

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-400

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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Applicant: Penederm Incorporated
Name of Drug: tretinoin (ACTICIN) 0.025% gel
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Medical Officer: Nancy Slifman, M.D., HFD-540

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I. INTRODUCTION

The applicant requests the following indication in the **Indications and Usage** section of the proposed label:

The following treatment regimen is suggested in the **Dosage and Administration** section of the proposed label:

In support of their claims, the applicant has submitted data from two primary studies, protocols PDC 004-003 and PDC 004-015. These studies compare the safety and efficacy of Acticin 0.025% tretinoin gel to Retin-A 0.025% tretinoin gel (PDC 004-003 only) or Acticin vehicle (PDC 004-003 and PDC 004-015) in the treatment of patients with mild to moderate acne vulgaris.

The two trials, described in section II below, are similar in design. Throughout the review, the terms "study 003" and "study 015" refer to protocols PDC 004-003 and PDC 004-015, respectively. The treatment name abbreviations ACT, RET, and VEH refer to Acticin, Retin-A, and vehicle, respectively.

II. METHODS

Studies 003 and 015 are randomized, double blind, multicenter, controlled, parallel group trials that were conducted in the US. Study 003 had three treatment arms (ACT, RET, and VEH), while study 015 had two treatment arms (ACT and VEH). The randomization schedules were designed to allocate patients equally across the treatment groups.

The studies were to include only those patients with mild to moderate facial acne (FDA grades II and III). As specified in the protocols, a patient met this criterion if he/she had at least 30 open and closed comedones (non-inflammatory lesions), at least 10 papules and pustules (inflammatory lesions), and no significant nodulocystic acne (<4 lesions) at study entry. Study 015 had the additional restriction that a patient must not have more than 200 lesions by total lesion count (non-inflammatory plus inflammatory lesions). Please refer to the Medical Officer's Review for the other inclusion/exclusion criteria.

Eligible patients were randomized to treatment and were to apply the test material to the forehead, nose, chin, and cheeks once daily in the evening for 12 weeks (84 days). Follow up assessments were to occur on days 7 (study 003 only), 14 (study 003 only), 28, 56, and 84.

At each follow up assessment, the following evaluations were to be made:

1. Lesion Counts: Actual counts of open comedones and closed comedones (non-inflammatory lesions) and papules and pustules (inflammatory lesions). The counts were to include lesions on the forehead, cheeks, and chin above the jawline. Lesions on the nose were to be excluded.
2. Skin parameters: Erythema, peeling, and dryness of the treatment sites were to be evaluated by the investigator. Burning/stinging, itching, and tightness of the treatment sites were to be evaluated by the patient. Four categories were to be used in each evaluation: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

3. **Global Assessment:** A clinical assessment of overall improvement in the patient's acne from baseline. The assessment was to incorporate reduction in lesions, skin parameters, and a general clinical evaluation. Five categories were to be used for the evaluation: 1 = excellent, 2 = good, 3 = fair, 4 = no change, 5 = worse.

REVIEWER NOTE: *The protocol failed to define the categories of the skin parameter scale and the global assessment scale.*

In protocol 003, the specified primary efficacy parameters are the change from baseline in total lesion count (defined as the sum of inflammatory and non-inflammatory lesions) and the global assessment. The primary visit of interest was not specified. The change in total lesion count was to be analyzed with an ANOVA model including treatment, investigator, and the treatment by investigator interaction. The global assessment was to be analyzed similarly using a categorical mean score model.

In protocol 015, the specified primary efficacy parameters are the change, percent change, and categorical percent change in total lesion count from baseline to day 84. The change and percent change in total lesion count was to be analyzed with an ANOVA model including treatment, investigator, and the treatment by investigator interaction. The categorical percent change in total lesion count was to be analyzed similarly using a categorical mean score model. The percent change in lesion count was to be categorized into four levels: worse/no change ($\leq 0\%$), 1-25%, 26-50%, 51-100%. The protocol states that any category that has too few observed patients may be combined with another appropriate category for analysis.

REVIEWER COMMENTS: *In NDA submissions for the indication of acne vulgaris, the test product is generally required to show superiority to vehicle on the last day of treatment for the following primary efficacy parameters simultaneously:*

1. *Percent change from baseline in non-inflammatory lesion count (or inflammatory lesion count, depending on the target lesion type)*
2. *Percent change from baseline in total lesion count*
3. *Global assessment*

All other parameters are generally considered to be secondary efficacy parameters.

This review emphasizes the percent change from baseline in non-inflammatory lesions, inflammatory lesions, and total lesions, and the global assessment. Day 84 is the last day of treatment and is the primary endpoint of interest. The percent change from baseline in lesion counts will be analyzed via ANOVA models that include the main effects of treatment and investigator, and also the treatment by investigator interaction. The Global Assessment will be analyzed via the Cochran-Mantel-Haenszel method controlling for investigator and using modified riddit scores. Main effects will be deemed significant at the 0.05 level. Interaction effects will be deemed significant at the 0.15 level.

If an overall treatment effect is significant, pairwise treatment comparisons will be performed. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. This reviewer will apply a Bonferroni adjustment for three pairwise comparisons, using a significance level of $0.05/3 = 0.017$.

It must be emphasized that the categories for the global assessment scale were not defined in the protocol. Therefore, the interpretation of the scale would most likely vary among the investigators. Without clear definitions of the scale categories, the usefulness of the global assessment scale is questionable.

Since ACTICIN is essentially a generic version of the innovator product Retin-A, equivalence of ACTICIN to Retin-A at day 84 must also be demonstrated. The regulatory definition of equivalence states that the

generic product must not be 20% better or 20% worse than the innovator product. A confidence interval approach will be used to assess efficacy equivalence. In this analysis approach, a center weighted, two-tailed 95% confidence interval of the Acticin minus Retin-A difference in the mean percent change in lesion count will be calculated. To be deemed equivalent, the lower and upper bounds of this interval must not exceed 20% of the Retin-A mean in absolute value. With respect to equivalence, total lesions and non-inflammatory lesions will be examined as primary parameters, and inflammatory lesions will be examined as a secondary parameter.

The protocols did not define the study populations that were to be included in the efficacy analyses. According to the statistical reports, there were two levels of evaluability status for the efficacy analyses, patient and visit. Protocol violators were excluded from all visits; however, an evaluable patient could be excluded from a particular visit if the visit did not fall within the specific time window for that visit. The evaluable visit windows were day 7 ± 2 (study 003 only), day 14 ± 2 (study 003 only), day 28 ± 7 , day 56 ± 7 , and day 84 ± 7 . All patients at all observed visits (regardless of window) were included in the intent-to-treat analyses.

REVIEWER COMMENTS: *This reviewer's EVAL population contains those patients who did not violate the protocol, and who were evaluable for visit 84. This reviewer's ITT population contains those patients who had at least one post baseline visit.*

The applicant performed observed-case (OC) analyses. This reviewer contends that last-observation carried forward analyses (LOCF) should also be performed, where values for missed visits are replaced with the values from the previous visit.

With two patient populations, and two analytical approaches, there are four potential analysis populations: 1. EVAL-OC 2. EVAL-LOCF 3. ITT-OC 4. ITT-LOCF. However, only efficacy results from the EVAL-OC and ITT-LOCF analyses are emphasized in this review. The EVAL-OC population is considered the primary efficacy analysis population.

Efficacy results at day 84 in the EVAL-OC population are of primary interest, and are presented in detail. Day 84 efficacy results from the ITT-LOCF population are also presented to assess consistency and robustness of the results.

Descriptive efficacy analyses of lesion counts over time are presented graphically. The graphical analyses are presented for the EVAL-OC analysis population by treatment, and by treatment for the following subgroups: center, sex, age (<30 , ≥ 30), and race (black/other, white).

According to the protocols, safety was to be assessed via the six skin parameters, and the patient incidence of adverse events. The skin parameter results were to be analyzed via a categorical mean score model which included the main effects of treatment and investigator, and the treatment by investigator interaction. The treatment incidences of clinical adverse events were to be compared via chi-square tests. The applicant performed these analyses using the ITT-OC approach. Differences will be deemed significant at the 0.05 level.

REVIEWER COMMENTS: *This reviewer used a different approach in the analysis of the skin safety parameters. In this review's analysis, the change in skin safety score from baseline to day 84 was computed, and then categorized as "worse" (any change value > 0), "no change" (any change value equal to 0), or "improve" (any change value < 0). The categorized change in skin safety parameters was analyzed via the Cochran-Mantel-Haenszel approach controlling for investigator and using modified riddit scores. The analysis of skin safety parameters was performed in both the ITT-OC and ITT-LOCF populations. The ITT-LOCF population is considered the primary safety analysis population.*

Descriptive safety analyses of changes in skin safety parameters over time are presented graphically. The graphical analyses are presented for the ITT-LOCF analysis population by treatment

For comparing treatments with respect to the incidence of clinical adverse events, this reviewer used Fisher's exact test. The ITT population was used in these analyses.

III. RESULTS

REVIEWER NOTE: *All analyses were performed by the reviewer. The tables and figures for this review could not be easily incorporated into the text. Therefore, they have been included as appendices. For quick referral to the tables and figures, it may be helpful for the reader to separate the text and appendices into two documents which can be read jointly.*

III A. STUDY 003

REVIEWER NOTE: *The tables and figures for Study 003 are located in review sections V and VI, respectively.*

Study 003 was initiated on September 19, 1990, and completed on February 13, 1991. A total of 215 patients were enrolled, where 71, 74, and 70 patients were randomized to receive ACT, RET, and VEH, respectively.

Three US investigators participated in the trial. Investigator Jarratt enrolled 125 patients where 42, 42, and 41 patients were randomized to receive ACT, RET, and VEH, respectively. Investigator Lucky enrolled 74 patients where 24, 26, and 24 patients were randomized to receive ACT, RET, and VEH, respectively. Investigator Cullen enrolled 16 patients where 5, 6, and 5 patients were randomized to receive ACT, RET, and VEH, respectively.

Table 1 displays the number of patients included in the EVAL and ITT populations by treatment, with reasons for patient exclusion. A total of 171 patients were included in the EVAL population, where 58, 58 and 55 patients received ACT, RET, and VEH, respectively. A total of 211 patients were included in the ITT population, where 69, 73 and 69 patients received ACT, RET, and VEH, respectively. There were no significant treatment differences in the proportion of patients included in the EVAL or ITT patient populations.

The demographic distribution by treatment for the EVAL population is displayed in Table 2. The distributions of age, race and sex were similar among the treatments.

Mean baseline lesion counts by treatment for all centers combined and for each center are displayed in Table 3. Results were similar in the EVAL and ITT populations. In all centers combined and for investigators Jarratt and Lucky, there were no significant treatment differences in the mean baseline non-inflammatory, inflammatory, or total lesion count. Among investigator Cullen's patients, there was a significant treatment difference in the mean baseline non-inflammatory lesion count, where VEH had a smaller mean lesion count than ACT and RET. There were no significant treatment differences in the mean baseline inflammatory or total lesion count for Cullen's patients.

Table 4 displays the results from analyses of variance by center for the percent change in lesion counts from baseline to day 84. In the EVAL-OC analysis for non-inflammatory lesions and total lesions, Jarratt showed a clearly significant treatment difference, Lucky showed a marginally significant treatment difference, and Cullen showed a clearly non-significant treatment difference. For inflammatory lesions, Jarratt showed a clearly significant treatment difference, while Lucky and Cullen showed clearly non-

significant treatment differences. The results from the ITT-LOCF analysis were generally similar to those from the EVAL-OC population.

REVIEWER COMMENT: *The data for the percent change from baseline to day 84 were not normally distributed. Given that the normality assumption is fairly robust, this reviewer decided to present results from analyses of the original, untransformed data. Although not presented in this review, analyses of variance on the rank transformed data (using descending ranks) were performed. The results using the rank transformed data were not substantially different from those obtained with the original data.*

Among the centers, the results from the ACT and RET treatment arms are fairly consistent. However, the results from the VEH treatment arm vary greatly. The mean percent reduction in lesion counts for Cullen's VEH patients is more than twice that for Jarratt's or Lucky's VEH patients. Although the number of Cullen VEH patients is small (5 patients), these patients are highly influential on the overall study results. The reason for the influential nature of Cullen's VEH patients is not clear. A listing of these patients is provided in Table 5.

Figure 1 displays the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment and center in the EVAL-OC population. For non-inflammatory lesions, all treatment arms at all centers decreased over time. With the exception of Cullen's VEH group, the ACT and RET groups had larger decreases in non-inflammatory lesions than the VEH groups. For inflammatory lesions, all the ACT and RET groups and Cullen's VEH group decreased over time. Jarratt's and Lucky's VEH groups did not show much decrease in inflammatory lesion counts over time. Although Figure 1 suggests potential treatment by center interactions with respect to the mean percent change from baseline in non-inflammatory and inflammatory lesion counts, at day 84, the treatment by center interaction terms from the analysis of variance models were not statistically significant.

Due to the highly influential nature of Cullen's VEH patients, this reviewer performed analyses of variance of the percent change in lesion counts from baseline to day 84 excluding all of Cullen's patients. These results were then compared to the results from a similar analysis which included all three centers. The results from both types of analyses are presented in Table 6A.

In the analysis of the EVAL-OC population with all three center combined, the treatment effect at day 84 is clearly not significant for non-inflammatory lesions, inflammatory lesions, and total lesions. However, when Cullen is excluded from the analysis, the treatment effect at day 84 becomes highly significant for all three lesion counts, where both ACT and RET have significantly greater percent reductions in lesion counts than VEH. RET had numerically greater, but not significantly greater percent reductions in lesion counts than ACT. Similar results were observed in the ITT-LOCF population.

Table 6B displays results from analyses of variance for the percent change from baseline to days 7, 14, 28, and 56 in non-inflammatory lesion count in the EVAL-OC population. These analyses exclude investigator Cullen. At days 7 and 56, there is a significant overall treatment effect, where ACT is significantly better than VEH. At days 14 and 28, ACT and RET have numerically larger mean decreases, but the overall treatment effect is only marginally significant.

Figures 2A and 2B present the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment, including and excluding Cullen's patients, respectively, in the EVAL-OC population. For non-inflammatory lesions with Cullen included and excluded, all treatment arms decreased over time; however, ACT and RET had larger decreases than VEH. For inflammatory lesions with Cullen included, all treatment arms decreased over time; however, ACT and RET had larger decreases than VEH. For inflammatory lesions with Cullen excluded, ACT and RET decreased over time, but VEH did not.

Figures 3, 4 and 5 present the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment and sex, treatment and race, and treatment and age,

respectively, in the EVAL-OC population. These figures include Cullen's patients. For non-inflammatory lesions in the ACT and RET groups, females and patients ≥ 30 had larger decreases than males and patients < 30 . No other noteworthy patterns of treatment effect were observed within the subgroups.

To compare the results of this study with those of study 015, an analysis of the percent change in lesion counts from baseline to day 84 which included only those patients with a baseline total lesion count ≤ 200 was performed. These results are displayed in Table 7. The results of this analysis are similar to those observed for the original set of patients.

