8	72/425 (16.9%)	33/218 (15.1%)	80/429 (18.6%)	39/216 (19.1%)	0.713
Wk 12	38/425 (8.9%)	22/218 (10.1%)	40/429 (9.3%)	23/216 (10.6%)	0.900

Source: Sponsor's electronic SAS data sets at \\cdsesub\1n21739\1n_000\2004-02-06\crt.
¹p-value is based on chi-square test.

Results of missing data rates in Table 6 are generally comparable among treatment groups over visit. It is not expected to have a great impact on the efficacy results due to different imputation methods. Analyses based on the LOCF approach and imputing missing as failures were done on the success rate of EGS score. The results were similar.

3.2 Evaluation of Safety

As studies 06 and 07 were identically designed, safety assessment based on the duration of drug exposure and the incidence rates of adverse events is summarized for studies 06 and 07 combined. Results of localized irritation are also reviewed. The safety parameters of localized irritation included erythema, scaling, itching, burning, and stinging.

For studies 06 and 07 combined, totals of 845, 426, 846 and 423 patients were treated with Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively.

3.2.1 Drug Exposure and Incidence of Adverse Events

Results of duration of drug exposure and adverse event incidence rates are presented in Tables 7-8, respectively. In addition, results of the comparison between treatments in the events that were reported by at least 5% of the subjects in any treatment group are summarized in Table A.11 of the Appendix. The following gives a summary:

- Treatment arms were generally comparable with the overall mean duration of drug exposure of 79.3, 78.6, 78.9 and 78.5 days for Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively. This also holds for patients who completed studies. The mean duration was 85.4, 84.9, 85.1 and 85.2 day in the respective group (Table 7).
- The overall adverse event incidence rate is comparable between Clin-RA and Tretinoin groups. They are slightly higher than those of Clindamycin and vehicle groups. The incidence rates were 27%, 24%, 27% and 22% for Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively. The treatment-related adverse event incidence rates were 4%, 1%, 4% and 2% in the respective group (Table 8).
- A total of 20 patients had non-serious adverse events that resulted in a discontinuation from the trials. Thirteen of them had adverse events judged by investigators to be treatment-related (7, 1, 5 and 0 in Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively). Two patients had serious adverse events that resulted in study discontinuation (one each in Clin-RA and Tretinoin groups, Table 8).
- The adverse event incidences occurred in at least 5% of patients were events related to respiratory, thoracic and mediastinal disorders (9%, 8%, 10% and 9% in the respective group), followed by skin and subcutaneous tissue disorders (7%, 4%, 8% and 4% in the respective group). For events related to skin and subcutaneous tissue disorders, Clin-RA and Tretinoin appear to have statistically higher incidence rates than Clindamycin (p-value = 0.052 and 0.024, respectively), and vehicle (p-value = 0.026 and 0.008, respectively, Table A.11 of the Appendix).

Table 7: Duration of Drug Exposure (in Days) – Studies 06 and 07 Combined

Subjects	Clin-RA (N = 845)	Clindamycin (N = 426)	Tretinoin (N = 846)	Vehicle (N = 423)
All subjects				
n	820	416	823	416
Mean (s.d.)	79.3 (18.6)	78.6 (18.0)	78.9 (18.1)	78.5 (18.8)
Median	84	84	84	84
Range	2 – 165	4 – 109	1 – 120	4 – 106
Subjects who completed studies				
n	718	359	710	355
Mean (s.d.)	85.4 (5.8)	84.9 (3.6)	85.1 (4.5)	85.2 (4.3)
Median	84	84	84	84
Range	62 – 165	76 – 109	76 – 120	66 – 106
Discontinued subjects				
n	102	57	113	61
Mean (s.d.)	36.6 (21.9)	38.9 (21.5)	39.6 (22.0)	39.5 (22.6)
Median	31	34	34	31
Range	2 – 91	4 – 87	1 – 85	4 – 89

Source: Sponsor's NDA submission (page 17 in ISS at \cdsesub\21739\000\2004-02-06\clinstat\iss).

Table 8: Number (%) of Patients with Adverse Events – Studies 06 and 07 Combined

Variable	Clin-RA (N = 845)	Clindamycin (N = 426)	Tretinoin (N = 846)	Vehicle (N = 423)
No. of subjects had AE	225 (27%)	102 (24%)	225 (27%)	91 (22%)
No. of AE reported	358	147	323	138
Severity –				
Mild	212	93	209	100
Moderate	127	49	96	37
Severe	18	5	16	1
Relationship to study drug –				
Unrelated	265	124	227	94
Unlikely	42	17	49	36
Possible	20	4	23	7
Probable	22	1	16	1
Related	9	1	7	0
No. of subjects had treatment-related AE	32 (4%)	6 (1%)	36 (4%)	8 (2%)
No. of treatment-related AE reported	51	6	46	8
Severity –				
Mild	30	4	33	6
Moderate	19	2	7	2
Severe	1	0	6	0
No. of subjects with AE resulted in study discontinuation	11 (1.3%)	2 (0.5%)	7 (0.8%)	2 (0.5%)
Treatment-unrelated non-serious AE	3	1	1	2
Treatment-related non-serious AE	7	1	5	0
Serious AE	1	0	1	0
Death	0	0	0	0

Source: Sponsor's NDA submission (pages 18-30 in ISS; pages 96-104, 269-270 in Clinical Study Report 7001-G2HP-06-02; pages 88-96, 261-263 in Clinical Study Report 7001-G2HP-07-02 at \\cdsesubl\n21739\n_000\2004-02-06\clinstat).

3.2.2 Events of Localized Irritation

Results of localized irritation (i.e., erythema, burning, scaling, stinging and itching) over assessment time are summarized in Table 9. The summary is:

- Mean erythema severity score increased from baseline at week 2 visit in Clin-RA group, and then decreased below the baseline level at weeks 8 and 12. Tretinoin group had a similar trend as Clin-RA group; while the erythema severity score decreased over time for Clindamycin and vehicle groups.
- Clin-RA and Tretinoin groups had similar trend in burning, scaling and stinging severity score over time. The mean score increased (week 2 or week 4) and then decreased subsequently. On the other hand, the mean severity scores in Clindamycin and vehicle groups generally did not change much over time.
- All treatment groups generally had similar trend in itching severity score over time. The mean score increased and then decreased after week 2 or week 4.

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Table 9: Localized Irritation – Studies 06 and 07 Combined

Irritation/treatment Mean (s.d.) Range	Baseline	Week 2	Week 4	Week 8	Week 12
Erythema					
Clin-RA	0.31 (0.54) 0-2	0.37 (0.60) 0-2	0.32 (0.56) 0-3	0.28 (0.53) 0-2	0.25 (0.51) 0-2
Clindamycin	0.36 (0.57) 0-2	0.28 (0.54) 0-2	0.25 (0.52) 0-2	0.21 (0.48) 0-3	0.21 (0.48) 0-3
Tretinoin	0.33 (0.57) 0-3	0.36 (0.59) 0-3	0.36 (0.59) 0-3	0.30 (0.56) 0-3	0.27 (0.51) 0-3
Vehicle	0.35 (0.60) 0-3	0.31 (0.57) 0-2	0.26 (0.51) 0-2	0.26 (0.52) 0-2	0.21 (0.49) 0-2
Burning					
Clin-RA	0.007 (0.08) 0-1	0.10 (0.33) 0-3	0.06 (0.31) 0-3	0.04 (0.22) 0-2	0.03 (0.18) 0-2
Clindamycin	0.005 (0.07) 0-1	0.02 (0.16) 0-2	0.02 (0.14) 0-2	0.008 (0.09) 0-1	0 0
Tretinoin	0.02 (0.12) 0-1	0.12 (0.40) 0-3	0.08 (0.29) 0-2	0.05 (0.25) 0-2	0.04 (0.23) 0-2
Vehicle	0.02 (0.20) 0-3	0.02 (0.16) 0-2	0.03 (0.22) 0-3	0.02 (0.15) 0-1	0.02 (0.13) 0-1
Scaling					
Clin-RA	0.10 (0.31) 0-2	0.28 (0.53) 0-3	0.24 (0.47) 0-2	0.18 (0.43) 0-3	0.14 (0.35) 0-2
Clindamycin	0.10 (0.33) 0-2	0.11 (0.32) 0-2	0.10 (0.32) 0-2	0.08 (0.30) 0-2	0.08 (0.29) 0-2
Tretinoin	0.10 (0.32) 0-2	0.31 (0.54) 0-3	0.32 (0.55) 0-3	0.21 (0.44) 0-2	0.18 (0.43) 0-3
Vehicle	0.08 (0.27) 0-1	0.11 (0.34) 0-3	0.11 (0.32) 0-2	0.10 (0.34) 0-2	0.08 (0.29) 0-2
Stinging					
Clin-RA	0.01 (0.10) 0-1	0.08 (0.31) 0-3	0.06 (0.30) 0-3	0.03 (0.21) 0-3	0.02 (0.13) 0-1
Clindamycin	0.005 (0.07) 0-1	0.005 (0.07) 0-1	0.005 (0.07) 0-1	0.01 (0.11) 0-1	0.008 (0.09) 0-1
Tretinoin	0.01 (0.10) 0-1	0.07 (0.30) 0-3	0.05 (0.25) 0-2	0.02 (0.16) 0-2	0.02 (0.18) 0-2
Vehicle	0.02 (0.16) 0-2	0.007 (0.09) 0-1	0.02 (0.13) 0-1	0.02 (0.14) 0-1	0.005 (0.07) 0-1
Itching					
Clin-RA	0.07 (0.31) 0-3	0.11 (0.35) 0-3	0.09 (0.31) 0-2	0.08 (0.32) 0-3	0.04 (0.21) 0-3
Clindamycin	0.05 (0.21) 0-1	0.06 (0.25) 0-2	0.05 (0.24) 0-2	0.03 (0.18) 0-2	0.03 (0.18) 0-2
Tretinoin	0.08 (0.30) 0-2	0.10 (0.35) 0-3	0.11 (0.35) 0-3	0.07 (0.29) 0-3	0.06 (0.27) 0-2
Vehicle	0.06 (0.28) 0-2	0.08 (0.34) 0-3	0.06 (0.25) 0-2	0.05 (0.23) 0-1	0.04 (0.24) 0-2

Source: Data summary is based on the sponsor's electronic SAS data sets at \\cdsesub\1\21739\1_000\2004-02-06\crt.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup efficacy results on the primary efficacy endpoints by gender, race, age and baseline EGS score are examined. The results are presented in Tables A.12 – A.16 of the Appendix. It should be noted that subgroup results are intended to explore efficacy trend over subgroups. The studies were not designed to test efficacy within subgroups.