Therapeutic equivalence of ACT to RET with respect to the percent decrease in lesion count from baseline to day 84 was assessed using the confidence interval approach described in review section II above. The results of this analysis are shown in Table 8. Whether Cullen is included or excluded from the analysis, the results from the EVAL-OC population fail to demonstrate therapeutic equivalence for non-inflammatory, inflammatory, or total lesions. Similar results are observed in the ITT-LOCF population.

Table 9 displays confidence interval results for the set of patients with baseline total lesion count ≤ 200 . The results are similar to those observed in the original set of patients.

Results from analyses of the investigator's global assessment at day 84 for the EVAL-OC population are presented in Table 10. There are significant treatment differences in the distribution of global assessment outcome, where ACT and RET have more patients with favorable outcomes than VEH. This result is observed whether Cullen is included or excluded from the analysis. When analyzed on a by center basis, Jarratt and Lucky showed a significant treatment difference in global assessment outcomes, but Cullen did not.

Change from baseline to day 84 results for the skin safety parameters are presented in Table 11. In the ITT-LOCF population, there are significant treatment differences in the distribution of itching and peeling outcomes. With respect to itching, ACT and RET have more patients with outcome "worse" than VEH. With respect to peeling, RET has more patients with outcome "worse" than VEH. Similar itching and peeling results were observed in the ITT-OC population.

Figures 6A, 6B, and 6C display the percentage of patients by treatment at each visit in the ITT-LOCF population who had a "worse" skin safety parameter outcome compared to baseline. For all the parameters at all visits, ACT and RET had a larger percentage of patients with "worse" outcome than VEH. With the exception of peeling, ACT and RET had similar profiles of the skin safety parameters. For peeling, ACT had smaller percentages of patients with "worse" outcome than RET. With the exception of itching, the percentage of patients with "worse" outcome in the ACT and RET groups was greatest at day 7, diminished between days 7 and 28, and then remained fairly constant between days 28 and 84. The percentage of patients in the ACT and RET groups with "worse" itching remained fairly constant over the entire study period.

Table 12 displays the rate of selected adverse events. The treatments are not significantly different with respect to the percentage of patients with at least one adverse event. However, there are significant treatment differences with respect to the percentage of patients with at least one event in the skin and appendage body system, where ACT and RET had a significantly higher rate than VEH.

REVIEWER CONCLUSIONS: *Based on results from the EVAL-OC population which exclude Cullen's patients, study 003 demonstrates that after 84 days of treatment, Acticin 0.025% gel has a significantly larger mean percent decrease from baseline in non-inflammatory lesion count and total lesion count than its vehicle. However, study 003 fails to show that after 84 days of treatment, Acticin 0.025% gel is therapeutically equivalent to Retin-A 0.025% gel with respect to the mean percent decrease from baseline in non-inflammatory lesion count and total lesion count.*

With respect to the investigator's global assessment at day 84, study 003 demonstrates that there are significant treatment differences in the distribution of outcomes, where Acticin 0.025% gel has more patients with favorable outcomes than its vehicle.

III B. STUDY 015

REVIEWER NOTE: *The tables and figures for Study 015 are located in review sections V and VI, respectively.*

Study 015 was initiated on September 28, 1992, and completed on January 13, 1993. A total of 180 patients were enrolled, where 91 and 89 patients were randomized to receive ACT and VEH, respectively.

Two US investigators participated in the trial. Investigator Jarratt enrolled 90 patients, where 45 and 45 patients were randomized to receive ACT and VEH, respectively. Investigator Jones enrolled 90 patients where 46 and 44 patients were randomized to receive ACT and VEH, respectively.

REVIEWER COMMENT: *Investigator Jarratt also participated in study 003; therefore study 015 cannot be considered independent of study 003.*

Table 13 displays the number of patients included in the EVAL and ITT populations by treatment, with reasons for patient exclusion. A total of 168 patients were included in the EVAL population, where 86 and 82 patients received ACT and VEH, respectively. A total of 175 patients were included in the ITT population, where 89 and 86 patients received ACT and VEH, respectively. There were no significant treatment differences in the proportion of patients included in the EVAL or ITT patient populations.

The demographic distribution by treatment for the EVAL population is displayed in Table 14. The distributions of age, race and sex were similar among the treatments.

Mean baseline lesion counts by treatment for all centers combined and for each center are displayed in Table 15. Results were similar in the EVAL and ITT populations. In all centers combined and for investigator Jarratt, the treatment difference in the mean baseline non-inflammatory, inflammatory, or total lesion count is not statistically significant. However, among investigator Jones' patients, there is a significant treatment difference in the mean baseline non-inflammatory and total lesion counts, where VEH has a larger mean lesion count than ACT. There is not a significant treatment difference in the mean baseline inflammatory lesion count for Jones' patients.

Table 16 displays results from analyses of variance by center for the percent change in lesion counts from baseline to day 84. In the EVAL-OC analysis for non-inflammatory lesions and total lesions, Jarratt showed a significantly higher decrease in lesion count for ACT; however, Jones did not. Jones' VEH patients had a much larger mean percent decrease in non-inflammatory lesions than Jarratt's VEH patients. For inflammatory lesions, neither Jarratt nor Jones showed a significant treatment difference. The results from the ITT-LOCF analysis were similar to those from the EVAL-OC population.

REVIEWER COMMENT: *The data for the percent change from baseline to day 84 were not normally distributed. Given that the normality assumption is fairly robust, this reviewer decided to present results from analyses of the original, untransformed data. Analyses of variance on the rank transformed data (using descending ranks) were also performed. The p-values from the rank analyses are presented in Tables 16 and 17, adjacent to the p-values from the original analyses. In general, the p-values from the ranked data are slightly larger than those from the original data.*

Figure 7 displays the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment and center in the EVAL-OC population. For non-inflammatory lesions, the treatment arms across centers did not behave similarly over time. In both treatment groups, Jarratt's patients had a gradual decrease in counts over days 28 to 84, whereas Jones' patients had a large decrease by day 28, and then remained fairly constant until day 84. Over time, the decrease in non-inflammatory lesions for Jones' VEH patients was much larger than for Jarratt's VEH patients; however, at day 84 the treatment by center interaction term from the analysis of variance model was not statistically significant. For inflammatory lesions, the treatment arms across centers behaved similarly over time. The ACT patients had a gradual decrease in counts over days 28 to 84, and the VEH patients showed a decrease by day 28, and then remained fairly constant until day 84.

Table 17A displays results from analyses of variance of the percent change in lesion counts from baseline to day 84 for all centers combined. In the EVAL-OC population using the original data, the treatment effect, in favor of ACT, is borderline significant for non-inflammatory lesions, and clearly significant for inflammatory lesions and total lesions. When the ranked data is used, the treatment effect, in favor of ACT, is marginally significant for non-inflammatory lesions, and borderline significant for inflammatory lesions and total lesions. Similar results were observed in the ITT-LOCF population.

Table 17B displays results from analyses of variance for the percent change from baseline to days 28 and 56 in non-inflammatory lesion count in the EVAL-OC population. In analyses of the original and ranked data, there is a significant treatment effect at day 56, but not at day 28.

Figure 8 presents the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment in the EVAL-OC population. For non-inflammatory lesions, although ACT had a larger decrease than VEH by day 28, both groups remained fairly constant from day 28 to day 84. For inflammatory lesions, ACT and VEH had a similar decrease by day 28; however, ACT continued to decrease from day 28 to 84, while VEH remained constant over the same time period.

Figures 9, 10 and 11 present the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment and sex, treatment and race, and treatment and age, respectively, in the EVAL-OC population. For non-inflammatory lesions in the ACT group, females and patients ≥ 30 had larger decreases than males and patients < 30 . The largest decreases in non-inflammatory lesions were observed in VEH patients ≥ 30 . No other noteworthy patterns of treatment effect were observed within the subgroups.

Results from analyses of the investigator's global assessment at day 84 for the EVAL-OC population are presented in Table 18. There is a borderline significant treatment difference in the distribution of global assessment outcome, where ACT has more patients with favorable outcomes than VEH. When analyzed on a by center basis, neither Jarratt nor Jones alone showed a significant treatment difference in global assessment.

Change from baseline to day 84 results for the skin safety parameters are presented in Table 19. In the ITT-LOCF population, there are significant treatment differences in the distribution of burning/stinging, erythema, and tightness outcomes. With respect to these parameter, ACT had more patients with "worse" outcome than VEH. Similar burning/stinging, erythema, and tightness outcomes were observed in the ITT-OC population.

Figures 12A, 12B, and 12C display the percentage of patients by treatment at each visit in the ITT-LOCF population who had a "worse" skin safety parameter outcome compared to baseline. For all the parameters at all visits, ACT a larger percentage of patients with "worse" outcome than VEH. For all parameters and both treatment groups, the percentage of patients with "worse" outcome remained fairly constant over the study period.

In the ITT population, 41/89 (46%) and 29/86 (34%) of the ACT and VEH patients, respectively, experienced at least one adverse clinical event during the study. This treatment difference is not statistically significant ($p=0.123$). With respect to the rate of adverse events by body system or individual events, a statistically significant treatment difference was not observed.

REVIEWER CONCLUSIONS: *Based on results from the EVAL-OC population using the original data, study 015 fails to clearly demonstrate that after 84 days of treatment, Acticin 0.025% gel has a significantly larger mean percent decrease from baseline in non-inflammatory lesion count than its vehicle; however, the treatment difference is very close to statistical significance. Study 015 clearly demonstrates that after 84 days of treatment, Acticin 0.025% gel has a significantly larger mean percent decrease from baseline in inflammatory lesion count and total lesion count than its vehicle.*

With respect to the investigator's global assessment at day 84, study 015 fails to clearly demonstrate that there is a significant treatment difference in the distribution of outcomes; however, the treatment difference in outcome distribution is very close to statistical significance, where Acticin 0.025% gel has more patients with favorable outcomes than its vehicle.

Study 015 cannot be considered independent of study 003, since investigator Jarratt enrolled at least 50% of the patients in both studies.

IV. SUMMARY AND CONCLUSIONS **(Which May be Conveyed to the Sponsor)**

In comparison to its vehicle, statistical evaluation of efficacy of Acticin 0.025% gel is based upon the mean percent change from baseline to day 84 in non-inflammatory lesion count and total lesion count, and the distribution of the investigator's global assessment at day 84. In comparison to the active control Retin-A 0.025% gel, statistical evaluation of efficacy of Acticin 0.025% gel is based upon the mean percent change from baseline to day 84 in non-inflammatory lesion count and total lesion count. The set of evaluable patients with observed case visits is the primary efficacy analysis population. The original, untransformed data are used in the lesion count analyses.

Statistical evaluation of safety is based upon treatment comparisons of the change from baseline to day 84 in skin safety parameters, and the rate of clinical adverse events. The set of intent-to-treat patients with the last observation carried forward is the primary safety analysis population.

It must be noted that the categories for the investigator's global assessment scale and the skin safety parameter scales were not defined in the protocol. Therefore, the interpretation of these scale would most likely vary among the investigators and patients. Without clear definitions of the scale categories, the usefulness of these scales is questionable.

IV.A. STUDY 003

Investigator Cullen was excluded from all efficacy analyses due to a small number of highly influential vehicle patients. The reason for the influential nature of Cullen's vehicle patients is not clear. Excluding Cullen's patients, Acticin 0.025% gel, Retin-A 0.025% gel, and Acticin vehicle gel patients, respectively, were included in the efficacy analyses. Cullen's patients were included in the safety analyses. Acticin 0.025% gel, Retin-A 0.025% gel, and Acticin vehicle gel patients, respectively, were included in the safety analyses.

1. Non-inflammatory Lesions: The mean decrease (standard error) is 41.8 (4.2) and 22.8 (4.8) for Acticin 0.025% gel and its vehicle, respectively. The difference between Acticin 0.025% gel and its vehicle is clearly statistically significant ($p=0.004$).

The mean decrease (standard error) is 42.8 (4.2) for Retin-A 0.025% gel. This mean is numerically larger but not significantly larger than the mean for Acticin 0.025% gel.

The center weighted treatment difference in the mean decrease between Acticin 0.025% gel and Retin-A 0.025% gel is -0.5, with standard error 6.0 and 95% confidence interval (-12.4, 11.3). The center weighted mean decrease for Retin-A 0.025% gel is 42.5. Twenty percent of the mean decrease for Retin-A is 8.6.

2. Total Lesions: The mean decrease (standard error) is 41.3 (3.7) and 22.3 (4.5) for Acticin 0.025% gel and its vehicle, respectively. The difference between Acticin 0.025% gel and its vehicle is clearly statistically significant ($p=0.002$).

The mean decrease (standard error) is 42.2 (3.8) for Retin-A 0.025% gel. This mean is numerically larger but not significantly larger than the mean for Acticin 0.025% gel.

The center weighted treatment difference in the mean decrease between Acticin 0.025% gel and Retin-A 0.025% gel is -0.7, with standard error 5.3 and 95% confidence interval (-11.3, 9.8). The center weighted mean decrease for Retin-A 0.025% gel is 42.0. Twenty percent of the mean decrease for Retin-A is 8.4.

3. Global Assessment: The distribution of global assessment outcomes are presented in Table 10. The distribution of global assessment outcome for Acticin 0.025% gel is significantly different from its vehicle ($p=0.003$), where Acticin 0.025% gel has more patients with favorable outcomes than its vehicle.

4. Safety: The distribution of skin safety parameter outcomes are presented in Table 11. The distribution of itching outcome for Acticin 0.025% gel is significantly different from its vehicle ($p=0.013$), where Acticin 0.025% gel has more patients with "worse" itching than its vehicle. With respect to the other skin safety parameters, Acticin 0.025% gel is not significantly different from its vehicle or Retin-A 0.025% gel.

The rate of at least one adverse event is 43%, 40%, and 36% for Acticin 0.025% gel, Retin-A 0.025% gel, and Acticin vehicle, respectively. The differences among the treatments are not statistically significant.

The rate of at least one skin and appendage body system adverse event is 16%, 18%, and 3% for Acticin 0.025% gel, Retin-A 0.025% gel, and Acticin vehicle, respectively. The differences between Acticin 0.025% and its vehicle and Retin-A 0.025% and Acticin vehicle are statistically significant ($p=0.017$ and $p=0.005$, respectively). With respect to the rate of adverse events in other body systems, and the rate of individual adverse events, Acticin 0.025% gel is not significantly different from its vehicle or Retin-A 0.025% gel.

REVIEWER CONCLUSIONS: *Study 003 provides clear evidence for the applicant's claim that Acticin 0.025% gel is superior in efficacy to its vehicle in the treatment of mild to moderate acne vulgaris.*

Study 003 fails to provide evidence for the applicant's claim that Acticin 0.025% gel is therapeutically equivalent in efficacy to Retin-A 0.025% gel in the treatment of mild to moderate acne vulgaris.

Study 003 supports the applicant's claim that Acticin 0.025% has tolerable safety profile. Any safety problems can be adequately addressed in the label.

IV.A. STUDY 015

Eighty-six and 82 Acticin 0.025% gel and vehicle patients, respectively, were included in the efficacy analyses. Eighty-nine and 86 Acticin 0.025% gel and vehicle patients, respectively, were included in the safety analyses.

1. Non-inflammatory Lesions: The mean decrease (standard error) is 33.2 (3.4) and 24.0 (4.1) for Acticin 0.025% gel and its vehicle, respectively. The difference between Acticin 0.025% gel and its vehicle is not clearly statistically significant, but is close to significance ($p=0.077$).