4.1 Gender, Race and Age

Approximately 52% enrolled patients are males in study 06; while about 46% of the patients are males in study 07 (Table A.12). The overall gender distribution was about 1:1. Generally, Clin-RA group had higher mean percentage of lesion reduction as well as percentage of patients with success in EGS score at week 12, as compared to other treatment groups regardless of gender. Note that female patients had numerically higher mean percentage of lesion reduction than males regardless of treatment groups. This also holds with respect to the percentage of patients with EGS score of clear or almost clear at week 12 in the two studies. No significant compliance issues are noted that resulted in higher response rates for female patients as compared to male patients.

Study 06 enrolled about 72% of Caucasian patients; while study 07 had about 68% (Table A.13). The race distribution among treatment groups was comparable in study 06; but not in study 07. Study 07 had a higher rate of Caucasian patients in Clin-RA group as compared to other treatment groups (i.e., 73% vs. 67%, 65%, and 63%). However, the mean percent lesion reduction and percent of success in EGS score for Clin-RA arm in study 07 are similar to those in study 06. Similar to subgroup results over gender, Clin-RA group generally had higher mean percent lesion reduction as well as percent of success in the EGS score than other treatment arms regardless of race groups.

Note that about 69% and 66% of enrolled patients were 18 years or younger in studies 06 and 07, respectively. Patients who were older than 45 years of age accounted for about 0.6% and 1.5% of the enrolled patients in the respective study. Age was divided into two groups based on median age of 16 (Table A.14). The summary is:

- For each of the two studies, Clin-RA group had numerically higher mean percent lesion reduction and percent of success in the EGS score than other treatment groups, regardless of age groups.
- Older age patients (i.e., patients with age > 16) had numerically higher mean percent lesion reduction and percent of success in the EGS score than younger age patients, regardless of treatment groups.

4.2 Other Special/Subgroup Populations

Subgroup efficacy results by baseline EGS score is examined. Results of lesion reduction and success rate of EGS at week 12 are presented in Tables A.15 and A.16 of the Appendix for studies 06 and 07, respectively. The summary is:

- Clin-RA group generally had higher mean percent lesion reduction and percent of success in the EGS score than other treatment groups, regardless of disease severity status at baseline. Each monad is generally more effective than vehicle with respect to the primary efficacy endpoints for each baseline severity level.
- The success rate of EGS score generally decreases as baseline disease severity increases regardless of treatment groups.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Per the Division's recommendation on the co-primary efficacy endpoint, the treatment success of EGS is defined as clear or almost clear in the EGS score at week 12.

The primary statistical issue for the sponsor's pivotal studies 06 and 07 is that the sponsor did not power the studies based on the treatment success rate of EGS score at the IND stage. The Division had made comments about this point at the EOP-2 Meeting (dated 12/16/02) and IND 65,531/SN-006. The sponsor was aware that it was their risk to proceed with their planned power calculations. This was documented in the Division's comments to the sponsor dated 3/27/03.

Sponsor's results of studies 06 and 07 demonstrate the efficacy of Clin-RA Gel in the lesion reduction; however, the superiority of Clin-RA Gel to Clindamycin is not established with respect to the treatment success rate of the EGS score in both pivotal trials (p-value = 0.172 and 0.094 for studies 06 and 07, respectively).

5.2 Conclusions and Recommendations

The sponsor in this submission presented results for two pivotal studies (06 and 07) in support of the efficacy and safety claim of Clin-RA Gel for the treatment of acne vulgaris. The dosing of Clin-RA Gel is once daily applied to the face before bedtime for 12 weeks. Results of the primary efficacy endpoints based on the ITT population with the last observation carried forward (LOCF) method for missing data are presented in Table E.1 for studies 06 and 07. In addition, results of the modified success rate are included in the table, where the modified success is defined as the percentage of patients with a score of 0 or 1 or had at least a 2-grade improvement in the EGS score.

The following summarizes the efficacy results.

Efficacy: (Studies 06 and 07)

- Study 06:
 - Clin-RA Gel is superior to Clindamycin, Tretinoin and vehicle in each type of lesion reduction from baseline to week 12.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA Gel to Clindamycin is not established (p-value = 0.172).
- Study 07:
 - Clin-RA Gel is superior to Clindamycin and to Tretinoin in inflammatory and total lesion reduction from baseline to week 12. The superiority is not established in the non-inflammatory lesion reduction. Clin-RA Gel is superior to its vehicle in each type of lesion reduction from baseline to week 12.
 - Clin-RA Gel is superior to Tretinoin and vehicle with respect to the percentage of patients with clear or almost clear in the EGS score at week 12. However, the superiority of Clin-RA to Clindamycin is not established (p-value = 0.094).

- The inclusion of patients with at least a 2-grade improvement in the EGS score to the success category warrants the superiority of Clin-RA Gel to Clindamycin with respect to the modified success rate for study 07 (p-value = 0.030); however, not for study 06 (p-value = 0.100).
- Subgroup results suggest that
 - Female patients had higher responses than males (both lesion reduction and treatment success rate in the EGS score).
 - Patients older than 16 years of age had higher responses than younger patients (both lesion reduction and treatment success rate in the EGS score).

Table E.1: Efficacy Results for Studies 06 and 07 (ITT)

Primary Endpoints	Study 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
Mean % Lesion Reduction Inflammatory	46.0%	39.7%	37.5%	19.6%
	NA	0.028	< 0.001	< 0.001
Non-inflammatory	37.6%	24.1%	31.9%	13.5%
	NA	< 0.001	0.018	< 0.001
Total	41.4%	31.3%	34.7%	16.5%
	NA	< 0.001	0.001	< 0.001
% of patients with EGS score of 0 or 1	88 (21%)	34 (16%)	64 (15%)	18 (9%)
	NA	0.172	0.032	< 0.001
Modified Success ¹ Rate	101 (24%)	38 (18%)	70 (17%)	20 (9.7%)
	NA	0.100	0.008	< 0.001
	Study 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
Mean % Lesion Reduction Inflammatory	50.6%	43.6%	40.1%	31.7%
	NA	0.020	< 0.001	< 0.001
Non-inflammatory	35.7%	30.1%	29.9%	18.5%
	NA	0.088	0.110	< 0.001
Total	41.8%	35.9%	34.2%	23.2%
	NA	0.018	0.002	< 0.001
% of patients with EGS score of 0 or 1	97 (23%)	38 (17%)	63 (15%)	17 (8%)
	NA	0.094	0.002	< 0.001
Modified Success ¹ Rate	118 (28%)	44 (20%)	83 (19%)	24 (11%)
	NA	0.030	0.003	< 0.001

¹ Modified success is defined as clear or almost clear or had at least a 2-grade improvement in the EGS score at week 12. For lesion reduction, p-value based on the ranked ANOVA analysis with terms of treatment, investigational group and treatment-by-investigational group interaction is reported. Success rates were analyzed based on Cochran-Mantel-Haenszel test adjusted for investigational group.

Safety:

With respect to the adverse event incidence, the safety profile of Clin-RA Gel is similar to that of Tretinoin based on studies 06 and 07 combined. The summary is:

- The overall adverse event incidence rate is comparable between Clin-RA and Tretinoin groups. They are slightly higher than those of Clindamycin and vehicle groups. The incidence rates were 27%, 24%, 27% and 22% for Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively. The treatment-related adverse event incidence rates were 4%, 1%, 4% and 2% in the respective group.
- A total of 20 patients had non-serious adverse events that resulted in a discontinuation from the trials. Thirteen of them had adverse events judged by investigators to be treatment-related (7, 1, 5 and 0 in Clin-RA, Clindamycin, Tretinoin, and vehicle, respectively). Two patients had serious adverse events that resulted in study discontinuation (one each in Clin-RA and Tretinoin groups).
- The adverse event incidences occurred in at least 5% of patients were events related to respiratory, thoracic and mediastinal disorders (9%, 8%, 10% and 9% in the respective group), followed by skin and subcutaneous tissue disorders (7%, 4%, 8% and 4% in the respective group). For events related to skin and subcutaneous tissue disorders, Clin-RA and Tretinoin appear to have statistically higher incidence rates than Clindamycin (p-value = 0.052 and 0.024, respectively), and vehicle (p-value = 0.026 and 0.008, respectively).

In summary, Clin-RA Gel demonstrates the efficacy in the lesion reduction from baseline to week 12 in each of studies 06 and 07. Clin-RA Gel is superior to Tretinoin and vehicle with respect to the Division's recommended co-primary efficacy endpoint, the treatment success rate, which is defined as the percentage of patients with EGS score of 0 or 1 at week 12, for each of studies 06 and 07. However, the superiority of Clin-RA to Clindamycin with respect to the treatment success according to the EGS score is not established. The inclusion of patients with at least a 2-grade improvement in the EGS score as successes warrants the superiority of Clin-RA Gel to Clindamycin with respect to the modified success rate for study 07, but not for study 06. As the treatment success rates in Clindamycin and Tretinoin groups are similar, the ultimate problem that the superiority of Clin-RA to Clindamycin is not established statistically is the sample size/power calculations. The enrollment of Clindamycin arm was only about 50% of that of each of Clin-RA and Tretinoin groups for each study.

As safety profile of Clin-RA Gel was similar to that of Tretinoin and data in studies 06 and 07 did not suggest noteworthy safety concerns, it is the judgment of the reviewing medical division to decide whether the drug should be approved.

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APPENDICES

Additional Tables

Table A.1.a: Patient Enrollment by Investigational Site – Study 06

Study Site	Total	Clin-RA	Clindamycin	Tretinoin	Vehicle
600 (Arthur)	97	33	16	32	16
601 (Gold)	47	16	7	16	8
602 (Dinehart)	92	31	16	30	15
603 (Fixler)	45	16	7	14	8
604 (Flores)	66	22	11	22	11
606 (Neumaier)	59	19	10	20	10
607 (Hanifin)	26	9	5	8	4
609 (Milbauer)	29	10	5	9	5
610 (Kempers)	45	15	8	14	8
611 (McDaniel)	33	10	6	12	5
612 (Menter)	36	12	6	12	6
613 (Nelson)	35	11	6	12	6
614 (Pariser)	26	9	4	9	4
616 (Sharata)	31	10	5	11	5
617 (Silos-Badalamenti)	2	2	0	0	0
618 (Smith)	54	18	9	18	9
619 (Stewart)	22	8	3	7	4
620 (Story)	39	12	7	14	6
621 (Stough)	62	22	10	20	10
622 (Swinyer)	66	22	11	22	11
623 (Tawfik)	46	15	8	16	7
624 (Torok)	55	18	9	19	9
625 (Tse)	10	3	2	4	1
626 (Draelos)	39	14	6	12	7
627 (Wiltz)	78	26	13	26	13
628 (Schlessinger)	29	10	4	10	5
629 (Childers)	38	12	7	12	7
630 (Kanof)	45	15	7	16	7
Total	1252	420	208	417	207
Source: Sponsor's NDA submission (Clinical Study Report 7001-G2HP-06-02, pages 110-111).					