2. Total Lesions: The mean decrease (standard error) is 34.6 (3.2) and 23.5 (4.0) for Acticin 0.025% gel and its vehicle, respectively. The difference between Acticin 0.025% gel and its vehicle is clearly statistically significant ($p=0.030$).

3. Global Assessment: The distribution of global assessment outcomes are presented in Table 18. The distribution of global assessment outcome for Acticin 0.025% gel is not clearly significantly different from its vehicle, but is close to significance ($p=0.055$). Acticin 0.025% gel has more patients with favorable outcomes than its vehicle.

4. Safety: The distribution of skin safety parameter outcomes are presented in Table 19. The distribution of burning/stinging, erythema, and tightness outcome for Acticin 0.025% gel is significantly different from its vehicle ($p=0.001$, $p=0.030$ and $p=0.045$, respectively), where Acticin 0.025% gel has more patients with "worse" outcomes than its vehicle. With respect to the other skin safety parameters, Acticin 0.025% gel is not significantly different from its vehicle.

The rate of at least one adverse event is 46% and 34% for Acticin 0.025% gel and its vehicle, respectively. The treatment difference is not statistically significant. With respect to the rate of adverse events by body systems, and the rate of individual adverse events, Acticin 0.025% gel is not significantly different from its vehicle.

REVIEWER CONCLUSIONS: *Study 015 fails to provide clear evidence for the applicant's claim that Acticin 0.025% gel is superior in efficacy to its vehicle in the treatment of mild to moderate acne vulgaris. However, the results are supportive of the applicant's efficacy claim.*

Study 015 supports the applicant's claim that Acticin 0.025% has a tolerable safety profile. Any safety problems can be adequately addressed in the label.

REVIEWER COMMENTS: *The major flaw of the two trials is that they are not independent. Investigator Jarratt participated in both trials, enrolling 58% (125/215) of the patients in study 003, and 50% (90/180) of the patients in study 015. The results of both trials are highly dependent on the results from this individual investigator.*

If Acticin 0.025% gel is considered a line extension of Retin-A 0.025% gel, one adequate and well controlled study which shows Acticin's superiority over vehicle and therapeutic equivalence to Retin-A would be required. Study 003 is generally adequate and well controlled in design, shows superiority over vehicle, but fails to meet the equivalence criterion for approvability.

If Acticin 0.025% gel is considered as a new drug product, two adequate and well controlled studies which show Acticin's superiority over vehicle would be required. Study 003 meets the efficacy criterion, and study 015 comes very close to meeting the efficacy criterion. However, the studies are not independent, and therefore are not adequate and well controlled in design.

The exceptional performance of investigator Cullen's vehicle patients is puzzling. Similar results were observed in Cullen's vehicle patients from the Acticin cream study 011 of NDA 20-404.

RECOMMENDED REGULATORY ACTION: *From a statistical standpoint, Acticin 0.025% gel is not approvable for the treatment of mild to moderate acne vulgaris. Investigator Cullen should be recommended for inspection by DSI.*

/S/

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3/2/95

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6-3-6-95

cc:
Orig. NDA 20-400
HFD-540
HFD-540/Chapman
HFD-540/Wilkin
HFD-540/Slifman
HFD-540/Labib
HFD-540/Chambers
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFD-713/Turney
HFD-344/Lisook
Chron.

This review contains 13 pages with two appendices containing 18 tables and 12 figures.
WordPerfect 6.0/NDA20400.wpd/3-2-95

V. APPENDIX OF TABLES**V.A. STUDY 003**

TABLE 1: Study 003 Patient Evaluability Status at Day 84						
patient status	EVAL			ITT		
	ACT	RET	VEH	ACT	RET	VEH
enrolled	71	74	70	71	74	70
evaluable at day 84	58 (82%)	58 (74%)	55 (79%)	69 (97%)	73 (99%)	69 (99%)
excluded total	13	16	15	2	1	1
excluded from all visits	9	7	9	2	1	1
excluded from day 84	4	9	6	0	0	0
reason for exclusion:						
adverse experience	0	1	0	0	0	0
lost to follow up	2	1	4	1	1	1
protocol violation	2	1	0	0	0	0
non-compliant	2	3	1	0	0	0
personal	3	0	4	1	0	0
other	0	1	0	0	0	0
visit early (day 84)	0	4	4	0	0	0
visit late (day 84)	4	5	1	0	0	0
requested unevaluable (day 84)	0	0	1	0	0	0

TABLE 2 : Study 003 Demographic Distribution for EVAL Population						
trt	sex n (%)		race n (%)		age n (%)	
	M	F	B/O	W	< 30	≥ 30
ACT (N = 58)	22 (38)	36 (62)	9 (16)	49 (84)	49 (84)	9 (16)
RET (N = 58)	25 (43)	33 (57)	11 (19)	47 (81)	54 (93)	4 (7)
VEH (N = 55)	27 (49)	28 (51)	9 (16)	46 (84)	52 (95)	3 (5)
p-value*	0.488		0.876		0.136	

*P-value from the chi-square test.

TABLE 3: Study 003 Baseline Lesion Counts For All Centers Combined and by Center

Lesion	center	trt	EVAL-OC						ITT-LOCF					
			n	mean	se	min	max	p*	n	mean	se	min	max	p*
non-inf	ALL	ACT	58	69.2	5.1			0.528	69	70.3	4.9			0.794
		RET	58	80.8	8.4				73	75.6	6.8			
		VEH	55	72.8	6.2				69	74.6	5.7			
	Jarratt	ACT	34	65.5	6.7			0.683	40	64.4	6.2			0.307
		RET	31	74.5	8.2				42	67.1	6.4			
		VEH	34	69.4	6.6				40	75.7	7.2			
	Lucky	ACT	19	80.1	9.1			0.987	24	83.8	8.9			0.805
		RET	22	93.5	18.7				25	91.4	16.5			
		VEH	16	90.8	15.2				24	80.5	10.7			
	Cullen	ACT	5	52.6	5.9			0.030	5	52.6	5.9			0.018
		RET	5	63.8	6.1				6	69.0	7.2			
		VEH	5	38.2	0.8				5	38.2	0.8			
inf	ALL	ACT	58	19.4	1.7			0.514	69	19.1	1.5			0.327
		RET	58	20.4	1.8				73	19.8	1.5			
		VEH	55	20.1	1.6				69	19.9	1.3			
	Jarratt	ACT	34	15.2	1.2			0.299	40	15.2	1.0			0.309
		RET	31	15.5	1.5				42	15.9	1.2			
		VEH	34	16.8	1.4				40	16.9	1.3			
	Lucky	ACT	19	27.4	4.3			0.881	24	25.9	3.5			0.900
		RET	22	27.6	3.8				25	26.9	3.5			
		VEH	16	26.1	3.1				24	24.3	2.3			
	Cullen	ACT	5	18.0	2.2			0.755	5	18.0	2.2			0.891
		RET	5	19.2	2.5				6	18.0	2.4			
		VEH	5	23.6	9.2				5	23.6	9.2			
total	ALL	ACT	58	88.6	6.2			0.517	69	89.4	5.7			0.636
		RET	58	101.2	9.4				73	95.4	7.7			
		VEH	55	92.9	6.6				69	94.6	5.9			
	Jarratt	ACT	34	80.8	7.5			0.589	40	79.6	6.8			0.209
		RET	31	89.9	9.0				42	83.0	7.0			
		VEH	34	86.1	6.7				40	92.5	7.2			
	Lucky	ACT	19	107.5	12.4			0.923	24	109.6	11.0			0.883
		RET	22	121.2	20.8				25	118.3	18.4			
		VEH	16	116.9	16.2				24	104.8	11.5			
	Cullen	ACT	5	70.6	4.7			0.097	5	70.6	4.7			0.054
		RET	5	83.0	7.5				6	87.0	7.3			
		VEH	5	61.8	9.8				5	61.8	9.8			

*P-value from the Kruskal-Wallis test.

TABLE 4: Study 003 Percent Change From Baseline to Day 84 in Lesion Counts by Center

lesion	center	trt	EVAL-OC						ITT-LOCF					
			n	mean	se	adj. se	overall p	pairwise p*	n	mean	se	adj. se	overall p	pairwise p*
non-inf	Jarratt	ACT	34	-37.5	5.4	5.6	0.031	A v. V: 0.036 R v. V: 0.015 A v. R: 0.688	40	-33.2	5.2	5.9	0.059	
		RET	31	-40.9	5.3	6.0			42	-34.9	5.9	5.7		
		VEH	34	-20.2	6.6	5.6			40	-16.9	6.3	5.9		
	Lucky	ACT	19	-49.4	6.5	6.6	0.078		24	-46.7	5.5	6.9	0.015	A v. V: 0.006 R v. V: 0.024 A v. R: 0.602
		RET	22	-45.4	7.0	6.1			25	-41.6	6.9	6.8		
		VEH	16	-28.1	5.3	7.2			24	-19.2	8.1	6.9		
	Cullen	ACT	5	-40.7	15.6	13.8	0.775		5	-40.7	15.6	14.2	0.628	
		RET	5	-42.6	17.0	13.8			6	-35.1	15.8	12.9		
		VEH	5	-53.7	6.0	13.8			5	-53.7	6.0	14.2		
inf	Jarratt	ACT	34	-42.0	4.6	6.5	0.004	A v. V: 0.019 R v. V: 0.001 A v. R: 0.328	40	-36.4	5.4	6.0	0.006	A v. V: 0.048 R v. V: 0.002 A v. R: 0.232
		RET	31	-51.3	5.0	6.8			42	-46.6	4.5	5.9		
		VEH	34	-20.0	9.0	6.5			40	-19.4	7.7	6.0		
	Lucky	ACT	19	-28.7	9.3	8.4	0.340		24	-25.7	8.0	9.1	0.071	
		RET	22	-30.1	7.7	7.9			25	-30.9	6.8	8.9		
		VEH	16	-13.4	8.1	9.2			24	-2.6	11.8	9.1		
	Cullen	ACT	5	-49.7	14.4	13.6	0.481		5	-49.7	14.4	14.7	0.348	
		RET	5	-52.1	17.7	13.6			6	-42.1	17.6	13.4		
		VEH	5	-71.6	5.9	13.6			5	-71.5	5.9	14.7		
total	Jarratt	ACT	34	-38.3	4.8	5.2	0.008	A v. V: 0.016 R v. V: 0.004 A v. R: 0.548	40	-33.8	4.8	5.2	0.012	A v. V: 0.025 R v. V: 0.005 A v. R: 0.548
		RET	31	-42.8	4.5	5.4			42	-38.1	4.7	5.1		
		VEH	34	-20.3	6.2	5.2			40	-17.1	5.8	5.2		
	Lucky	ACT	19	-46.8	5.6	6.1	0.074		24	-43.2	4.7	6.6	0.013	A v. V: 0.006 R v. V: 0.020 A v. R: 0.646
		RET	22	-41.4	6.7	5.6			25	-39.0	6.2	6.5		
		VEH	16	-26.4	5.1	6.6			24	-16.8	8.3	6.6		
	Cullen	ACT	5	-40.6	13.6	12.5	0.500		5	-40.6	13.6	13.2	0.384	
		RET	5	-44.0	16.6	12.5			6	-36.2	15.6	12.0		
		VEH	5	-60.6	3.2	12.5			5	-60.6	3.2	13.2		

*The adjusted standard error, overall treatment p-value, and pairwise treatment p-values are from an analysis of variance of treatment using SAS PROC GLM type III sums of squares. The adjusted standard error is the standard error that would be expected if the treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3 = 0.017$.

TABLE 5: Study 003 Listing of Lesion Counts for Cullen Patients Who Received Vehicle

SUBJECT	SEX	RACEGRP	AGEGRP	EVALUABLE	BASELINE	DAY84	%CHANGE
NON-INFLAMMATORY LESIONS							
F		W	<30	Y	36	14	-61.1
M		W	<30	Y	38	15	-60.5
F		W	<30	Y	40	16	-60.0
M		W	<30	Y	40	28	-30.0
F		W	<30	Y	37	16	-56.8
INFLAMMATORY LESIONS							
F		W	<30	Y	14	1	-92.9
M		W	<30	Y	12	4	-66.7
F		W	<30	Y	20	8	-60.0
M		W	<30	Y	60	22	-63.3
F		W	<30	Y	12	3	-75.0
TOTAL LESIONS							
F		W	<30	Y	50	15	-70.0
M		W	<30	Y	50	19	-62.0
F		W	<30	Y	60	24	-60.0
M		W	<30	Y	100	50	-50.0
F		W	<30	Y	49	19	-61.2

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 6A: Study 003 Percent Change From Baseline to Day 84 in Lesion Counts for all Centers and Excluding Cullen

lesion	anal.	trt	EVAL-OC							ITT-LOCF						
			n	mean	se	adj. mean	adj. se	overall p: trt (trt*cen)	pairwise p: trt	n	mean	se	adj. mean	adj. se	overall p: trt (trt*cen)	pairwise p: trt
non-inf	all center	ACT	58	-41.7	4.0	-42.6	5.6	0.457 (0.522)		69	-38.4	3.8	-40.2	6.2	0.478 (0.406)	
		RET	58	-42.8	4.1	-43.0	5.6			73	-37.2	4.3	-37.2	5.7		
		VEH	55	-25.6	4.6	-34.0	5.7			69	-20.4	4.7	-29.9	6.2		
	excl. Cullen	ACT	53	-41.8	4.2	-43.5	4.6	0.005 (0.847)	A v. V: 0.004 R v. V: 0.004 A v. R: 0.960	64	-38.3	3.9	-40.0	4.7	0.001 (0.700)	A v. V: 0.001 R v. V: 0.002 A v. R: 0.791
		RET	53	-42.8	4.2	-43.2	4.4			67	-37.8	4.5	-38.3	4.6		
		VEH	50	-22.8	4.8	-24.2	4.8			64	-17.8	4.9	-18.0	4.7		
inf	all center	ACT	58	-38.3	4.3	-40.2	6.6	0.595 (0.280)		69	-33.7	4.4	-37.3	6.9	0.648 (0.247)	
		RET	58	-43.3	4.4	-44.5	6.5			73	-40.9	3.8	-39.9	6.4		
		VEH	55	-22.8	6.4	-35.0	6.7			69	-17.3	6.4	-31.2	6.9		
	excl. Cullen	ACT	53	-37.3	4.5	-35.3	5.4	0.007 (0.639)	A v. V: 0.019 R v. V: 0.002 A v. R: 0.479	64	-32.5	4.5	-31.1	5.3	0.001 (0.910)	A v. V: 0.008 R v. V: <0.001 A v. R: 0.299
		RET	53	-42.5	4.5	-40.7	5.2			67	-40.8	3.9	-38.8	5.1		
		VEH	50	-17.9	6.6	-16.7	5.7			64	-13.1	6.6	-11.0	5.3		
total	all center	ACT	58	-41.3	3.5	-41.9	5.1	0.583 (0.206)		69	-37.5	3.4	-39.2	5.6	0.585 (0.165)	
		RET	58	-42.4	3.6	-42.8	5.1			73	-38.2	3.6	-37.8	5.2		
		VEH	55	-25.8	4.4	-35.8	5.2			69	-20.2	4.6	-31.5	5.6		
	excl. Cullen	ACT	53	-41.3	3.7	-42.6	4.1	0.002 (0.672)	A v. V: 0.002 R v. V: 0.002 A v. R: 0.942	64	-37.3	3.5	-38.5	4.2	<0.001 (0.668)	A v. V: <0.001 R v. V: <0.001 A v. R: 0.994
		RET	53	-42.2	3.8	-42.1	4.0			67	-38.4	3.7	-38.5	4.1		
		VEH	50	-22.3	4.5	-23.4	4.4			64	-17.0	4.8	-17.0	4.2		

The adjusted mean, adjusted standard error, overall p-values, and pairwise treatment p-values are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall p-value for treatment is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3 = 0.017$.