Table A.1.b: Patient Enrollment by Investigational Site – Study 07

Study Site	Total	Clin-RA	Clindamycin	Tretinoin	Vehicle
700 (Chambers)	55	19	9	18	9
701 (Jones)	47	16	8	16	7
702 (Kaplan)	29	10	5	9	5
703 (Aton)	52	17	8	18	9
704 (Barker)	27	8	5	9	5
705 (Breneman)	51	16	9	18	8
706 (Bucko)	78	26	13	26	13
707 (Camden)	13	4	3	4	2
708 (Eichenfield)	39	14	7	12	6
709 (Fleischer)	58	19	10	20	9
710 (Weiss)	21	7	3	7	4
711 (Hebert)	39	13	6	14	6
712 (Proper)	54	18	9	18	9
713 (Ilowite)	7	2	1	3	1
714 (Jarratt)	48	16	8	16	8
715 (Kaminester)	24	8	4	8	4
716 (Loss)	40	13	7	13	7
717 (Loven)	27	9	5	8	5
718 (Martin)	14	5	2	4	3
719 (Groisser)	46	15	8	15	8
720 (Robinson)	9	3	2	3	1
721 (Rich)	29	9	5	10	5
722 (Westmoreland)	44	14	8	14	8
723 (Yamauchi)	48	16	8	16	8
724 (Egan)	32	10	5	11	6
725 (Fowler)	60	20	10	20	10
726 (Miller)	33	10	6	11	6
727 (Hogan)	90	30	15	30	15
728 (Sobell)	6	2	1	2	1
729 (Olson)	24	8	4	8	4
730 (Peredo)	72	24	12	24	12
731 (Vesper)	72	24	12	24	12
Total	1288	425	218	429	216

Source: Sponsor's NDA submission (Clinical Study Report 7001-G2HP-07-02, pages 103-104).

Table A.2: Demographic and Baseline Characteristics (ITT) – Study 06

Variable	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)	Comparison ¹
Age (years) Mean (S.D.) Range	18.36 (6.68) 12 – 54	18.99 (7.16) 11 – 51	18.98 (7.31) 11 – 47	18.60 (7.52) 12 – 47	0.554
Gender Male Female	222 (53%) 198 (47%)	117 (56%) 91 (44%)	215 (52%) 202 (48%)	97 (47%) 110 (53%)	0.290
Race White Black Asian/Pacific Hispanic American/Alaskan Other	304 (72%) 44 (10%) 6 (1%) 62 (15%) 1 (< 1%) 3 (1%)	155 (75%) 17 (8%) 5 (2%) 29 (14%) 0 2 (1%)	298 (71%) 44 (11%) 5 (1%) 64 (15%) 1 (< 1%) 5 (1%)	151 (73%) 23 (11%) 3 (1%) 28 (14%) 0 2 (1%)	0.811
Evaluator's Global Severity Clear Almost clear Mild Moderate Severe Very severe Missing	0 0 68 (16%) 304 (72%) 48 (11%) 0 0	0 0 34 (16%) 148 (71%) 26 (13%) 0 0	0 0 52 (13%) 325 (78%) 39 (9%) 0 1 (< 1%)	0 0 30 (14%) 153 (74%) 24 (12%) 0 0	0.922
Inflammatory Lesion Mean (S.D.) Range	30.10 (8.64) 19 – 54	29.30 (8.38) 17 – 63	29.44 (8.40) 5 – 54	30.15 (8.43) 20 – 54	0.455
Non-inflammatory Lesion Mean (S.D.) Range	50.86 (22.21) 20 – 141	47.64 (20.77) 15 – 99	49.53 (21.13) 13 – 117	49.28 (22.00) 20 – 100	0.327
Total Lesion Mean (S.D.) Range	80.96 (25.69) 41 – 195	76.94 (23.57) 38 – 147	78.97 (24.20) 21 – 155	79.43 (24.50) 40 – 142	0.232
<p>Source: Sponsor's NDA submission (pages 114 and 122, Clinical Study Report 7001-G2HP-06-02). ¹ p-value is based on two-way ANOVA with factors of treatment and investigational group for continuous data and CMH test, stratified by investigational group, for categorical data.</p>					

Table A.3: Demographic and Baseline Characteristics (ITT) – Study 07

Variable	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)	Comparison ¹
Age (years) Mean (S.D.) Range	19.22 (8.01) 11 – 59	19.25 (8.11) 12 – 52	19.38 (8.14) 12 – 55	19.04 (7.82) 11 – 52	0.967
Gender Male Female	190 (45%) 235 (55%)	107 (49%) 111 (51%)	193 (45%) 236 (55%)	106 (49%) 110 (51%)	0.563
Race White Black Asian/Pacific Hispanic American/Alaskan Other	312 (73%) 61 (14%) 6 (1%) 40 (9%) 5 (1%) 1 (< 1%)	145 (67%) 40 (18%) 5 (2%) 22 (10%) 3 (1%) 3 (1%)	279 (65%) 81 (19%) 12 (3%) 47 (11%) 5 (1%) 5 (1%)	135 (63%) 46 (21%) 7 (3%) 22 (10%) 2 (1%) 4 (2%)	0.010
Evaluator's Global Severity Clear Almost clear Mild Moderate Severe Very severe Missing	0 0 50 (12%) 301 (71%) 71 (17%) 1 (< 1%) 2 (0.5%)	0 0 18 (8%) 153 (71%) 45 (21%) 1 (< 1%) 1 (< 1%)	0 0 39 (9%) 310 (72%) 79 (18%) 0 1 (< 1%)	0 0 16 (7%) 161 (75%) 38 (18%) 1 (< 1%) 0	0.161
Inflammatory Lesion Mean (S.D.) Range	28.84 (8.15) 4 – 50	29.44 (8.18) 19 – 58	29.02 (8.07) 13 – 52	29.91 (8.50) 20 – 53	0.400
Non-inflammatory Lesion Mean (S.D.) Range	46.35 (21.00) 14 – 113	49.83 (22.39) 15 – 100	48.11 (21.55) 11 – 126	48.64 (21.84) 9 – 110	0.207
Total Lesion Mean (S.D.) Range	75.19 (24.23) 24 – 159	79.27 (25.52) 41 – 146	77.14 (24.73) 27 – 156	78.56 (24.81) 29 – 145	0.148
<p>Source: Sponsor's NDA submission (pages 105 and 113, Clinical Study Report 7001-G2HP-07-02). ¹ p-value is based on two-way ANOVA with factors of treatment and investigational group for continuous data and CMH test, stratified by investigational group, for categorical data.</p>					

**Table A.4: Comparison of Lesion Reduction from Baseline to Week 12
 (PP Analyses) Studies 06 and 07**

Lesion Type Mean (s.d.)	STUDY 06			
	Clin-RA (n = 317)	Clindamycin (n = 155)	Tretinoin (n = 313)	Vehicle (n = 163)
Inflammatory				
Mean baseline count	30.15 (8.50)	29.26 (7.84)	29.38 (8.09)	29.36 (8.01)
Mean number reduction	14.2 (13.0)	11.5 (12.8)	11.2 (13.1)	5.1 (16.0)
Mean % reduction	48.4% (42.3%)	39.6% (45.0%)	40.0% (43.0%)	19.9% (55.1%)
p-value (ranked ANOVA) ¹	NA	0.012	0.002	< 0.001
p-value (ranked ANOVA) ²	NA	0.026	0.003	< 0.001
Non-inflammatory				
Mean baseline count	50.63 (21.97)	49.03 (21.32)	49.08 (19.74)	49.15 (21.93)
Mean number reduction	20.5 (21.3)	12.0 (19.4)	16.9 (21.3)	6.5 (24.5)
Mean % reduction	41.1% (35.1%)	24.3% (40.0%)	33.7% (41.6%)	13.5% (52.7%)
p-value (ranked ANOVA) ¹	NA	< 0.001	0.041	< 0.001
p-value (ranked ANOVA) ²	NA	< 0.001	0.050	< 0.001
Total				
Mean baseline count	80.79 (25.46)	78.30 (23.61)	78.46 (23.17)	78.51 (24.26)
Mean number reduction	34.7 (28.2)	23.5 (27.1)	28.1 (28.8)	11.5 (34.4)
Mean % reduction	44.3% (32.6%)	31.6% (32.7%)	37.0% (35.4%)	16.4% (44.6%)
p-value (ranked ANOVA) ¹	NA	< 0.001	0.005	< 0.001
p-value (ranked ANOVA) ²	NA	< 0.001	0.010	< 0.001
Lesion Type Mean (s.d.)	STUDY 07			
	Clin-RA (n = 293)	Clindamycin (n = 161)	Tretinoin (n = 306)	Vehicle (n = 144)
Inflammatory				
Mean baseline count	29.02 (7.78)	29.50 (8.24)	28.83 (7.69)	30.08 (8.28)
Mean number reduction	16.6 (12.1)	13.9 (12.8)	13.4 (12.6)	8.4 (14.3)
Mean % reduction	58.3% (41.2%)	49.7% (40.4%)	46.3% (41.8%)	31.8% (45.8%)
p-value (ranked ANOVA) ¹	NA	0.014	< 0.001	< 0.001
p-value (ranked ANOVA) ²	NA	0.003	< 0.001	< 0.001
Non-inflammatory				
Mean baseline count	47.76 (21.30)	50.89 (22.20)	48.92 (21.02)	49.81 (21.53)
Mean number reduction	18.7 (22.8)	16.2 (22.6)	17.7 (27.1)	9.2 (28.2)
Mean % reduction	41.3% (41.7%)	33.3% (46.4%)	36.6% (47.8%)	21.4% (47.6%)
p-value (ranked ANOVA) ¹	NA	0.170	0.850	< 0.001
p-value (ranked ANOVA) ²	NA	0.034	0.469	< 0.001
Total				
Mean baseline count	76.79 (24.05)	80.39 (25.43)	77.75 (23.70)	79.90 (24.54)
Mean number reduction	35.4 (30.0)	30.0 (29.7)	31.1 (34.1)	17.6 (35.6)
Mean % reduction	47.9% (36.7%)	40.0% (37.3%)	41.0% (38.4%)	25.4% (40.8%)
p-value (ranked ANOVA) ¹	NA	0.029	0.213	< 0.001
p-value (ranked ANOVA) ²	NA	0.008	0.037	< 0.001
Source: Sponsor's NDA submission (pages 122-125, 149-160, 169-174, 178-190, Clinical Study Report 7001-G2HP-06-02; pages 113-116, 140-148, 160-165, 168-182, Clinical Study Report 7001-G2HP-07-02); sponsor's responses (dated 6/4/04) to information requests.				
¹ p-values listed are the comparisons of mean absolute lesion reduction for Clin-RA vs. each of other three treatments.				
² p-values listed are the comparisons of mean percent lesion reduction for Clin-RA vs. each of other three treatments.				