TABLE 6B: Study 003 Percent Change From Baseline to Days 7, 14, 28, and 56 in Non-Inflammatory Lesion Count For EVAL-OC Population Excluding Cullen										
lesion	day	trt	EVAL-OC							
			n	mean	se	adj. mean	adj. se	overall p [*] trt (trt*cen)	pairwise p [*]	
non-inf	7	ACT	52	-11.0	3.5	-13.4	2.9	0.014	A v. V: 0.006	
		RET	52	-10.6	2.7	-11.5	2.8			R v. V: 0.018
		VEH	45	0.2	2.4	-1.2	3.3			(0.500)
	14	ACT	52	-14.4	4.4	-16.8	4.2	0.076		
		RET	53	-17.1	4.2	-18.8	4.0			R v. V: 0.018
		VEH	45	-5.2	3.5	-5.9	4.5			(0.420)
	28	ACT	53	-24.2	4.5	-26.6	4.4	0.076		
		RET	50	-24.5	4.9	-25.9	4.4			R v. V: 0.018
		VEH	47	-11.6	3.9	-13.2	4.8			(0.809)
	56	ACT	52	-34.3	4.4	-35.8	4.6	0.004	A v. V: 0.005	
		RET	50	-37.0	4.7	-37.2	4.5			R v. V: 0.003
		VEH	48	-17.1	4.4	-16.7	4.9			(0.571)

*The adjusted standard error, overall treatment p-value, and pairwise treatment p-values are from an analysis of variance of treatment using SAS PROC GLM type III sums of squares. The adjusted standard error is the standard error that would be expected if the treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3 = 0.017$.

**TABLE 7: Study 003 Percent Change From Baseline to Day 84 in Lesion Counts for all Centers and Excluding Cullen
For Those Patients with Baseline Total Lesion Count <200**

lesion	anal.	trt	EVAL-OC							ITT-LOCF						
			n	mean	se	adj. mean	adj. se	overall p: trt (trt*cen)	pairwise p: trt	n	mean	se	adj. mean	adj. se	overall p: trt (trt*cen)	pairwise p: trt
non-inf	all center	ACT	56	-42.7	4.1	-43.2	5.7	0.386 (0.492)		66	-39.4	3.8	-41.0	6.3	0.393 (0.362)	
		RET	55	-42.2	4.2	-42.5	5.7			70	-36.5	4.4	-36.6	5.8		
		VEH	53	-24.7	4.7	-33.0	5.8			66	-19.5	4.9	-28.9	6.3		
	excl. Cullen	ACT	51	-42.9	4.2	-44.4	4.7	0.004 (0.853)	A v. V: 0.002 R v. V: 0.005 A v. R: 0.757	61	-39.3	4.0	-41.1	4.9	0.001 (0.611)	A v. V: <0.001 R v. V: 0.003 A v. R: 0.578
		RET	50	-42.1	4.4	-42.4	4.6			64	-36.6	4.6	-37.4	4.7		
		VEH	48	-21.7	5.0	-22.7	5.1			61	-16.7	5.1	-16.6	4.9		
inf	all center	ACT	56	-38.1	4.4	-39.8	6.7	0.735 (0.253)		66	-33.7	4.5	-37.1	7.1	0.730 (0.290)	
		RET	55	-42.5	4.6	-43.9	6.6			70	-40.1	3.9	-39.2	6.6		
		VEH	53	-24.2	6.6	-36.4	6.9			66	-18.2	6.6	-31.7	7.1		
	excl. Cullen	ACT	51	-36.9	4.7	-34.8	5.6	0.032 (0.454)	A v. V: 0.053 R v. V: 0.011 A v. R: 0.531	61	-32.4	4.8	-30.8	5.5	0.003 (0.925)	A v. V: 0.016 R v. V: 0.001 A v. R: 0.365
		RET	50	-41.6	4.8	-39.7	5.5			64	-40.0	4.0	-37.8	5.4		
		VEH	48	-19.3	6.8	-18.8	6.0			61	-13.8	6.9	-11.7	5.5		
total	all center	ACT	56	-42.1	3.6	-42.4	5.2	0.531 (0.199)		66	-38.3	3.5	-39.8	5.7	0.510 (0.151)	
		RET	55	-41.7	3.8	-42.2	5.1			70	-37.5	3.7	-37.2	5.3		
		VEH	53	-25.1	4.5	-35.0	5.3			66	-19.5	4.8	-30.7	5.7		
	excl. Cullen	ACT	51	-42.2	3.7	-43.3	4.3	0.001 (0.708)	A v. V: 0.001 R v. V: 0.003 A v. R: 0.738	61	-38.1	3.6	-39.4	4.4	<0.001 (0.609)	A v. V: <0.001 R v. V: 0.001 A v. R: 0.775
		RET	50	-41.5	4.0	-41.3	4.2			64	-37.7	3.7	-37.6	4.3		
		VEH	48	-21.4	4.6	-22.2	4.6			61	-16.1	4.9	-15.8	4.4		

The adjusted mean, adjusted standard error, overall p-values, and pairwise treatment p-values are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall p-value for treatment is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3 = 0.017$.

TABLE 8: Study 003 95% Confidence Intervals of the Center Weighted Acticin minus Retin-A Difference in Mean Percent Decrease From Baseline in Lesion Count at Day 84												
lesion	analysis	EVAL-OC					ITT-LOCF					
		wgt diff	wgt se	95% CI	wgt. RET mean	20% of RET mean	wgt diff	wgt se	95% CI	wgt. RET mean	20% of RET mean	
non-inf	all centers	-0.6	5.8	(-12.1, 10.8)	42.8	8.6	1.2	5.8	(-10.1, 12.6)	36.2	7.2	
	excl. Cullen	-0.5	6.0	(-12.4, 11.3)	43.6	8.7	0.9	5.9	(-10.9, 12.7)	39.1	7.8	
inf	all centers	-5.9	6.0	(-17.8, 6.0)	48.4	9.7	-7.1	5.7	(-18.3, 4.2)	40.6	8.1	
	excl. Cullen	-6.2	6.2	(-18.6, 6.1)	38.9	7.8	-8.3	5.9	(-19.9, 3.3)	36.8	7.4	
total	all centers	-0.9	5.2	(-11.2, 9.3)	43.5	8.7	-0.7	5.0	(-10.6, 9.2)	36.9	7.4	
	excl. Cullen	-0.7	5.3	(-11.3, 9.8)	42.0	8.4	-1.1	5.2	(-11.3, 9.1)	38.6	7.7	

TABLE 9: Study 003 95% Confidence Intervals of the Center Weighted Acticin minus Retin-A Difference in Mean Percent Decrease From Baseline in Lesion Count at Day 84 For Those Patients with Baseline Total Lesion Count <200												
lesion	analysis	EVAL-OC					ITT-LOCF					
		wgt diff	wgt se	95% CI	wgt. RET mean	20% of RET mean	wgt diff	wgt se	95% CI	wgt. RET mean	20% of RET mean	
non-inf	all centers	0.9	5.9	(-10.8, 12.7)	42.6	8.5	3.0	5.9	(-8.7, 14.7)	36.0	7.2	
	excl. Cullen	1.2	6.1	(-11.0, 13.4)	42.7	8.5	2.8	6.1	(-9.4, 15.0)	38.1	7.6	
inf	all centers	-5.6	6.2	(-17.9, 6.8)	48.0	9.6	-6.5	5.9	(-18.3, 5.2)	40.2	8.0	
	excl. Cullen	-5.9	6.5	(-18.7, 7.0)	37.9	7.6	-7.8	6.1	(-19.9, 4.3)	35.7	7.1	
total	all centers	0.5	5.3	(-10.0, 11.0)	43.2	8.6	0.8	5.2	(-9.4, 11.1)	36.6	7.3	
	excl. Cullen	0.9	5.5	(-10.0, 11.7)	41.1	8.2	0.5	5.3	(-10.0, 11.1)	37.6	7.5	

*NOTE: This analysis was performed in terms of decrease from baseline. When calculating the difference in means, the negative signs were dropped from the analysis.

TABLE 10: Study 003 Investigator Global Assessment at Day 84 for EVAL-OC

center	trt	total n	outcome n (%)					CMH p-values	
			excell.	good	fair	no change	worse	overall	pairwise
Jarratt	ACT	34	4 (12)	13 (38)	9 (26)	6 (18)	2 (6)	0.029	A v. V: 0.078 R v. V: 0.013 A v. R: 0.260
	RET	31	5 (16)	15 (48)	6 (19)	4 (13)	1 (3)		
	VEH	34	6 (18)	5 (15)	5 (15)	12 (35)	6 (18)		
Lucky	ACT	19	4 (21)	8 (42)	5 (26)	1 (5)	1 (5)	0.036	A v. V: 0.008 R v. V: 0.100 A v. R: 0.391
	RET	22	4 (18)	7 (32)	6 (27)	3 (14)	2 (9)		
	VEH	16	0 (0)	3 (19)	8 (50)	4 (25)	1 (6)		
Cullen	ACT	5	1 (20)	2 (40)	1 (20)	1 (20)	0 (0)	0.965	
	RET	5	1 (20)	2 (40)	1 (20)	1 (20)	0 (0)		
	VEH	5	0 (0)	4 (80)	1 (20)	0 (0)	0 (0)		
ALL	ACT	58	9 (16)	23 (40)	15 (26)	8 (14)	3 (5)	0.006	A v. V: 0.005 R v. V: 0.005 A v. R: 0.740
	RET	58	10 (17)	24 (41)	13 (22)	8 (14)	3 (5)		
	VEH	55	6 (11)	12 (22)	14 (25)	16 (29)	7 (13)		
excl. Cullen	ACT	53	8 (15)	21 (40)	14 (26)	7 (13)	3 (6)	0.003	A v. V: 0.003 R v. V: 0.003 A v. R: 0.729
	RET	53	9 (17)	22 (42)	12 (23)	7 (13)	3 (6)		
	VEH	50	6 (12)	8 (16)	13 (26)	16 (32)	7 (14)		

*Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3=0.017$.

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TABLE 11: Study 003 Change From Baseline In Assessment of Skin Safety Parameters at Day 84

parameter	trt	ITT-OC						ITT-LOCF					
		n	outcome n (%)			CMH p-values		n	outcome n (%)			CMH p-values	
			worse	no change	improve	overall	pairwise		worse	no change	improve	overall	pairwise
burning/ stinging	ACT	62	4 (6)	58 (94)	0 (0)	0.271		69	7 (10)	62 (90)	0 (0)	0.079	
	RET	67	7 (10)	59 (88)	1 (1)			73	9 (12)	63 (86)	1 (1)		
	VEH	61	1 (2)	60 (98)	0 (0)			69	1 (1)	68 (99)	0 (0)		
dryness	ACT	62	6 (10)	56 (90)	0 (0)	0.042	A v. V: 0.764 R v. V: 0.030 A v. R: 0.060	69	9 (13)	60 (87)	0 (0)	0.132	
	RET	67	15 (22)	52 (78)	0 (0)			73	15 (21)	58 (79)	0 (0)		
	VEH	61	5 (8)	56 (92)	0 (0)			69	6 (9)	63 (91)	0 (0)		
erythema	ACT	62	8 (13)	52 (84)	2 (3)	0.107		69	8 (12)	59 (86)	2 (3)	0.076	
	RET	67	12 (18)	53 (79)	2 (3)			73	14 (19)	57 (78)	2 (3)		
	VEH	61	3 (5)	56 (92)	2 (3)			69	4 (6)	63 (91)	2 (3)		
itching	ACT	62	4 (6)	58 (94)	0 (0)	0.034	A v. V: 0.046 R v. V: 0.006 A v. R: 0.380	69	6 (9)	63 (91)	0 (0)	0.013	A v. V: 0.013 R v. V: <0.002 A v. R: 0.462
	RET	67	7 (10)	60 (90)	0 (0)			73	9 (12)	64 (88)	0 (0)		
	VEH	61	0 (0)	61 (100)	0 (0)			69	0 (0)	69 (100)	0 (0)		
peeling	ACT	62	5 (8)	57 (92)	0 (0)	0.001	A v. V: 0.161 R v. V: 0.001 A v. R: 0.024	69	7 (10)	62 (90)	0 (0)	0.001	A v. V: 0.054 R v. V: <0.001 A v. R: 0.040
	RET	67	15 (22)	52 (78)	0 (0)			73	17 (23)	56 (77)	0 (0)		
	VEH	61	2 (3)	58 (95)	1 (2)			69	2 (3)	66 (96)	0 (0)		
tightness	ACT	62	6 (10)	56 (90)	0 (0)	0.591		69	8 (12)	61 (88)	0 (0)	0.378	
	RET	67	10 (15)	56 (84)	1 (1)			73	12 (16)	60 (82)	1 (1)		
	VEH	61	6 (10)	54 (89)	1 (2)			69	6 (9)	62 (90)	1 (1)		

*Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3=0.017$.

TABLE 12: Study 003 Clinical Adverse Events *					
event	trt	total n	event n (%)	p-values *	
				overall	pairwise
any AE	ACT RET VEH	69 73 69	30 (43) 29 (40) 25 (36)	0.689	
skin and appendage body system	ACT RET VEH	69 73 69	11 (16) 13 (18) 2 (3)	0.008	A v. V: 0.017 R v. V: 0.005 A v. R: 0.825
dry skin	ACT RET VEH	69 73 69	1 (1) 6 (8) 0 (0)	0.018	A v. V: > 0.999 R v. V: 0.028 A v. R: 0.117

*Results are displayed only for those body systems and the individual events within the body system which have a significant overall p-value. Only those patients with at least one post baseline visit were included in the analysis. P-values are from the two-sided Fisher's exact test. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for three pairwise comparisons would use a significance level of $0.05/3 = 0.017$.

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V.B. STUDY 015

TABLE 13: Study 015 Patient Evaluability Status at Day 84				
patient status	EVAL		ITT	
	ACT	VEH	ACT	VEH
enrolled	91	89	91	89
evaluable at day 84	86 (95%)	82 (92%)	89 (98%)	86 (97%)
excluded total	5	7	2	3
excluded from all visits	2	3	2	3
excluded from day 84	3	4	0	0
reason for exclusion:				
lost to follow up	1	4	1	3
non-compliant	1	1	1	0
other	1	0	0	0
visit early (day 84)	1	0	0	0
visit late (day 84)	1	2	0	0

TABLE 14: Study 015 Demographic Distribution for EVAL Population							
trt	sex n (%)		race n (%)		age n (%)		
	M	F	B/O	W	<30	>30	missing
ACT (N=86)	47 (55)	39 (45)	18 (21)	68 (79)	81 (94)	5 (6)	0 (0)
VEH (N=82)	45 (55)	37 (45)	14 (17)	68 (83)	72 (88)	8 (10)	2 (2)
p-value*	>0.999		0.560		0.198		

*P-value from the two tailed Fisher's exact test.

TABLE 15: Study 015: Baseline Lesion Counts Overall and by Center

lesion	center	trt	EVAL						ITT					
			n	mean	se	min	max	p [*]	n	mean	se	min	max	p [*]
non-inf	ALL	ACT	86	57.3	3.2			0.136	89	57.6	3.1			0.164
		VEH	82	60.3	2.9				86	60.0	2.8			
	Jarratt	ACT	42	66.7	6.0			0.676	44	66.9	5.7			0.736
		VEH	40	66.7	5.4				42	66.2	5.2			
	Jones	ACT	44	48.3	1.8			0.031	45	48.5	1.7			0.032
		VEH	42	54.2	2.2				44	54.2	2.1			
inf	ALL	ACT	86	16.2	0.6			0.837	89	16.3	0.5			0.787
		VEH	82	16.9	0.7				86	17.1	0.7			
	Jarratt	ACT	42	15.6	0.7			0.900	44	15.8	0.7			0.842
		VEH	40	16.5	1.0				42	16.8	1.0			
	Jones	ACT	44	16.8	0.9			0.928	45	16.8	0.8			0.921
		VEH	42	17.4	1.0				44	17.3	0.9			
total	ALL	ACT	86	73.5	3.2			0.164	89	73.9	3.1			0.194
		VEH	82	77.2	3.2				86	77.1	3.1			
	Jarratt	ACT	42	82.4	6.0			0.874	44	82.7	5.6			0.938
		VEH	40	83.1	6.0				42	83.0	5.7			
	Jones	ACT	44	65.1	2.2			0.022	45	65.4	2.2			0.021
		VEH	42	71.6	2.5				44	71.5	2.4			

* P-value from the Wilcoxon rank sum test.

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TABLE 16: Study 015: Percent Change From Baseline to Day 84 in Lesion Counts by Center														
lesion	center	trt	EVAL-OC						ITT-LOCF					
			n	mean	se	adj. se	p-value [*] trt	rank p-value [*] trt	n	mean	se	adj. se	p-value [*] trt	rank p-value [*] trt
non-inf	Jarratt	ACT	42	-32.5	4.7	5.5	0.050	0.092	44	-32.7	4.6	5.4	0.054	0.107
		VEH	40	-16.8	6.4	5.7			42	-17.6	6.3	5.5		
	Jones	ACT	44	-33.8	4.8	4.9	0.669	0.628	45	-34.5	4.8	4.8	0.701	0.640
		VEH	42	-30.8	5.1	5.0			44	-31.9	4.9	4.9		
inf	Jarratt	ACT	42	-36.1	6.7	7.9	0.166	0.160	44	-36.9	6.4	7.5	0.125	0.105
		VEH	40	-20.4	9.2	8.1			42	-20.1	8.8	7.7		
	Jones	ACT	44	-40.0	6.1	6.8	0.154	0.226	45	-40.8	6.0	6.8	0.108	0.163
		VEH	42	-26.1	7.6	6.9			44	-25.1	7.6	6.8		
total	Jarratt	ACT	42	-33.6	4.5	5.3	0.031	0.054	44	-33.8	4.3	5.1	0.030	0.053
		VEH	40	-17.0	6.2	5.4			42	-17.5	6.0	5.3		
	Jones	ACT	44	-35.5	4.6	4.8	0.409	0.462	45	-36.2	4.6	4.7	0.374	0.390
		VEH	42	-29.8	5.1	4.9			44	-30.2	4.9	4.8		

* Adjusted standard error and p-values are from an analysis of variance of treatment using SAS PROC GLM type III sums of squares on the original data. The rank p-values are from an analysis of variance using the rank-transformed data. The adjusted standard error is the standard error that would be expected if the treatment arms had equal sample sizes. The rank p-values are from an analysis of variance using the rank-transformed data.

TABLE 17A: Study 015: Percent Change From Baseline to Day 84 for All Centers Combined															
lesion	trt	EVAL-OC							ITT-LOCF						
		n	mean	se	adj. mean	adj. se	p-value [*] trt (trt*cen)	rank p-value [*] trt (trt*cen)	n	mean	se	adj. mean	adj. se	p-value [*] trt (trt*cen)	rank p-value [*] trt (trt*cen)
non-inf	ACT	86	-33.2	3.4	-33.2	3.7	0.077	0.118	89	-33.6	3.3	-33.6	3.6	0.087	0.133
	VEH	82	-24.0	4.1	-23.8	3.8	(0.229)	(0.370)	86	-24.9	4.0	-24.7	3.7	(0.228)	(0.388)
inf	ACT	86	-38.1	4.5	-38.0	5.2	0.047	0.063	89	-38.8	4.4	-38.8	5.1	0.026	0.033
	VEH	82	-23.3	5.9	-23.2	5.3	(0.898)	(0.852)	86	-22.7	5.8	-22.6	5.1	(0.940)	(0.857)
total	ACT	86	-34.6	3.2	-34.6	3.6	0.030	0.055	89	-35.0	3.1	-35.0	3.5	0.026	0.044
	VEH	82	-23.5	4.0	-23.4	3.7	(0.285)	(0.358)	86	-24.0	3.9	-23.9	3.5	(0.303)	(0.403)

^{*}In the analyses with all centers combined, the adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The rank p-values are from an analysis of variance using the rank-transformed data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes.

TABLE 17B: Study 015 Percent Change From Baseline to Days 28 and 56 in Non-Inflammatory Lesion Count For EVAL-OC Population									
lesion	day	trt	EVAL-OC						
			n	mean	se	adj. mean	adj. se	p-value [*] trt (trt*cen)	rank p-value [*] trt (trt*cen)
non-inf	28	ACT	85	-20.4	3.0	-20.3	3.0	0.154	0.241
		VEH	82	-14.4	3.5	-14.1	3.1	(0.253)	(0.228)
	56	ACT	86	-29.9	3.0	-29.7	3.3	0.016	0.034
		VEH	82	-18.4	3.9	-18.2	3.4	(0.659)	(0.584)

^{*}In the analyses with all centers combined, the adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The rank p-values are from an analysis of variance using the rank-transformed data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes.

TABLE 18: Study 015: Investigator's Global Assessment at Day 84 - EVAL-OC								
center	trt	total n ¹	outcome n (%) [*]					CMH p-value [*]
			excell.	good	fair	no change	worse	
ALL	ACT	86	12 (14)	16 (19)	33 (38)	20 (23)	5 (6)	0.055
	VEH	82	7 (9)	14 (17)	24 (29)	28 (34)	9 (11)	
Jarratt	ACT	42	4 (10)	10 (24)	17 (40)	7 (17)	4 (10)	0.173
	VEH	40	3 (8)	9 (23)	10 (25)	9 (23)	9 (23)	
Jones	ACT	44	8 (18)	6 (14)	16 (36)	13 (30)	1 (2)	0.177
	VEH	42	4 (10)	5 (12)	14 (33)	19 (45)	0 (0)	

¹Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores.

TABLE 19: Study 015: Change From Baseline In Assessment of Skin Safety Parameters at Day 84											
parameter	trt	ITT-OC					ITT-LOCF				
		n	outcome n (%) [*]			CMH p-value [*]	n	outcome n (%) [*]			CMH p-value [*]
			worse	no change	improve			worse	no change	improve	
burning/ stinging	ACT	88	11 (13)	77 (88)	0 (0)	0.002	89	12 (13)	77 (87)	0 (0)	0.001
	VEH	84	1 (1)	82 (98)	1 (1)		86	1 (1)	84 (98)	1 (1)	
dryness	ACT	88	18 (20)	65 (74)	5 (6)	0.073	89	18 (20)	66 (74)	5 (6)	0.078
	VEH	84	12 (14)	61 (73)	11 (13)		86	12 (14)	63 (73)	11 (13)	
erythema	ACT	88	23 (26)	57 (65)	8 (9)	0.042	89	24 (27)	57 (64)	8 (9)	0.030
	VEH	84	11 (13)	63 (75)	10 (12)		86	11 (13)	65 (76)	10 (12)	
itching	ACT	88	4 (5)	81 (92)	3 (3)	0.748	89	4 (4)	82 (92)	3 (3)	0.724
	VEH	84	3 (4)	80 (95)	1 (1)		86	3 (3)	82 (95)	1 (1)	
peeling	ACT	88	8 (9)	80 (91)	0 (0)	0.140	89	8 (9)	81 (91)	0 (0)	0.137
	VEH	84	3 (4)	81 (96)	0 (0)		86	3 (3)	83 (97)	0 (0)	
tightness	ACT	88	23 (26)	63 (72)	2 (2)	0.048	89	23 (26)	64 (72)	2 (2)	0.045
	VEH	84	11 (13)	71 (85)	2 (2)		86	11 (13)	73 (85)	2 (2)	

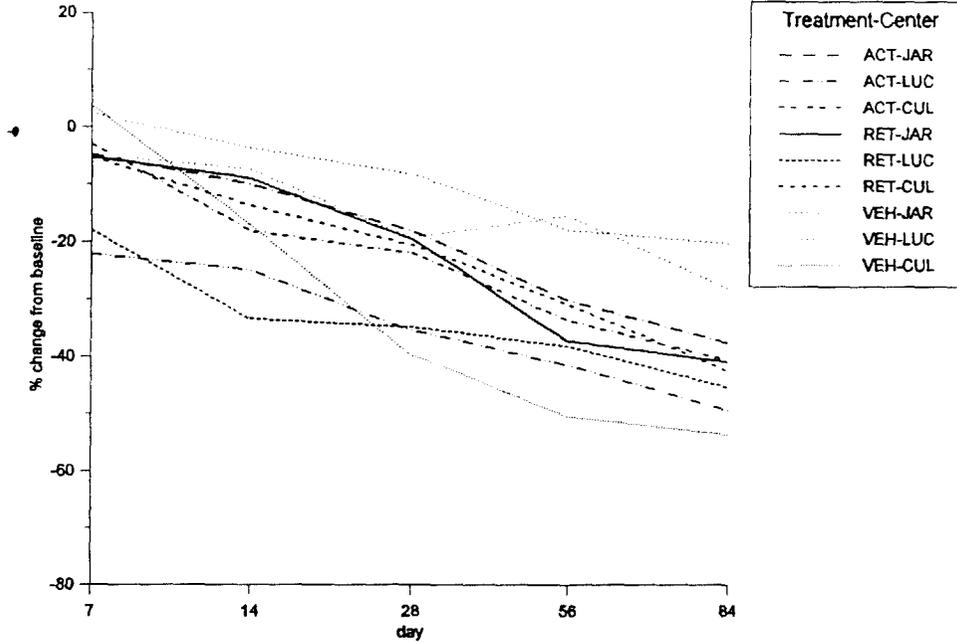
^{*}Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores.

VI. APPENDIX OF FIGURES

VI.A. STUDY 003

FIGURE 1: Study 003 Lesion Counts by Center

S-003: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Center



S-003: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Center

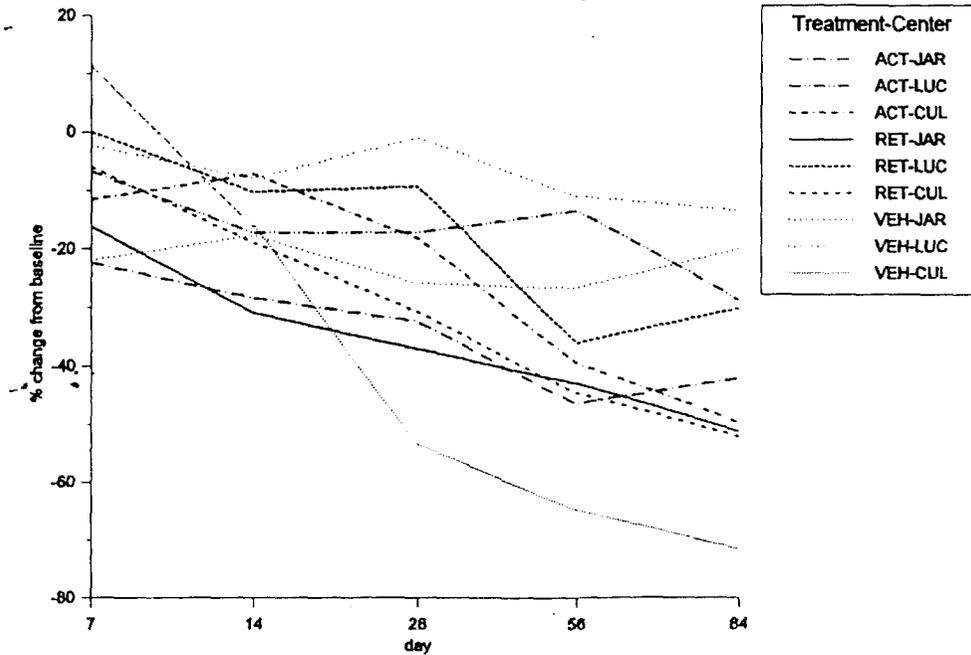


FIGURE 2A: Study 003 Non-Inflammatory Lesion Counts by Treatment

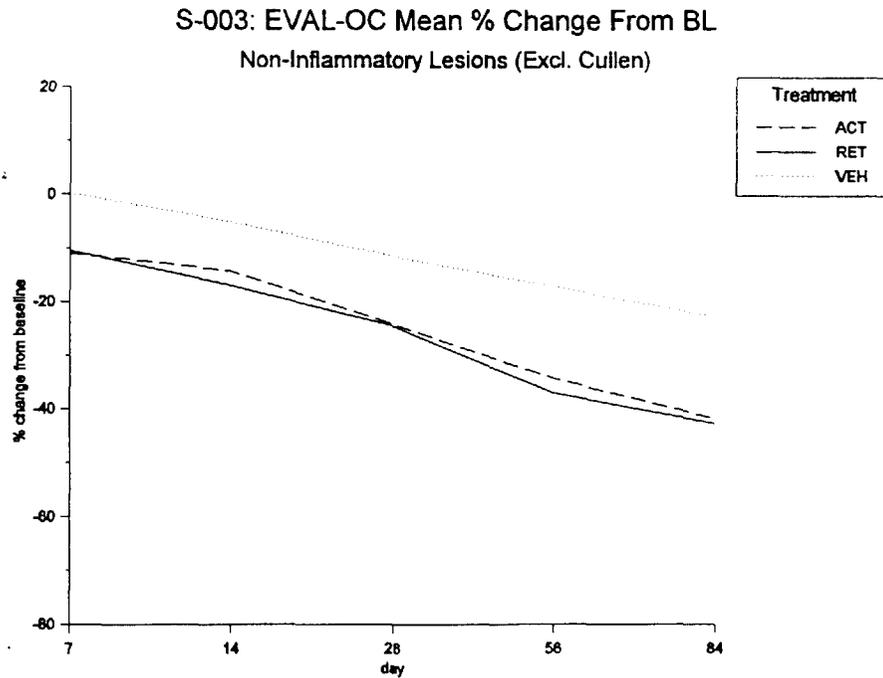
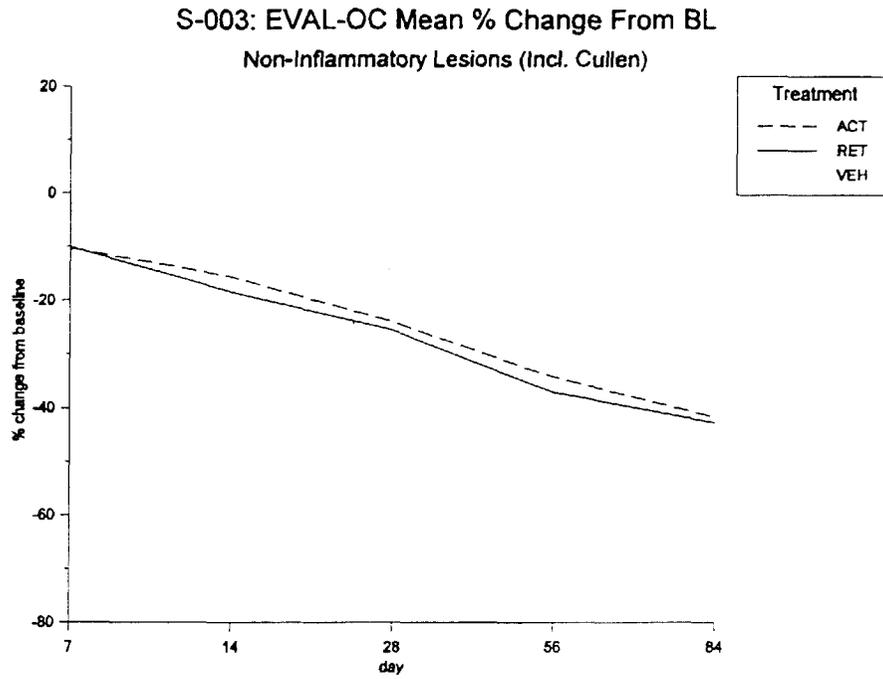