Table A.5: EGS Score at Week 12 (PP Analyses) – Studies 06 and 07

Distribution of EGS at wk 12	STUDY 06			
	Clin-RA (n = 317)	Clindamycin (n = 155)	Tretinoin (n = 313)	Vehicle (n = 163)
Clear	4 (1%)	2 (1%)	4 (1%)	2 (1%)
Almost Clear	75 (24%)	23 (15%)	51 (16%)	16 (10%)
Mild	124 (39%)	65 (42%)	121 (39%)	48 (29%)
Moderate	102 (32%)	61 (39%)	126 (40%)	80 (49%)
Severe	12 (4%)	3 (2%)	11 (4%)	15 (9%)
Very Severe	0	1 (1%)	0	2 (1%)
Percentage of patients with Clear or Almost Clear Comparison (p-value) ¹	79 (25%) NA	25 (16%) 0.037	55 (18%) 0.015	18 (11%) < 0.001
Distribution of EGS at wk 12	STUDY 07			
	Clin-RA (n = 293)	Clindamycin (n = 161)	Tretinoin (n = 306)	Vehicle (n = 144)
Clear	9 (3%)	3 (2%)	2 (1%)	1 (1%)
Almost Clear	72 (25%)	31 (19%)	53 (17%)	13 (9%)
Mild	122 (42%)	53 (33%)	115 (38%)	49 (34%)
Moderate	83 (28%)	63 (39%)	121 (40%)	60 (42%)
Severe	7 (2%)	11 (7%)	15 (5%)	21 (15%)
Very Severe	0	0	0	0
Percentage of patients with Clear or Almost Clear Comparison (p-value) ¹	81 (28%) NA	34 (21%) 0.130	55 (18%) 0.005	14 (10%) < 0.001

Source: Sponsor's NDA submission (pages 147-148, 179, 185, and 191, Clinical Study Report 7001-G2HP-06-02; pages 138-139, 169, 174, and 179, Clinical Study Report 7001-G2HP-07-02).

¹p-value is the comparison between Clin-RA and each of other three treatments and is based on CMH test adjusting for investigational group.

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Table A.6: Mean (S.D.) Percent Lesion Reduction by Baseline Severity for Success and Failure Patients in the EGS (ITT) – Studies 06 and 07

Study Lesion type	Baseline EGS	EGS Failure					EGS Success ¹				
		Clin-RA	Clindamycin	Tretinoin	Vehicle	Clin-RA	Clindamycin	Tretinoin	Vehicle		
06 Inflammatory	Mild	37.4 (38.5)	45.4 (27.2)	40.4 (33.2)	38.6 (36.2)	75.1 (17.8)	69.0 (16.4)	68.6 (18.0)	74.0 (17.1)		
	Moderate	35.5 (43.3)	29.1 (45.9)	30.1 (42.8)	9.6 (53.2)	84.4 (13.3)	82.7 (14.4)	78.3 (15.9)	90.5 (12.7)		
	Severe	40.6 (37.4)	32.3 (31.8)	21.2 (37.8)	8.8 (44.1)	82.5 (12.9)	70.6 (.)	90.1 (17.3)	na		
	Very Severe	na	na	na	na	na	na	na	na		
Non-inflammatory	Mild	22.5 (35.6)	26.8 (18.1)	19.0 (51.4)	18.1 (27.9)	59.0 (23.6)	34.3 (57.9)	52.5 (24.9)	69.9 (9.9)		
	Moderate	30.3 (38.4)	13.4 (46.4)	27.1 (36.7)	5.4 (52.6)	67.0 (22.6)	67.7 (21.6)	69.4 (23.0)	75.3 (17.1)		
	Severe	37.3 (32.3)	25.7 (38.7)	23.0 (41.1)	11.1 (37.1)	78.4 (13.8)	68.8 (.)	74.7 (15.8)	na		
	Very Severe	na	na	na	na	na	na	na	na		
Total	Mild	29.1 (31.2)	33.2 (17.2)	27.7 (38.3)	26.2 (25.2)	64.9 (17.0)	48.7 (30.5)	59.7 (17.6)	72.5 (6.1)		
	Moderate	32.9 (32.3)	21.4 (34.0)	28.9 (32.2)	8.1 (41.7)	74.3 (15.6)	74.2 (14.8)	73.1 (17.4)	81.1 (12.5)		
	Severe	39.5 (28.4)	28.1 (25.0)	23.7 (31.3)	8.4 (35.9)	79.7 (12.0)	69.3 (.)	83.6 (10.8)	na		
	Very Severe	na	na	na	na	na	na	na	na		
07 Inflammatory	Mild	24.8 (42.0)	30.3 (57.0)	21.8 (40.0)	34.4 (40.1)	77.2 (13.5)	75.6 (11.2)	79.6 (15.4)	80.0 (.)		
	Moderate	42.5 (55.4)	37.3 (49.4)	31.5 (41.7)	29.2 (42.3)	85.0 (13.6)	79.9 (20.1)	83.1 (12.0)	88.6 (8.9)		
	Severe	43.6 (37.5)	32.4 (39.8)	41.2 (40.1)	16.2 (42.4)	89.8 (4.3)	91.3 (8.4)	92.3 (9.6)	78.9 (26.8)		
	Very Severe	na	7.7 (.)	na	-20.0 (.)	88.0 (.)	na	na	na		
Non-inflammatory	Mild	19.6 (40.6)	25.0 (20.5)	-0.5 (69.2)	2.7 (50.1)	62.0 (32.0)	49.3 (27.4)	54.7 (28.8)	26.5 (.)		
	Moderate	25.7 (45.2)	23.0 (47.5)	24.5 (48.5)	15.2 (46.3)	66.6 (27.1)	59.1 (25.5)	62.1 (25.1)	69.9 (25.6)		
	Severe	35.6 (36.6)	25.6 (44.2)	34.9 (38.7)	19.6 (38.1)	62.9 (27.3)	77.4 (15.5)	58.9 (47.4)	72.2 (20.0)		
	Very Severe	na	0 (.)	na	-121.7 (.)	90.9 (.)	na	na	na		
Total	Mild	21.1 (33.2)	28.0 (27.6)	7.8 (49.5)	15.0 (30.9)	67.8 (21.1)	61.1 (17.7)	65.2 (19.8)	51.6 (.)		
	Moderate	32.5 (38.8)	28.6 (36.1)	27.4 (38.2)	19.5 (39.1)	74.3 (18.0)	67.7 (19.1)	70.6 (16.0)	78.4 (15.4)		
	Severe	38.8 (30.9)	30.5 (33.7)	38.0 (32.8)	18.7 (32.2)	75.1 (16.0)	83.7 (9.4)	78.9 (21.7)	74.9 (22.6)		
	Very Severe	na	2.2 (.)	na	-54.4 (.)	88.9 (.)	na	na	na		

Source: Sponsor's electronic SAS data set at \\cdsesub\h21739\w_000\2004-02-06\crt.

¹ Success is defined as a score of 0 or 1 (i.e., clear or almost clear) in the EGS score at week 12.

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Table A.7: Patients with Increasing Lesion Counts and Achieved Success in EGS at Week 12

Patient ID	Treatment	Age	Gender	Race	Infl. at baseline	Infl. at Wk 12	Noninfl. at baseline	Noninfl. at Wk 12	Total at baseline	Total at Wk 12	EGS at baseline	EGS at Wk 12	% infl. change	% noninfl. change	% total change
Study 06															
642	Clin-RA	29	Female	White	21	2	38	44	59	46	2	1	90.5%	-15.8%	22.0%
130	Clindamycin	14	Female	White	20	2	27	54	47	56	2	1	90%	-100%	-19.1%
478	Tretinoin	14	Female	Black	32	17	91	112	123	129	3	1	46.9%	-23.1%	-4.9%
Study 07															
1641	Clin-RA	15	Female	White	20	10	25	29	45	39	2	1	50%	-16%	13.3%
2371	Clin-RA	19	Male	White	26	10	22	34	48	44	3	1	61.5%	-54.5%	8.3%
2552	Clindamycin	18	Male	Hispanic	26	6	39	41	65	47	3	1	76.9%	-5.1%	27.7%
1671	Tretinoin	17	Male	White	26	7	28	31	54	38	2	1	73.1%	-10.7%	29.6%
1683	Tretinoin	23	Female	Black	25	5	22	23	47	28	3	1	80%	-4.5%	40.4%

Source: Sponsor's electronic SAS data sets at \\cdsesub\21739n_000\2004-02-06\crt.

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Figure 1: Box-Plot of % Lesion Reduction for Treatment Groups – Study 06