FIGURE 2B: Study 003 Inflammatory Lesion Counts by Treatment

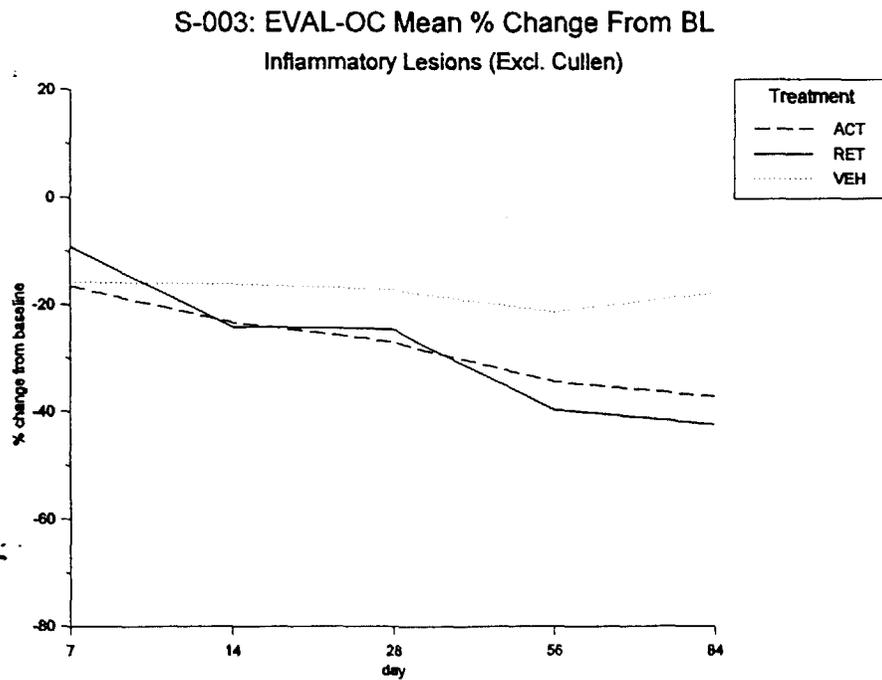
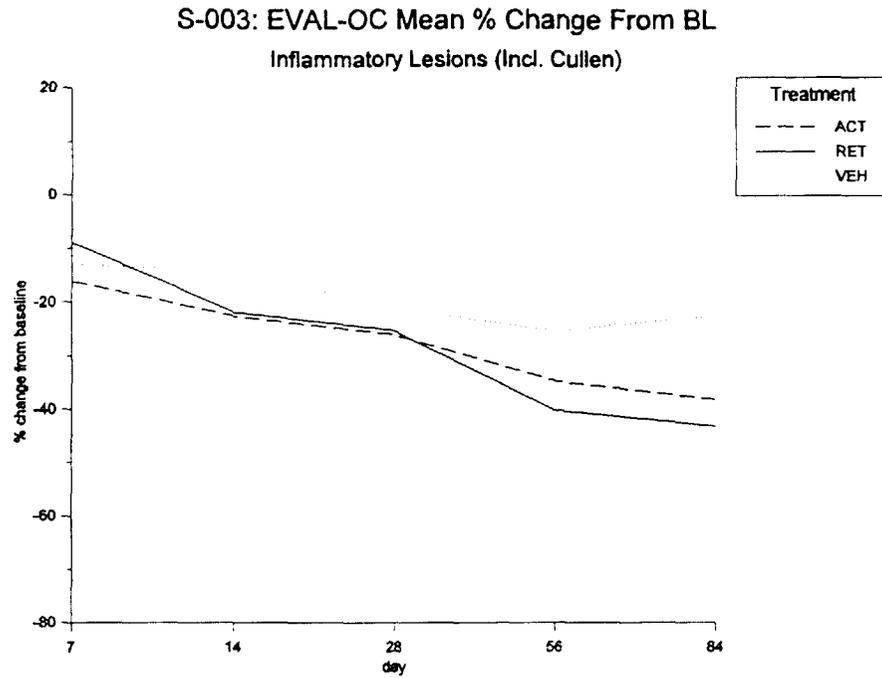
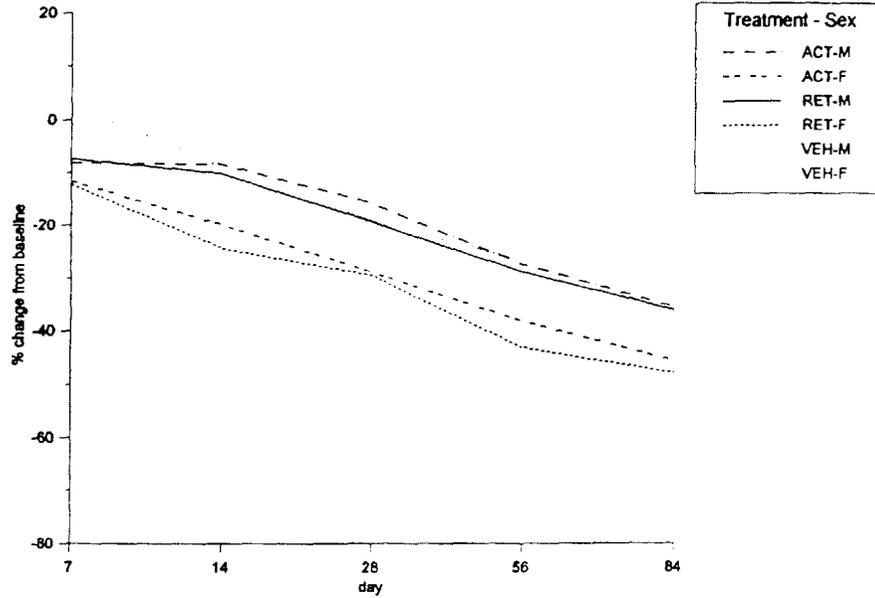


FIGURE 3: Study 003 Lesion Counts by Sex

S-003: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Sex



S-003: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Sex

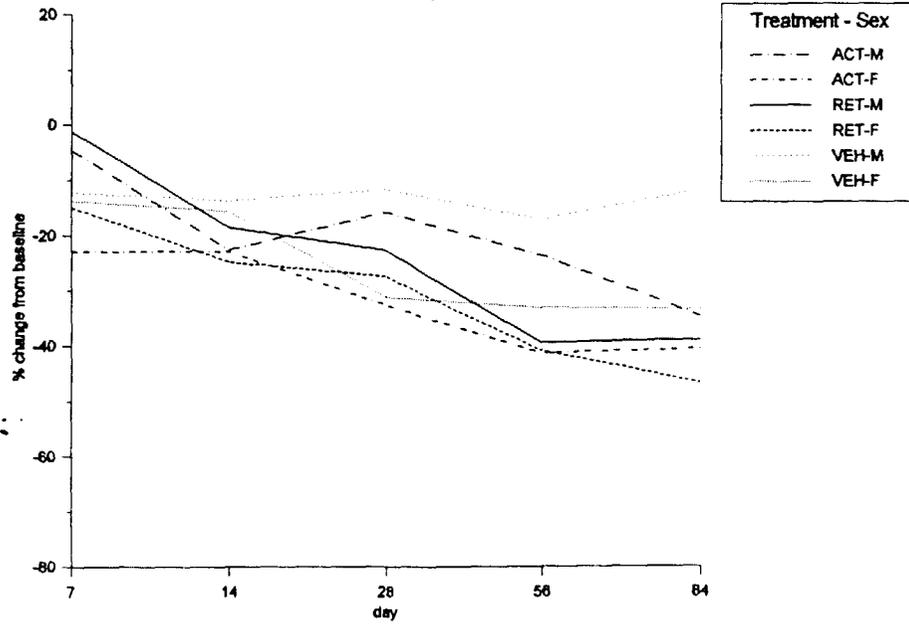
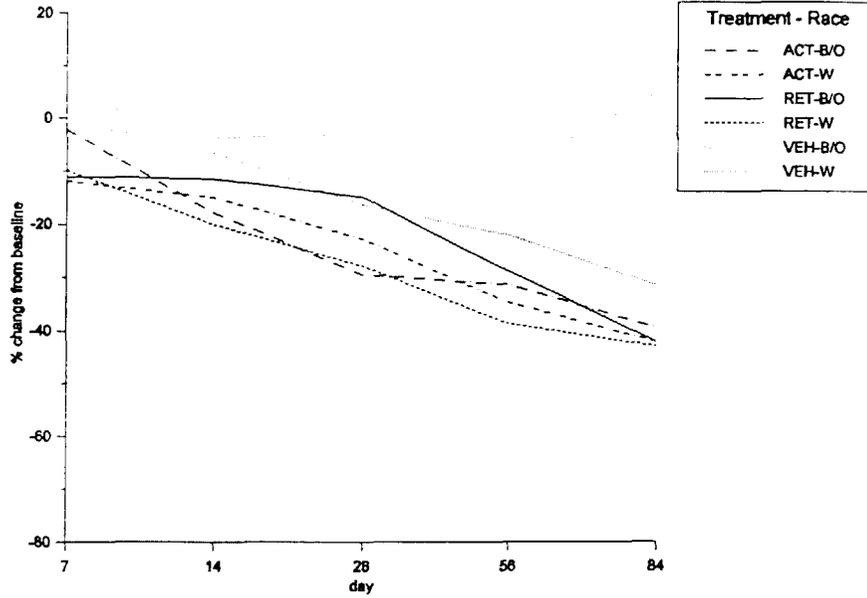


FIGURE 4: Study 003 Lesion Counts by Race

S-003: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Race



S-003: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Race

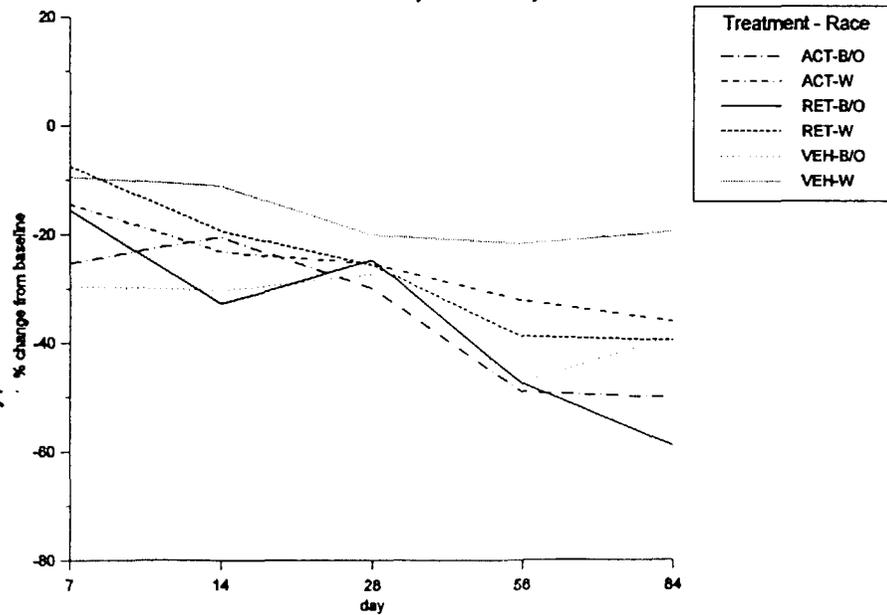
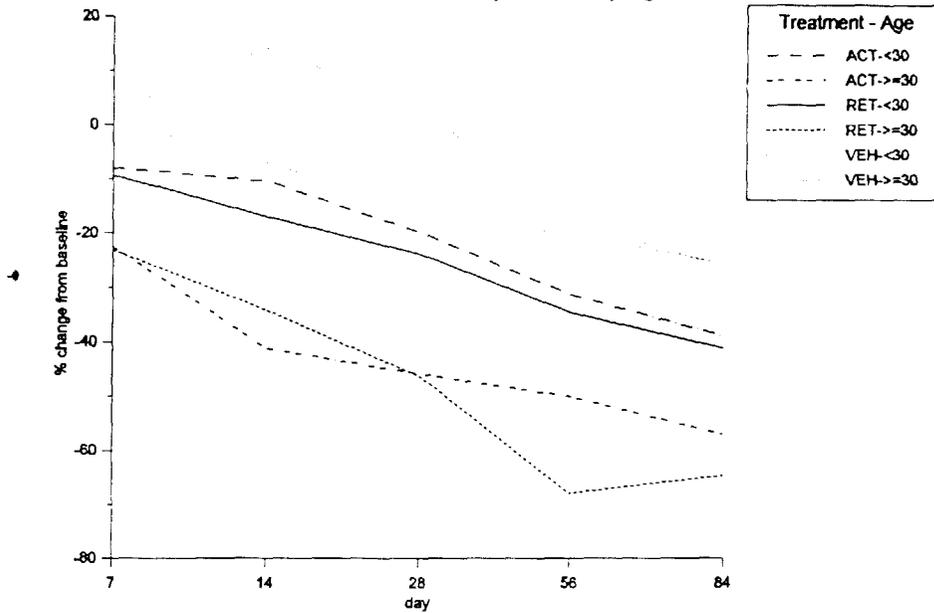


FIGURE 5: Study 003 Lesion Counts by Age

S-003: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Age



S-003: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Age

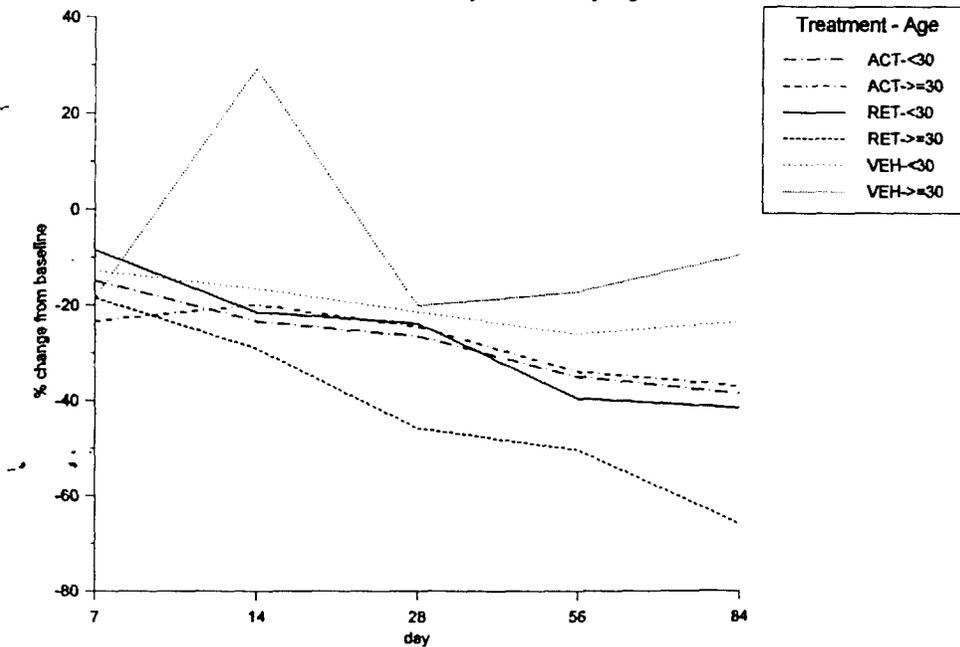


FIGURE 4: Study 003 Lesion Counts by Race

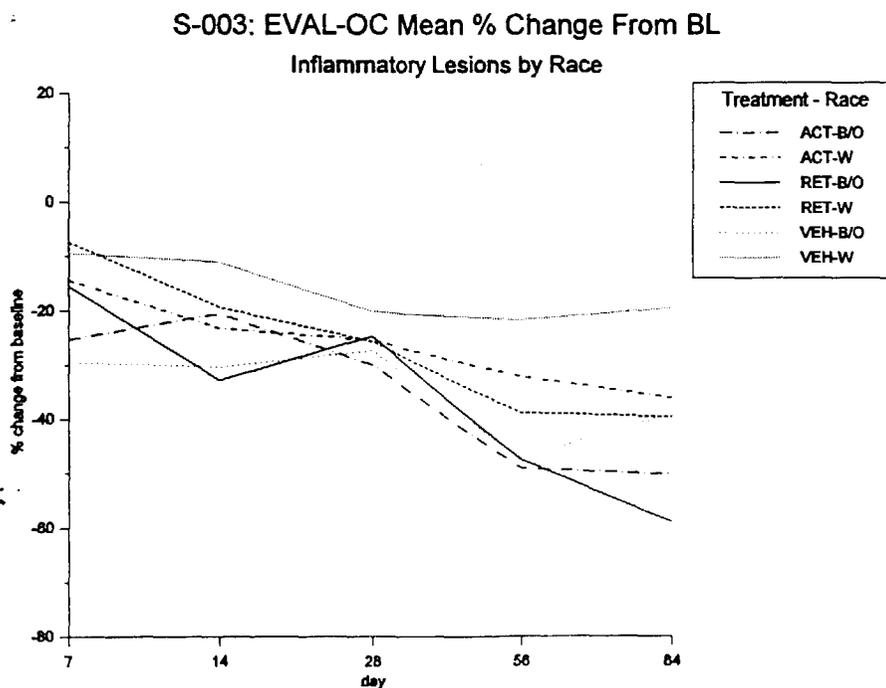
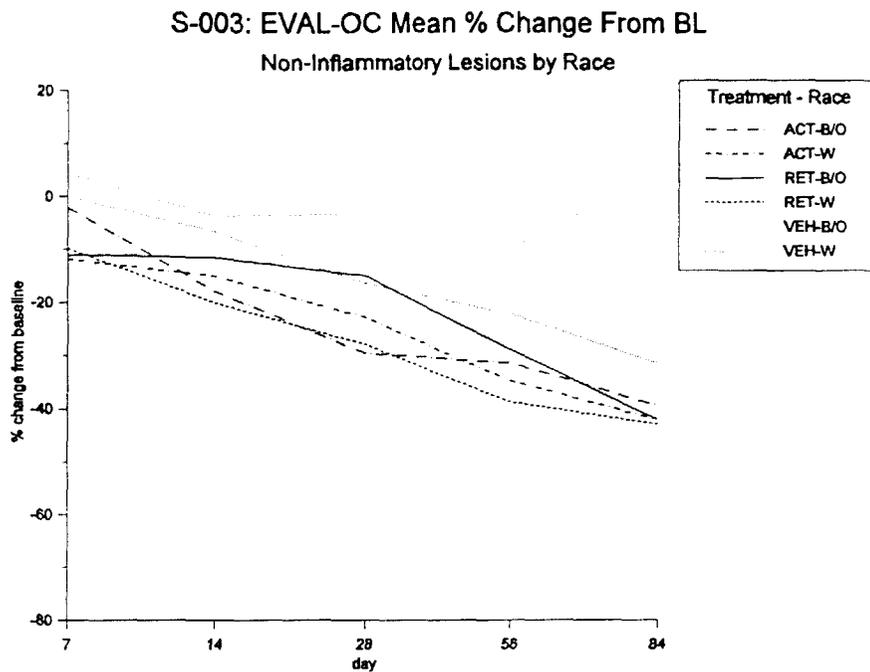


FIGURE 6A: Study 003 Burning/Stinging and Dryness

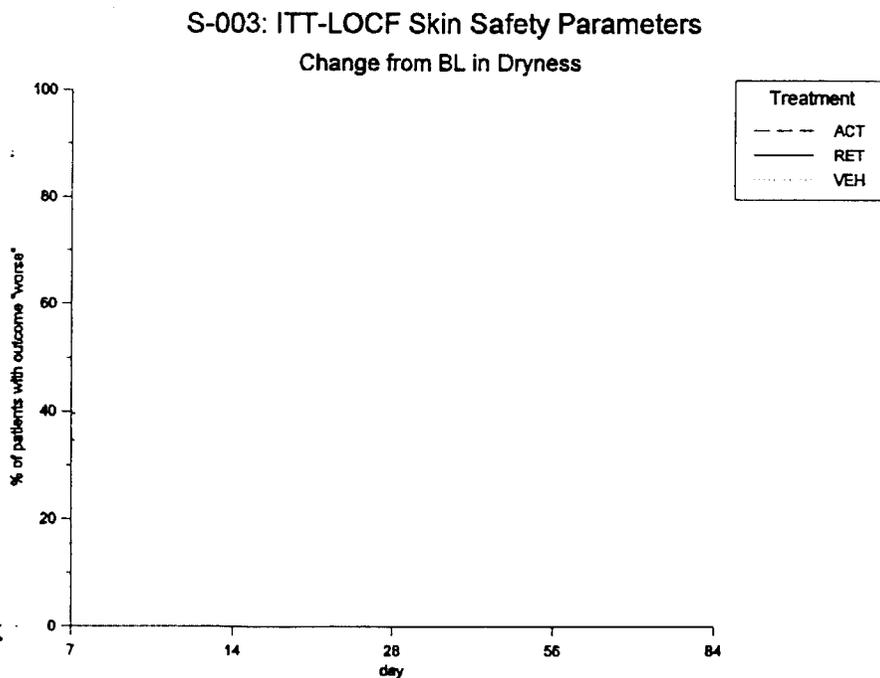
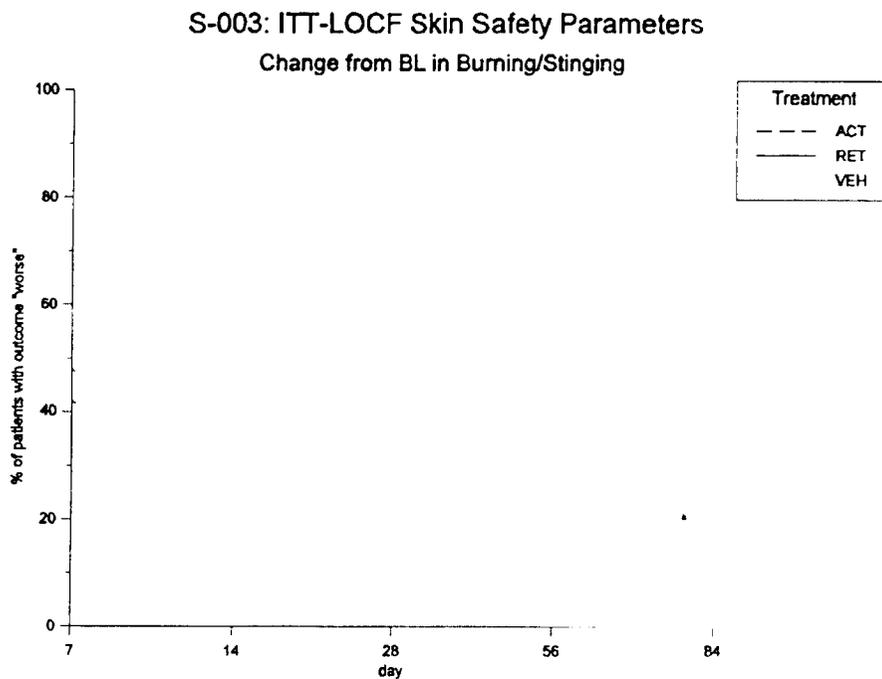
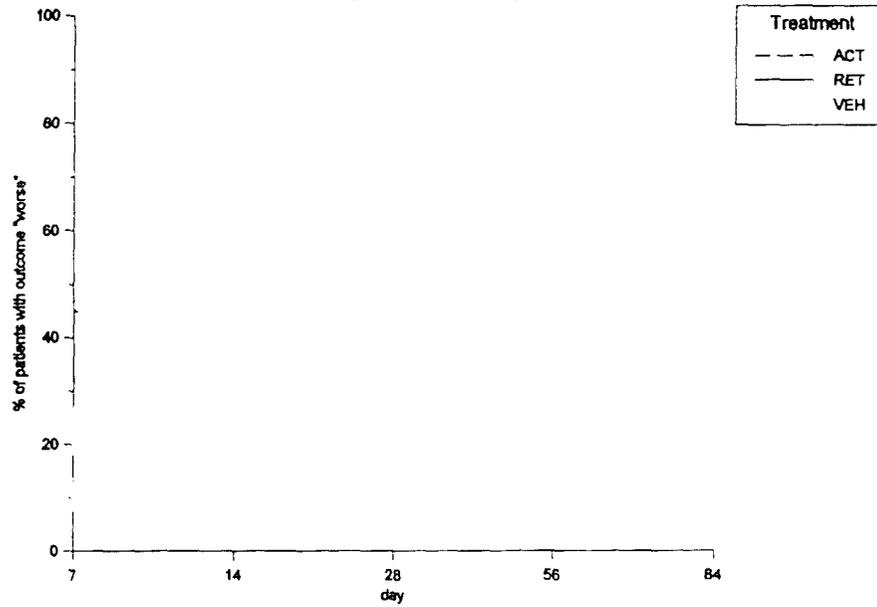


FIGURE 6B: Study 003 Erythema and Itching

S-003: ITT-LOCF Skin Safety Parameters
Change from BL in Erythema



S-003: ITT-LOCF Skin Safety Parameters
Change from BL in Itching

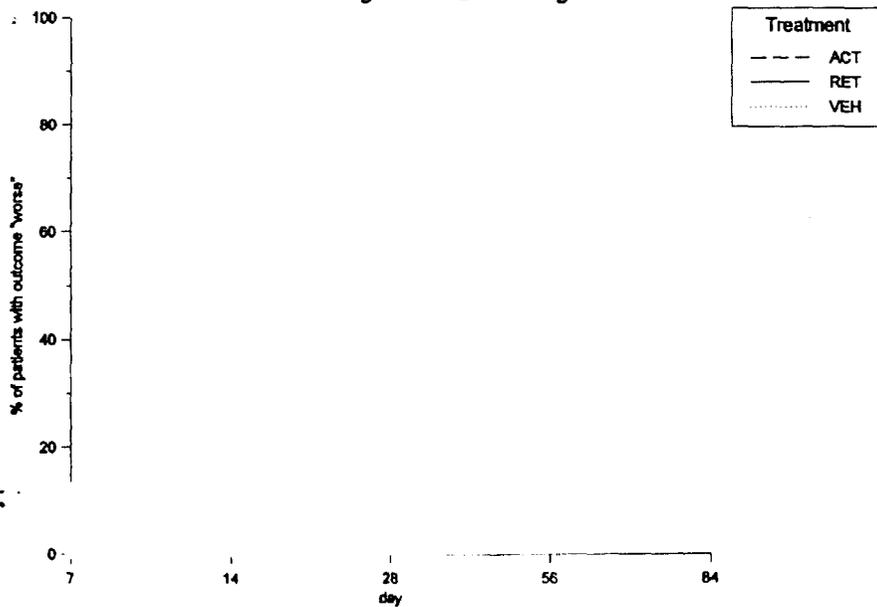
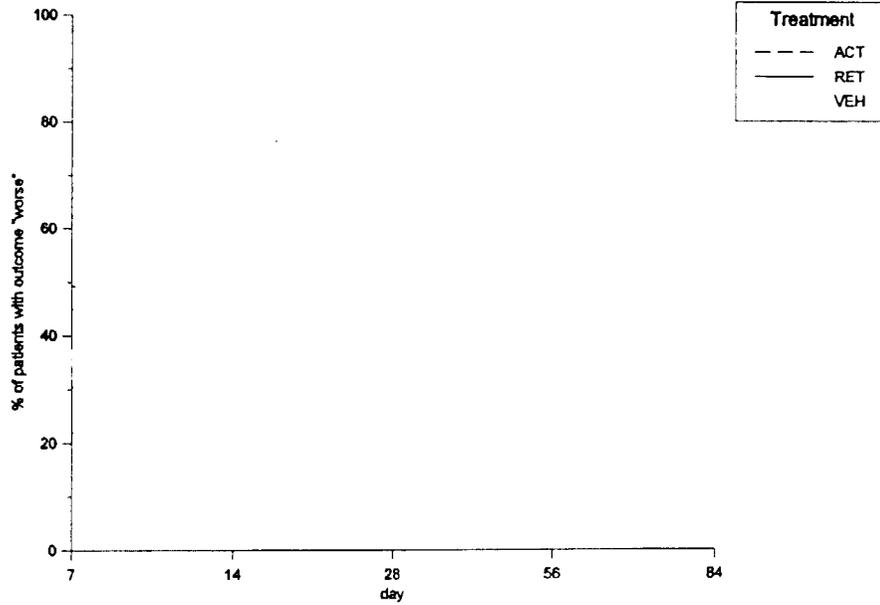
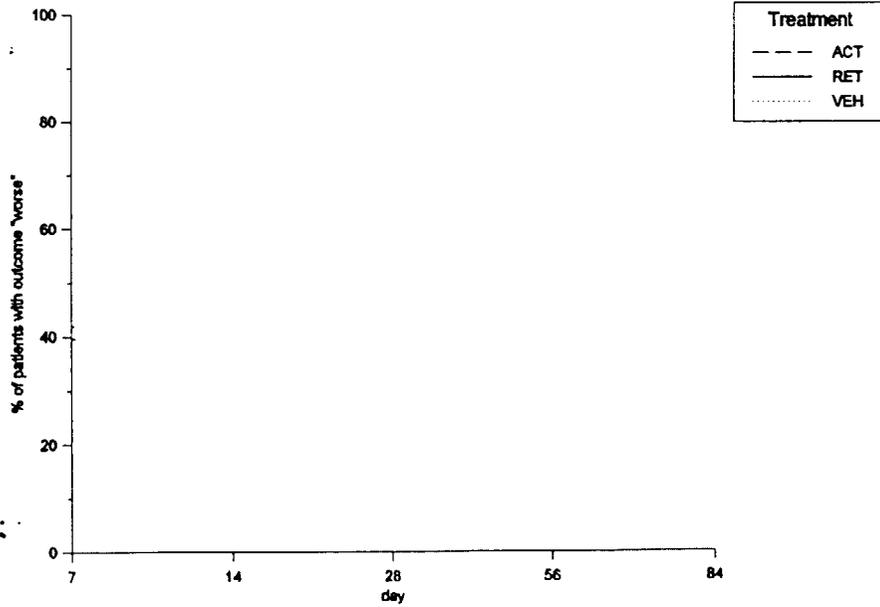