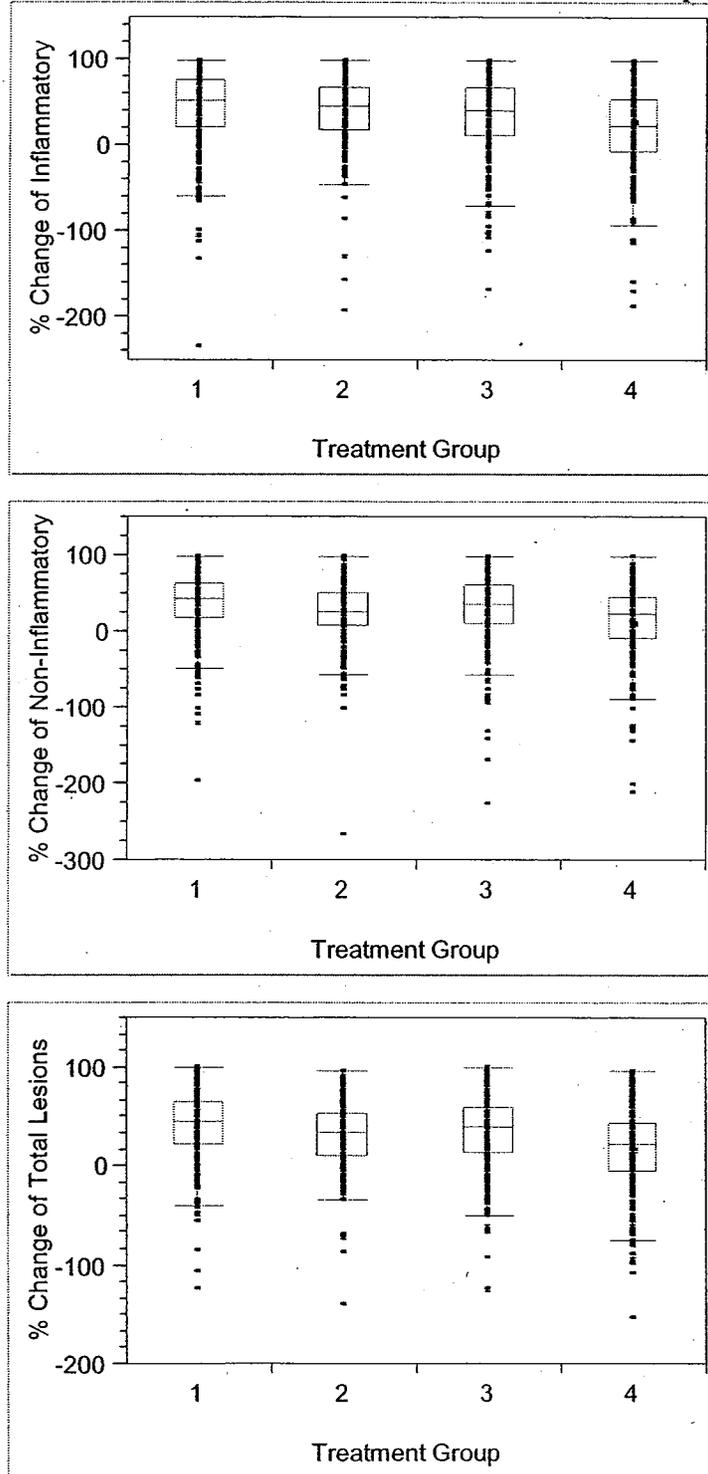


Figure 2: Box-Plot of % Lesion Reduction for Treatment Groups – Study 07

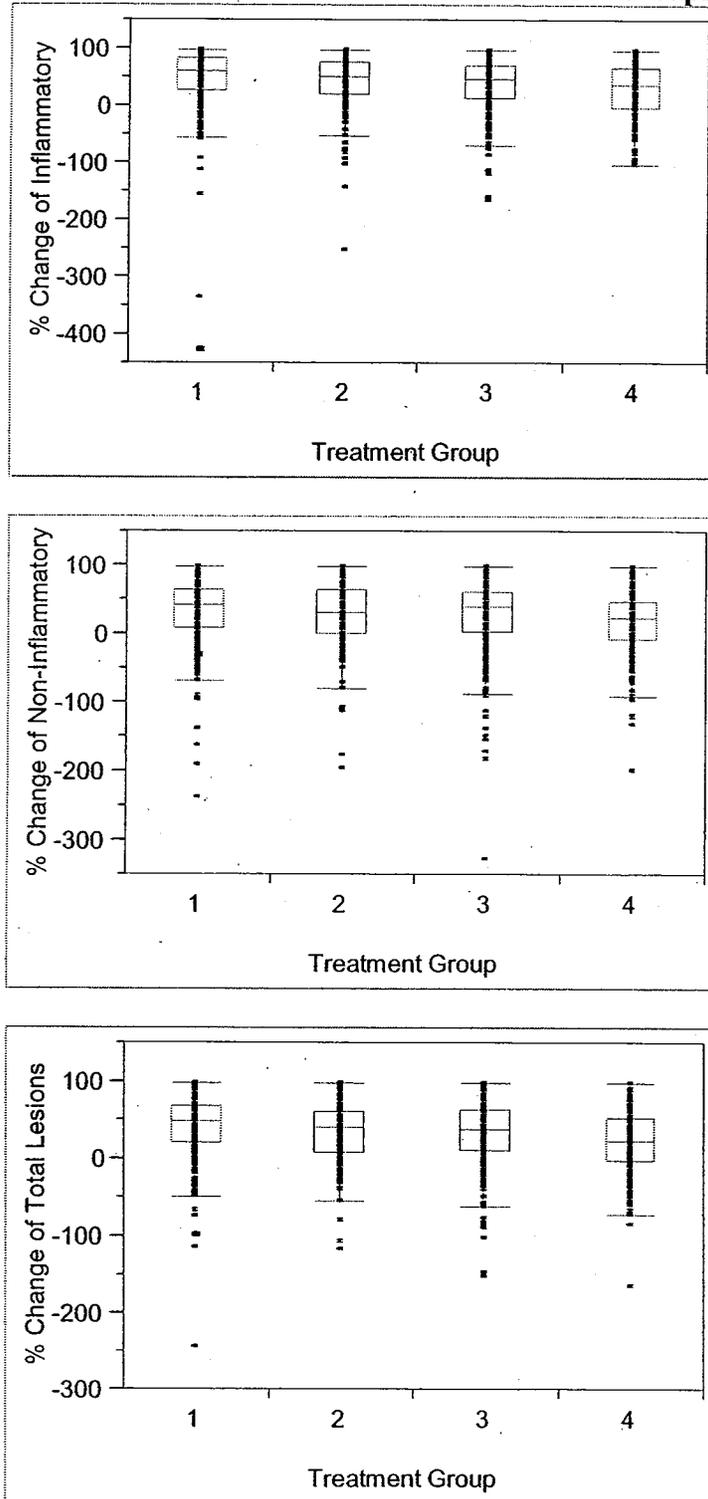


Table A.8: Number of Patients in Categories of Baseline Lesion Count for Clin-RA vs. Clindamycin – Studies 06 and 07

Category	1	2	3	4	5	6	7	8	9	10
STUDY 06										
Inflammatory	17 – 20	21 – 22	23 – 23	24 – 25	26 – 27	28 – 29	30 – 32	33 – 37	38 – 43	44 – 63
Baseline count	36	49	38	41	39	33	50	50	38	46
Clin-RA, n	17	35	16	16	28	20	13	26	19	18
Clindamycin, n										
Non-Inflammatory	15 – 25	26 – 30	31 – 34	35 – 38	39 – 44	45 – 50	51 – 59	60 – 68	69 – 83	84 – 141
Baseline count	40	36	45	35	38	47	45	46	41	47
Clin-RA, n	20	30	20	22	24	17	17	22	17	19
Clindamycin, n										
Total	38 – 50	51 – 57	58 – 62	63 – 68	69 – 73	74 – 81	82 – 90	91 – 103	104 – 116	117 – 195
Baseline count	36	42	46	39	35	43	44	46	40	49
Clin-RA, n	24	22	17	30	19	19	25	17	19	16
Clindamycin, n										
STUDY 07										
Inflammatory	4 – 20	21 – 22	23 – 23	24 – 25	26 – 26	27 – 28	29 – 31	32 – 35	36 – 41	42 – 58
Baseline count	34	67	32	52	26	41	50	38	40	45
Clin-RA, n	22	21	16	26	15	20	29	26	22	21
Clindamycin, n										
Non-Inflammatory	14 – 22	23 – 27	28 – 33	34 – 38	39 – 43	44 – 47	48 – 54	55 – 65	66 – 80	81 – 113
Baseline count	52	33	47	46	47	41	34	47	41	37
Clin-RA, n	14	22	28	19	16	19	29	16	28	27
Clindamycin, n										
Total	24 – 48	49 – 54	55 – 60	61 – 66	67 – 71	72 – 76	77 – 85	86 – 99	100 – 114	115 – 159
Baseline count	42	49	45	44	46	37	39	44	42	37
Clin-RA, n	19	22	19	19	16	24	26	24	19	30
Clindamycin, n										

Source: Sponsor's electronic SAS data sets at \cdsesub\in21739\in_000\2004-02-06\ert.

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Figure 3: % Lesion Reduction and Success in EGS by Baseline Lesion Category for Clin-RA vs. Clindamycin – Study 06

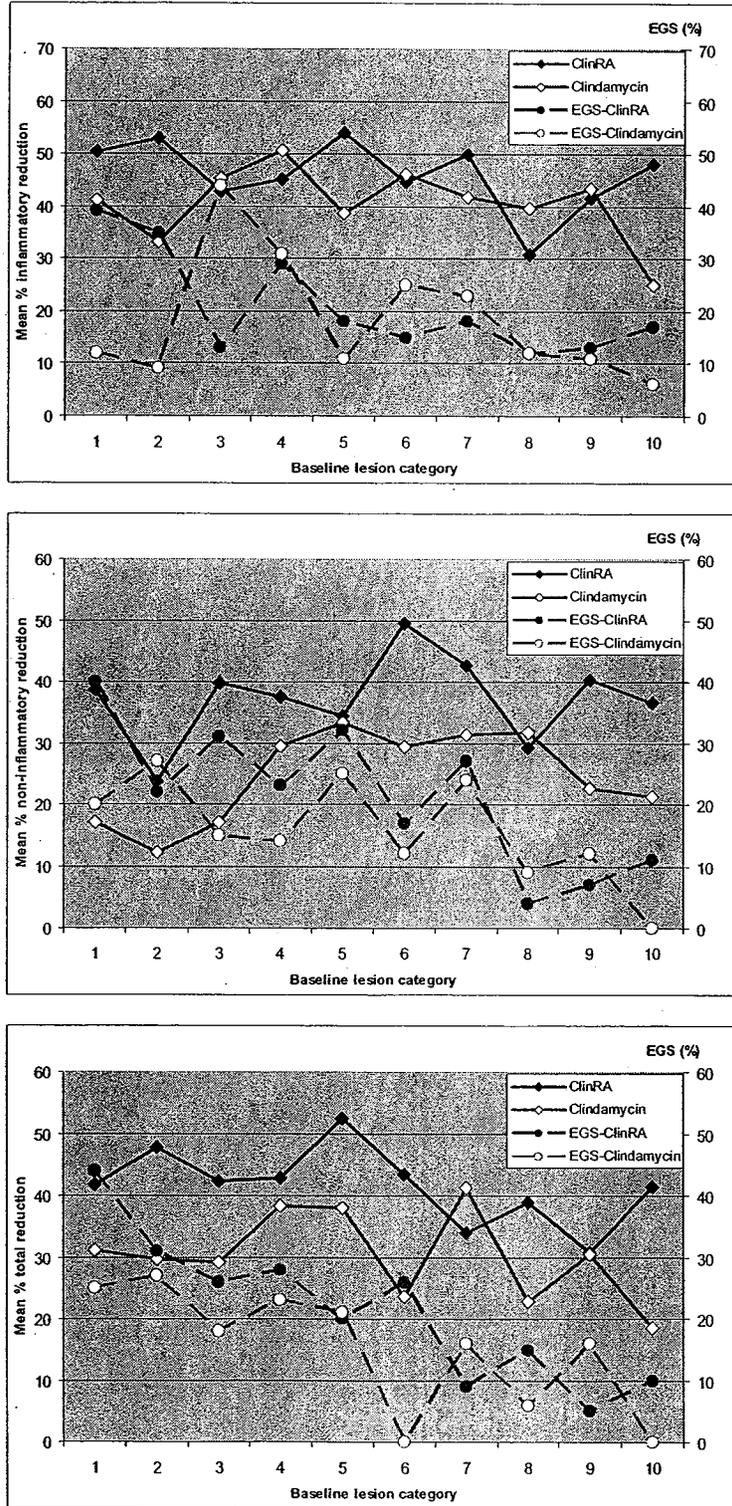
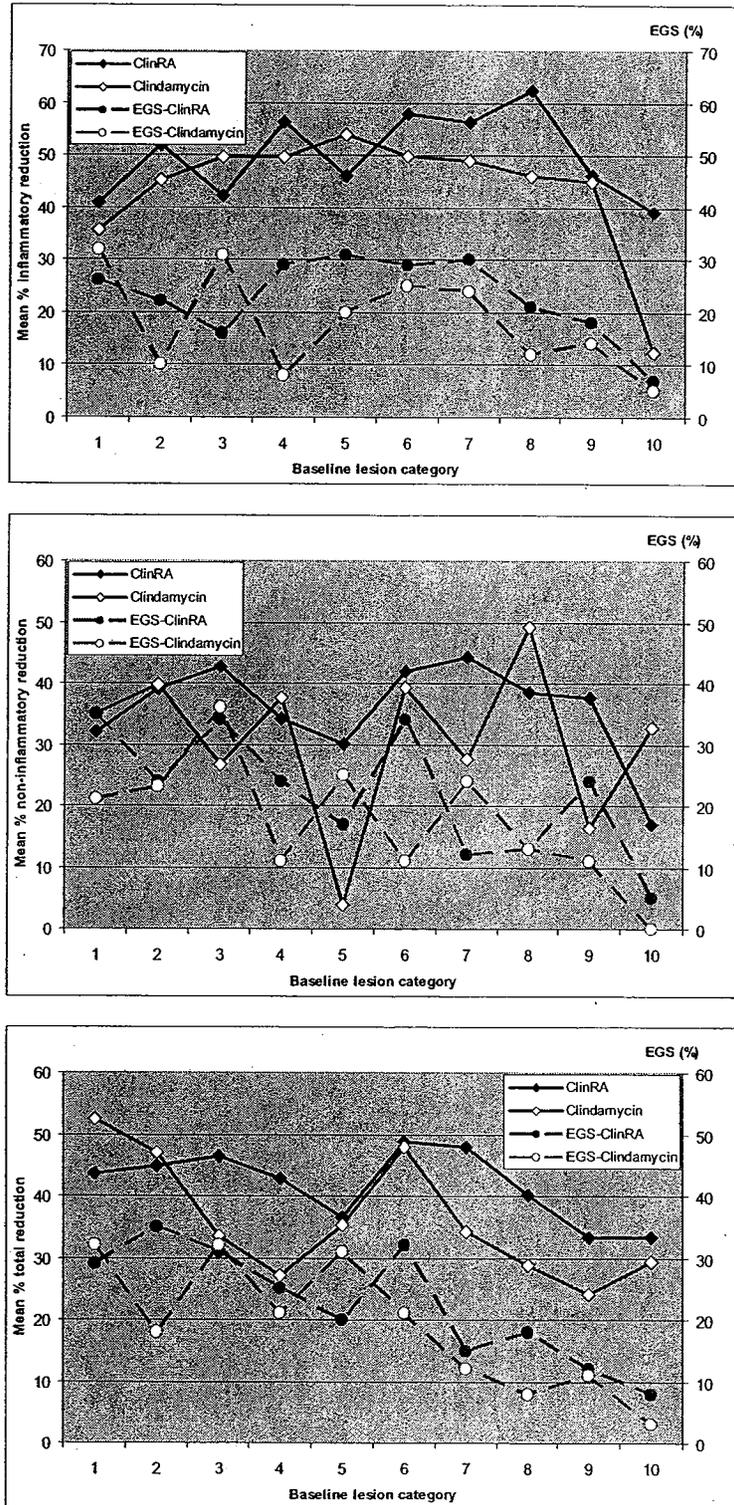


Figure 4: % Lesion Reduction and Success in EGS by Baseline Lesion Category for Clin-RA vs. Clindamycin – Study 07



**Table A.9: Comparison of Modified Success¹ Rates in EGS Score (ITT Analyses)
 Studies 06 and 07**

Study	Treatment	Clin-RA	Clindamycin	Tretinoin	Vehicle
06	Success Rate	101/420 (24.0%)	38/208 (18.3%)	70/417 (16.8%)	20/207 (9.7%)
	Comparison ²	na	0.100	0.008	< 0.001
07	Success Rate	118/425 (27.8%)	44/218 (20.2%)	83/429 (19.3%)	24/216 (11.1%)
	Comparison ²	na	0.030	0.003	< 0.001

Source: Sponsor's electronic SAS data sets at \cdsesub\21739\000\2004-02-06\crt.

¹ Modified success is defined as an EGS score of 0 or 1 or at least a 2-grade improvement from baseline. The LOCF approach was used for imputation at week 12.

² Comparison is Clin-RA vs. each of the other three treatments. Each pair comparison is based on CMH test adjusting for investigational group.

**Table A.10: Comparison of Modified Success¹ Rates in EGS Score (PP Analyses)
 Studies 06 and 07**

Study	Treatment	Clin-RA	Clindamycin	Tretinoin	Vehicle
06	Success Rate	90/317 (28.4%)	28/155 (18.1%)	60/313 (19.2%)	19/163 (11.7%)
	Comparison ²	na	0.020	0.003	< 0.001
07	Success Rate	100/293 (34.1%)	40/161 (24.8%)	73/306 (23.9%)	20/144 (13.9%)
	Comparison ²	na	0.031	0.005	< 0.001

Source: Sponsor's electronic SAS data sets at \cdsesub\21739\000\2004-02-06\crt.

¹ Modified success is defined as an EGS score of 0 or 1 or at least a 2-grade improvement from baseline. The LOCF approach was used for data imputation at week 12.

² Comparison is Clin-RA vs. each of the other three treatments. Each pair comparison is based on CMH test adjusting for investigational group.

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Figure 5: % Lesion Reduction over Time (ITT) – Study 06

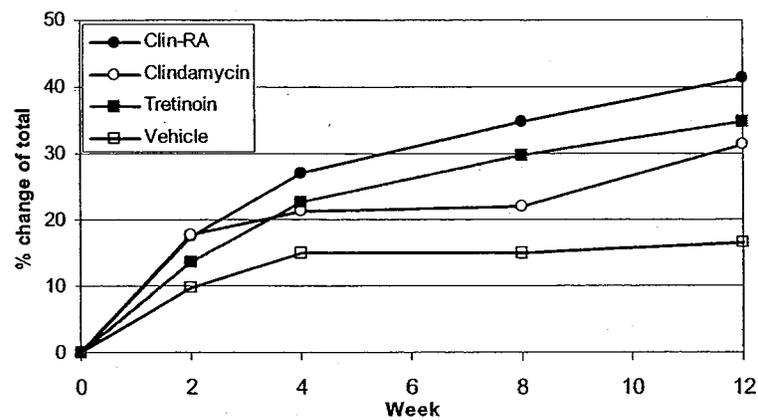
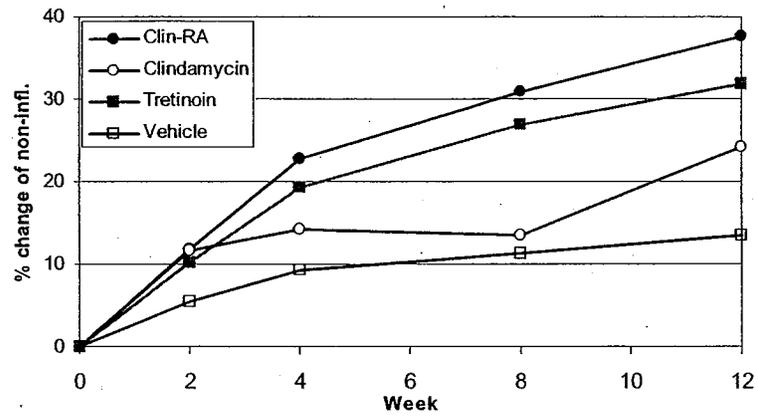
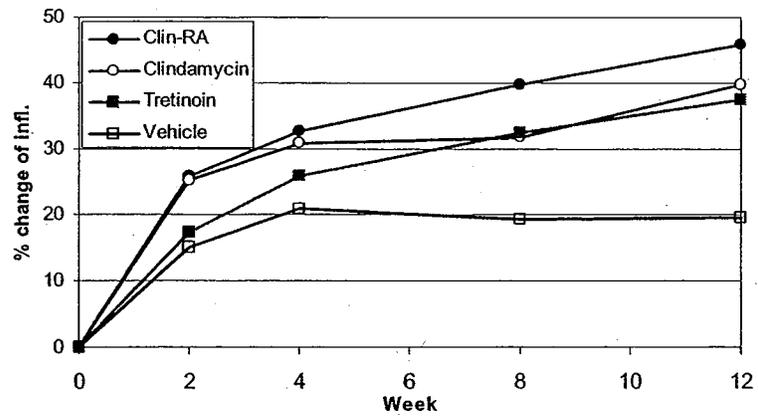


Figure 6: % Lesion Reduction over Time (ITT) – Study 07

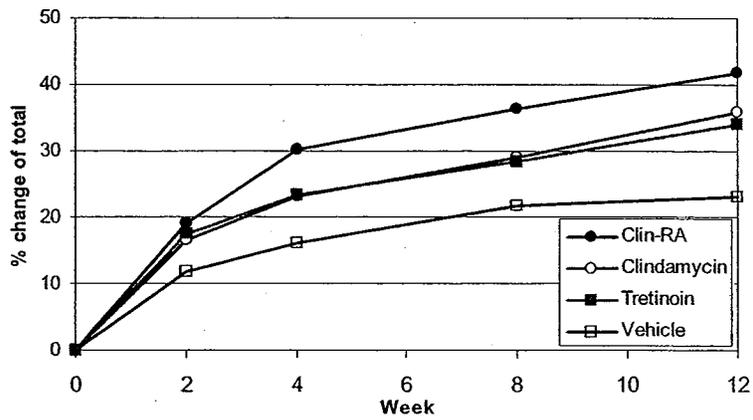
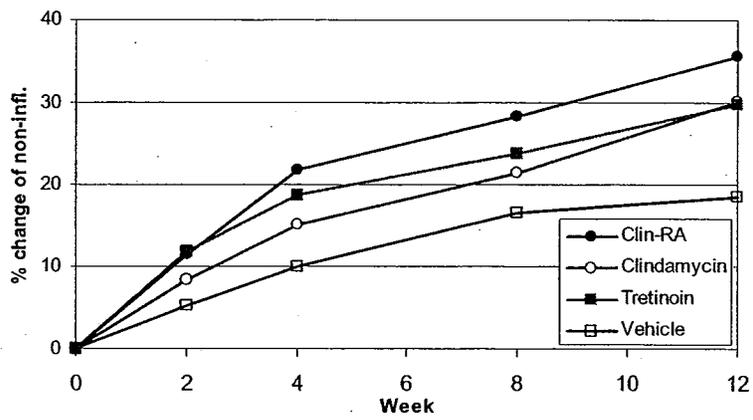
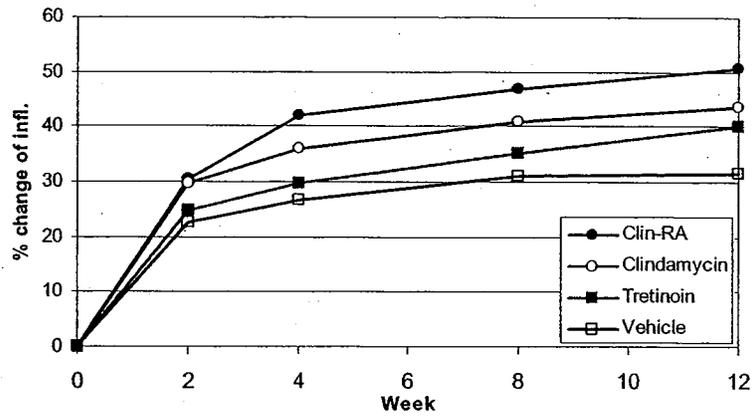
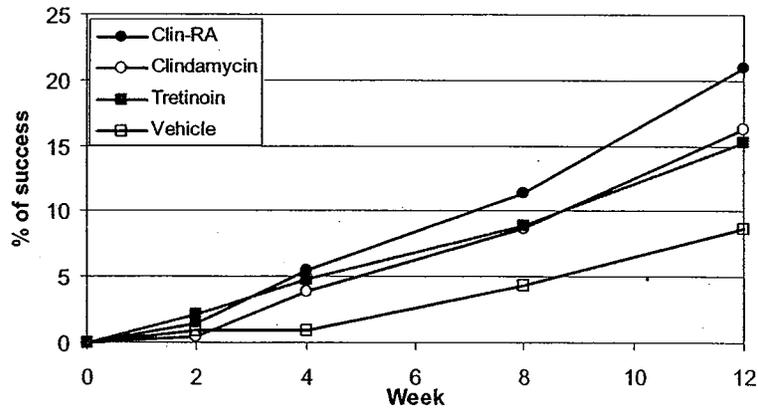
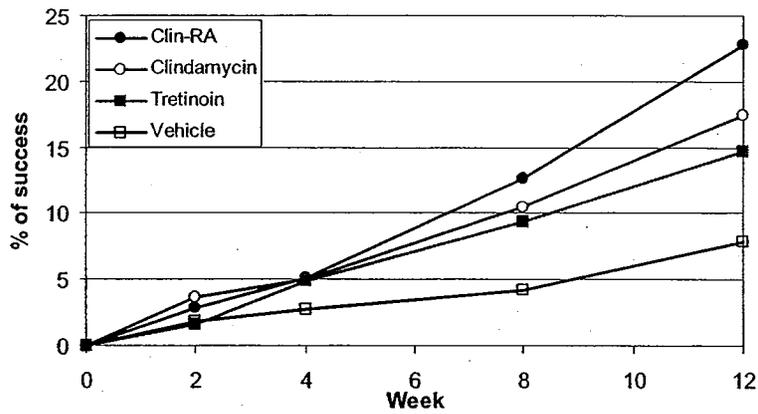


Figure 7: Percentage of Patients with Clear or Almost Clear in the EGS Score over Time (ITT) – Studies 06 and 07

Study 06



Study 07



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Table A.11: Comparisons of Adverse Events That Occurred at a Frequency of At Least 5% of Patients (Safety Population) – Studies 06 and 07 Combined

Variable	Clin-RA (N = 845) 225 (27%)	Clindamycin (N = 426) 102 (24%)	Tretinoin (N = 846) 225 (27%)	Vehicle (N = 423) 91 (22%)
No. of patients had AE				
Body system				
Respiratory, thoracic and mediastinal disorders	76 (9%)	36 (8%)	87 (10%)	38 (9%)
Skin and subcutaneous tissue disorders	62 (7%)	19 (4%)	67 (8%)	17 (4%)
Pairwise Comparison ¹	Clin-RA vs. Clindamycin 0.309	Clin-RA vs. Tretinoin 1.000	Clin-RA vs. Vehicle 0.054	Clindamycin vs. Tretinoin 0.341
Over AE incidence				
Body system				
Respiratory, thoracic and mediastinal disorders	0.834	0.410	1.000	0.316
Skin and subcutaneous tissue disorders	0.052	0.714	0.026	0.024
Source: Sponsor's NDA submission (pages 29 in ISS at \\cdsesub\ln21739\in_000\2004-02-06\cinstat).				
¹ p-value was based on Fisher's exact test.				
			Clindamycin vs. Vehicle 0.414	Tretinoin vs. Vehicle 0.054
			0.809	0.486
			0.865	0.008

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**Table A.12: Subgroup Results of Primary Efficacy Endpoints By Gender (ITT)
 Studies 06 and 07**

Endpoints	Clin-RA	Clindamycin	Tretinoin	Vehicle
STUDY 06				
# of patients				
Male	222	117	215	97
Female	198	91	202	110
% change in infl., mean (s.d.)				
Male	39.1 (46.0)	36.2 (38.8)	31.6 (44.4)	15.7 (48.1)
Female	53.7 (36.0)	44.3 (46.9)	43.8 (39.1)	23.0 (56.9)
% change in noninf, mean (s.d.)				
Male	37.1 (35.6)	25.7 (36.6)	24.5 (44.4)	13.5 (46.1)
Female	38.1 (40.1)	22.1 (52.7)	39.8 (33.0)	13.5 (53.3)
% change in total, mean (s.d.)				
Male	38.3 (34.1)	30.6 (29.9)	28.0 (36.6)	15.0 (38.8)
Female	44.9 (32.0)	32.3 (38.6)	41.9 (31.2)	17.8 (45.6)
% of success in EGS, n (%)				
Male	45 (20%)	15 (13%)	25 (12%)	6 (6%)
Female	43 (22%)	19 (21%)	39 (19%)	12 (11%)
STUDY 07				
# of patients				
Male	190	107	193	106
Female	235	111	236	110
% change in infl., mean (s.d.)				
Male	45.9 (40.6)	38.0 (48.0)	31.6 (43.9)	18.2 (46.3)
Female	54.5 (54.4)	49.0 (46.3)	47.0 (40.1)	44.8 (37.1)
% change in noninf, mean (s.d.)				
Male	31.9 (40.5)	27.4 (44.9)	22.9 (52.9)	5.6 (49.5)
Female	38.8 (45.6)	32.8 (44.8)	35.7 (43.3)	30.9 (41.0)
% change in total, mean (s.d.)				
Male	37.9 (33.2)	31.7 (37.0)	27.2 (41.2)	10.1 (40.1)
Female	44.9 (40.9)	40.0 (35.3)	39.9 (36.7)	35.9 (34.6)
% of success in EGS, n (%)				
Male	33 (17%)	11 (10%)	21 (11%)	5 (5%)
Female	64 (27%)	27 (24%)	42 (18%)	12 (11%)
<p>Source: Sponsor's NDA submission (pages 196-199, Clinical Study Report 7001-G2HP-06-02; pages 183-186, Clinical Study Report 7001-G2HP-07-02) and electronic SAS data sets. * The LOCF approach is used for missing data imputation at week 12.</p>				

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**Table A.13: Subgroup Results of Primary Efficacy Endpoints By Race (ITT)
 Studies 06 and 07**

Endpoints	Clin-RA	Clindamycin	Tretinoin	Vehicle
STUDY 06				
# of patients				
Caucasian	304	155	298	151
Black	44	17	44	23
Hispanic	62	29	64	28
Others	10	7	11	5
% change in infl., mean (s.d.)				
Caucasian	43.4 (44.0)	38.9 (41.5)	36.2 (43.4)	11.3 (54.8)
Black	62.0 (37.1)	55.7 (35.0)	47.7 (37.2)	52.6 (43.7)
Hispanic	46.4 (34.1)	33.1 (53.6)	35.8 (37.8)	38.4 (33.6)
Others	53.7 (39.0)	47.5 (27.5)	43.5 (53.3)	14.4 (50.7)
% change in noninfl., mean (s.d.)				
Caucasian	38.8 (35.4)	25.9 (46.6)	32.7 (39.7)	10.5 (48.7)
Black	38.7 (33.4)	17.2 (37.1)	32.6 (44.2)	26.1 (64.6)
Hispanic	30.8 (50.6)	19.9 (35.9)	26.0 (40.0)	19.0 (44.9)
Others	36.2 (34.9)	19.0 (44.0)	41.5 (28.8)	14.2 (37.7)
% change in total, mean (s.d.)				
Caucasian	41.5 (32.2)	32.1 (35.2)	34.6 (34.8)	11.6 (42.3)
Black	47.0 (31.3)	31.2 (27.2)	39.7 (36.0)	38.3 (45.4)
Hispanic	36.9 (39.1)	26.8 (32.9)	30.8 (33.8)	25.3 (35.6)
Others	41.7 (33.7)	31.9 (26.3)	42.2 (36.6)	13.7 (40.7)
% of success in EGS, n (%)				
Caucasian	62 (20%)	27 (17%)	42 (14%)	9 (6%)
Black	12 (27%)	1 (6%)	12 (27%)	6 (26%)
Hispanic	13 (21%)	5 (17%)	9 (14%)	3 (11%)
Others	1 (10%)	1 (14%)	1 (9%)	0
STUDY 07				
# of patients				
Caucasian	312	145	279	135
Black	61	40	81	46
Hispanic	40	22	47	22
Others	12	11	22	13
% change in infl., mean (s.d.)				
Caucasian	46.8 (45.5)	39.6 (48.6)	35.6 (42.9)	27.2 (43.0)
Black	58.8 (71.8)	50.8 (48.8)	56.6 (35.7)	42.9 (42.5)
Hispanic	63.4 (28.1)	48.5 (38.7)	42.5 (41.5)	35.0 (46.6)
Others	67.5 (26.7)	59.5 (38.9)	30.2 (49.2)	34.2 (49.7)
% change in noninfl., mean (s.d.)				
Caucasian	34.1 (44.8)	33.4 (40.6)	30.8 (50.7)	20.1 (40.9)
Black	33.2 (44.3)	24.5 (50.2)	30.8 (39.4)	16.2 (58.6)
Hispanic	46.5 (30.2)	13.5 (59.2)	24.3 (47.2)	14.3 (53.1)
Others	52.4 (37.0)	40.4 (40.4)	27.4 (50.4)	17.0 (55.1)
% change in total, mean (s.d.)				
Caucasian	39.5 (38.4)	36.6 (33.3)	33.4 (39.5)	22.4 (34.1)
Black	43.2 (41.6)	34.2 (42.3)	40.1 (33.4)	25.8 (48.7)
Hispanic	52.7 (24.0)	27.3 (43.8)	31.8 (43.8)	21.2 (47.8)
Others	58.8 (31.1)	50.0 (33.8)	27.0 (45.8)	26.3 (44.0)
% of success in EGS, n (%)				
Caucasian	68 (22%)	19 (13%)	37 (13%)	7 (5%)
Black	13 (21%)	11 (28%)	13 (16%)	6 (13%)
Hispanic	11 (28%)	5 (23%)	10 (21%)	2 (9%)
Others	5 (42%)	3 (27%)	3 (14%)	2 (15%)
<p>Source: Sponsor's NDA submission (pages 196-199, Clinical Study Report 7001-G2HP-06-02; pages 183-186, Clinical Study Report 7001-G2HP-07-02) and electronic SAS data sets.</p> <p>* The LOCF approach is used for missing data imputation at week 12.</p>				

**Table A.14: Subgroup Results of Primary Efficacy Endpoints By Age (ITT)
 Studies 06 and 07**

Endpoints	Clin-RA	Clindamycin	Tretinoin	Vehicle
STUDY 06				
# of patients				
Age ≤ 16	242	112	231	118
Age > 16	178	96	186	89
% change in infl., mean (s.d.)				
Age ≤ 16	41.5 (47.1)	37.1 (41.7)	30.7 (43.6)	6.6 (57.6)
Age > 16	52.2 (33.5)	42.8 (43.7)	45.9 (39.1)	36.9 (40.3)
% change in noninf, mean (s.d.)				
Age ≤ 16	35.8 (36.4)	19.6 (47.5)	24.4 (40.1)	4.4 (51.0)
Age > 16	40.0 (39.6)	29.4 (39.8)	41.2 (38.0)	25.6 (46.1)
% change in total, mean (s.d.)				
Age ≤ 16	38.7 (33.6)	27.5 (35.1)	27.5 (34.2)	6.4 (44.9)
Age > 16	45.1 (32.5)	35.7 (32.0)	43.7 (33.4)	29.8 (35.2)
% of success in EGS, n (%)				
Age ≤ 16	45 (19%)	16 (14%)	23 (10%)	6 (5%)
Age > 16	43 (24%)	18 (19%)	41 (22%)	12 (13%)
STUDY 07				
# of patients				
Age ≤ 16	220	118	229	119
Age > 16	205	100	200	97
% change in infl., mean (s.d.)				
Age ≤ 16	45.2 (48.1)	32.8 (53.8)	36.8 (45.7)	21.9 (43.1)
Age > 16	56.5 (49.0)	56.3 (34.7)	43.8 (38.3)	43.8 (41.9)
% change in noninf, mean (s.d.)				
Age ≤ 16	31.1 (48.9)	26.7 (42.4)	27.7 (45.3)	5.1 (44.3)
Age > 16	40.6 (36.3)	34.1 (47.3)	32.5 (51.4)	35.0 (45.2)
% change in total, mean (s.d.)				
Age ≤ 16	36.6 (41.5)	30.0 (34.5)	31.4 (38.9)	10.9 (34.3)
Age > 16	47.3 (32.6)	42.9 (37.2)	37.4 (39.5)	38.3 (40.2)
% of success in EGS, n (%)				
Age ≤ 16	41 (19%)	11 (9%)	30 (13%)	2 (2%)
Age > 16	56 (27%)	27 (27%)	33 (17%)	15 (15%)
Source: Sponsor's NDA submission (pages 212-215, Clinical Study Report 7001-G2HP-06-02; pages 199-202, Clinical Study Report 7001-G2HP-07-02) and electronic SAS data sets. * The LOCF approach is used for missing data imputation at week 12.				

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Table A.15: Subgroup Results of the Primary Efficacy Endpoints by Baseline EGS Score (ITT) Study 06

Endpoints	Clin-RA	Clindamycin	Tretinoin	Vehicle
# of patients				
Mild	68	34	52	30
Moderate	304	148	325	153
Severe	48	26	39	24
Very severe	0	0	0	0
Missing	0	0	1	0
% change in infl., mean (s.d.)				
Mild	48.5 (37.8)	51.0 (26.8)	46.9 (32.5)	44.5 (36.1)
Moderate	45.5 (34.8)	38.2 (46.7)	37.1 (43.4)	16.4 (55.8)
Severe	45.8 (37.9)	33.8 (32.1)	30.0 (42.7)	8.8 (44.1)
Very severe	NA	NA	NA	NA
Missing	NA	NA	-10.0	NA
% change in noninf, mean (s.d.)				
Mild	33.2 (36.5)	28.6 (31.1)	26.8 (48.6)	26.8 (32.3)
Moderate	37.8 (38.7)	22.6 (47.7)	33.2 (38.1)	11.3 (54.2)
Severe	42.4 (33.4)	27.4 (38.8)	29.6 (42.4)	11.1 (37.1)
Very severe	NA	NA	NA	NA
Missing	NA	NA	-36.7	NA
% change in total, mean (s.d.)				
Mild	39.6 (32.2)	36.9 (21.6)	35.1 (37.0)	33.9 (29.0)
Moderate	41.3 (34.0)	30.3 (37.3)	35.3 (34.2)	14.3 (44.9)
Severe	44.5 (30.0)	29.7 (25.8)	31.4 (35.7)	8.4 (35.9)
Very severe	NA	NA	NA	NA
Missing	NA	NA	-32.2	NA
% of success in EGS, n (%)				
Mild	20 (29%)	8 (24%)	12 (23%)	5 (17%)
Moderate	62 (20%)	25 (17%)	47 (14%)	13 (8%)
Severe	6 (13%)	1 (4%)	5 (13%)	0
Very severe	NA	NA	NA	NA
Missing	NA	NA	0	NA

Source: Sponsor's NDA submission (pages 196-199, Clinical Study Report 7001-G2HP-06-02).
 * The LOCF approach is used for missing data imputation at week 12.

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Table A.16: Subgroup Results of the Primary Efficacy Endpoints by Baseline EGS Score (ITT) Study 07

Endpoints	Clin-RA	Clindamycin	Tretinoin	Vehicle
# of patients				
Mild	50	18	39	16
Moderate	301	153	310	161
Severe	71	45	79	38
Very severe	1	1	0	1
Missing	2	1	1	0
% change in infl., mean (s.d.)				
Mild	42.7 (42.9)	45.4 (51.2)	36.6 (43.5)	37.3 (40.4)
Moderate	52.8 (51.9)	43.7 (48.6)	39.8 (42.9)	34.4 (43.9)
Severe	47.5 (38.2)	44.2 (42.9)	43.1 (40.6)	19.5 (43.9)
Very severe	88.0	7.7	NA	-20
Missing	19.2 (0.2)	0	0	NA
% change in noninf, mean (s.d.)				
Mild	34.0 (42.7)	33.1 (25.1)	13.7 (65.8)	4.2 (48.8)
Moderate	35.6 (45.1)	28.5 (46.7)	30.6 (47.5)	19.9 (47.4)
Severe	37.9 (36.6)	36.0 (45.1)	35.8 (38.9)	22.4 (39.0)
Very severe	90.9	0	NA	-121.7
Missing	-12.0 (29.0)	0	0	NA
% change in total, mean (s.d.)				
Mild	37.0 (36.9)	39.1 (29.0)	22.5 (50.4)	17.3 (31.2)
Moderate	42.7 (39.2)	34.4 (36.8)	34.4 (38.9)	24.7 (41.1)
Severe	41.9 (31.5)	41.1 (37.2)	39.5 (33.2)	21.7 (34.0)
Very severe	88.9	2.2	NA	-54.4
Missing	1.6 (15.9)	0	0	NA
% of success in EGS, n (%)				
Mild	17 (34%)	6 (33%)	10 (26%)	1 (6%)
Moderate	73 (24%)	23 (15%)	50 (16%)	14 (9%)
Severe	6 (8%)	9 (20%)	3 (4%)	2 (5%)
Very severe	1 (100%)	0	NA	0
Missing	0	0	0	NA
Source: Sponsor's NDA submission (pages 196-199, Clinical Study Report 7001-G2HP-06-02).				
* The LOCF approach is used for missing data imputation at week 12.				

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SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer:
Date:

Shiowjen Lee, Ph.D., Biometrics III
09/13/2004

Concurring Reviewer/
Statistical Team Leader:

Mohamed Alesh, Ph.D., Biometrics III

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This statistical review contains 51 pages (1 cover page, 1 page of table of contents, 25 pages of text, 23 pages of Appendix and one page of distribution list).

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Statistical Review and Evaluation: Filing Meeting Review

NDA: 21,739/N-000
Submission Date: 02/06/04
Name of Drug: Clin-RA Gel (Clindamycin phosphate 1.2% and Tretinoin 0.025%)
Applicant: Dow Pharmaceuticals
Indication(s): Acne vulgaris
Rout of Administration: Topically once daily for 12 weeks
Clinical Studies: Two pivotal clinical trials (G2HP-07-02 and G2HP-06-02)
Related INDs, NDAs: IND65,531
Clinical Reviewer: Brenda Carr, M.D., HFD-540
Statistical Reviewer: Shiojwen Lee, Ph.D., HFD-725
Project Manager: Jacquelyn Smith, HFD-540

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.). | ✓ | — | — |
| @D. Is the data have been submitted electronically? | ✓ | — | — |
| If the data have been submitted electronically, has adequate documentation of the data sets been provided? | ✓ | — | — |
| If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?
(No lab. data for pivotal trials) | — | — | ✓ |

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?
- *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?

The submission is reviewable. The following information is requested.

According to the submitted clinical study report (for both pivotal trials), drug supplies were numbered sequentially in order and were dispensed sequentially to the subjects entering the study within an investigational site. Please explain any deviation about the treatment allocation.

Shiowjen Lee, Ph.D.
Mathematical Statistician, Biometrics III

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

cc:

Archival: NDA 21,739/N-000

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HFD-725/Dr. Lee

Chron.

This NDA filing review contains 3 pages.

* 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.

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