FIGURE 6C: Study 003 Peeling and Tightness

S-003: ITT-LOCF Skin Safety Parameters
Change from BL in Peeling



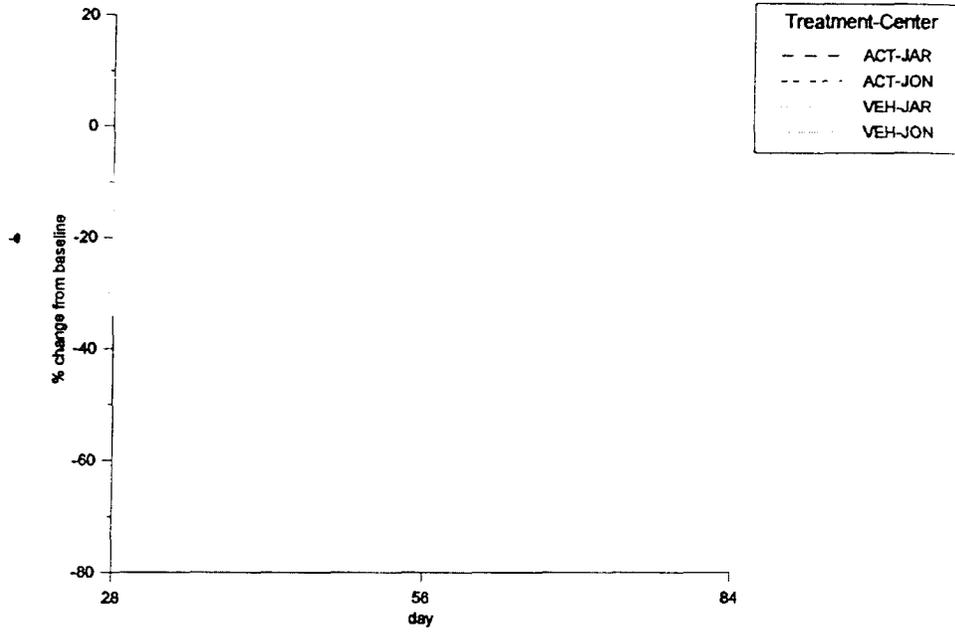
S-003: ITT-LOCF Skin Safety Parameters
Change from BL in Tightness



VI.B. STUDY 015

FIGURE 7: Study 015 Lesion Counts by Center

S-015: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Center



S-015: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Center

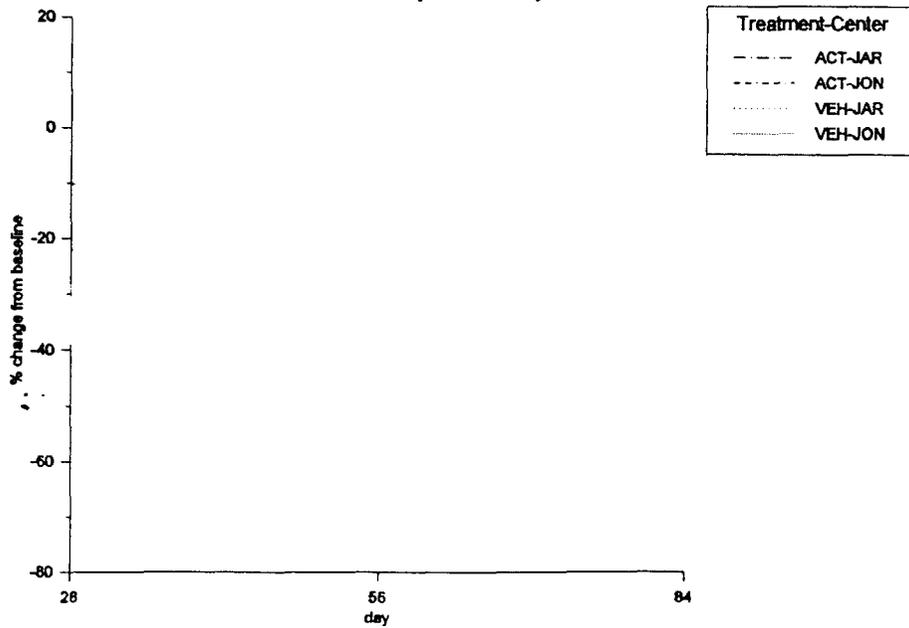


FIGURE 8: Study 015 Lesion Counts by Treatment

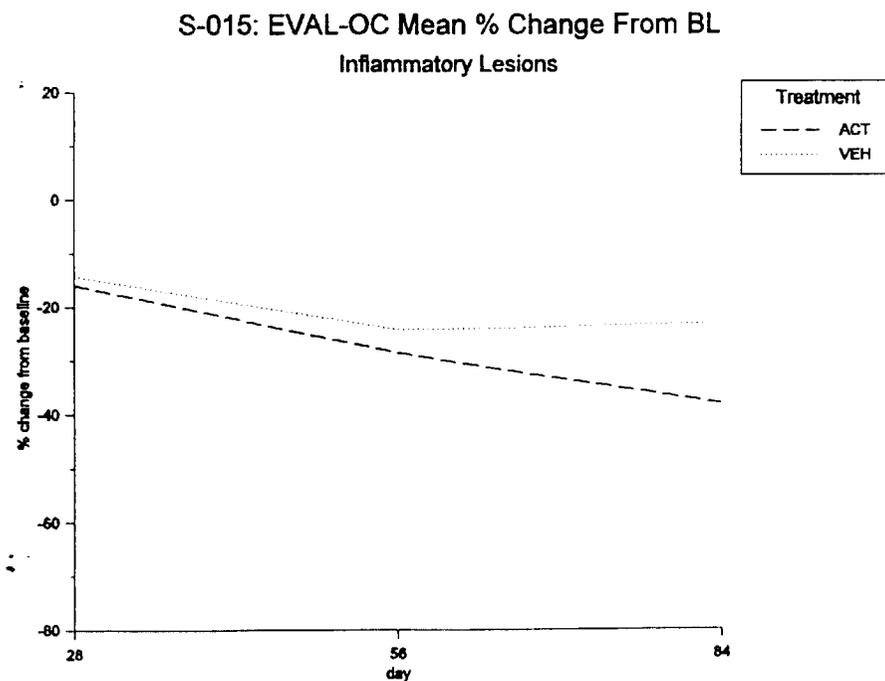
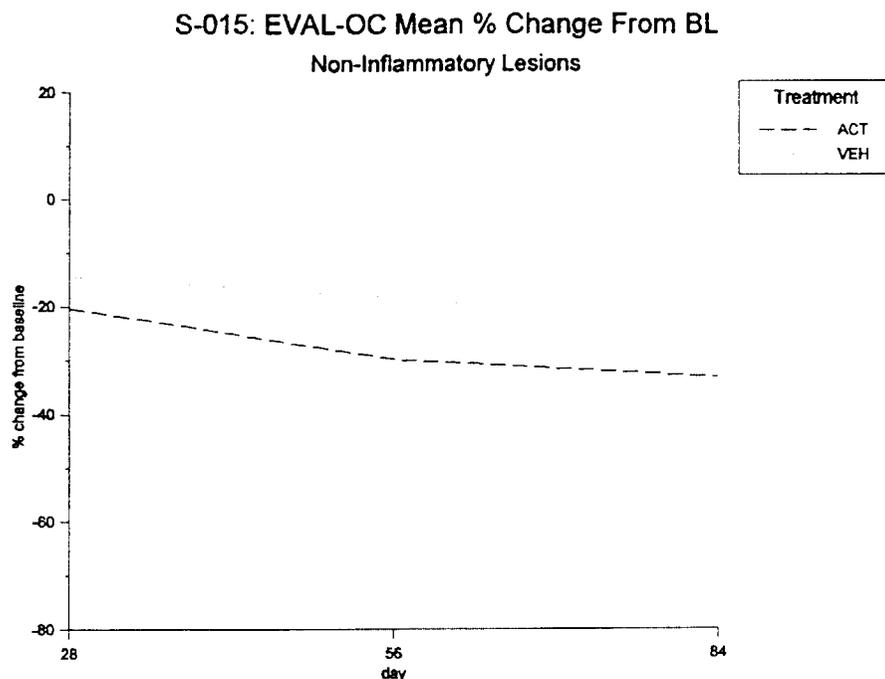
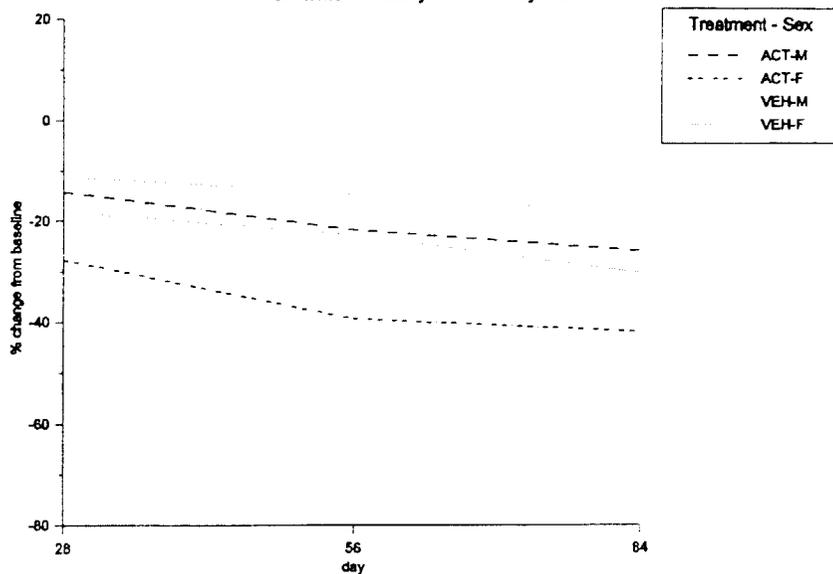


FIGURE 9: Study 015 Lesion Counts by Sex

**S-015: EVAL-OC Mean % Change From BL
Non-Inflammatory Lesions by Sex**



**S-015: EVAL-OC Mean % Change From BL
Inflammatory Lesions by Sex**

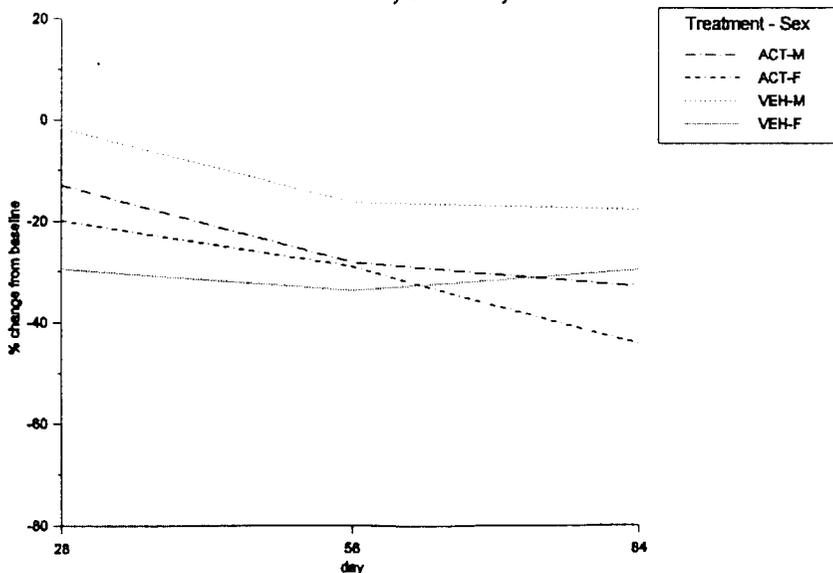


FIGURE 10: Study 015 Lesion Counts by Race

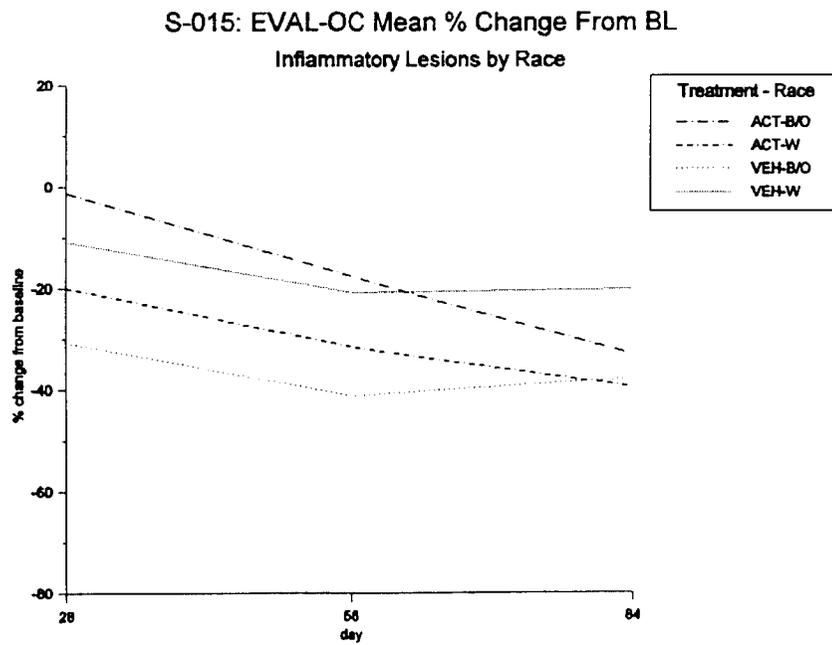
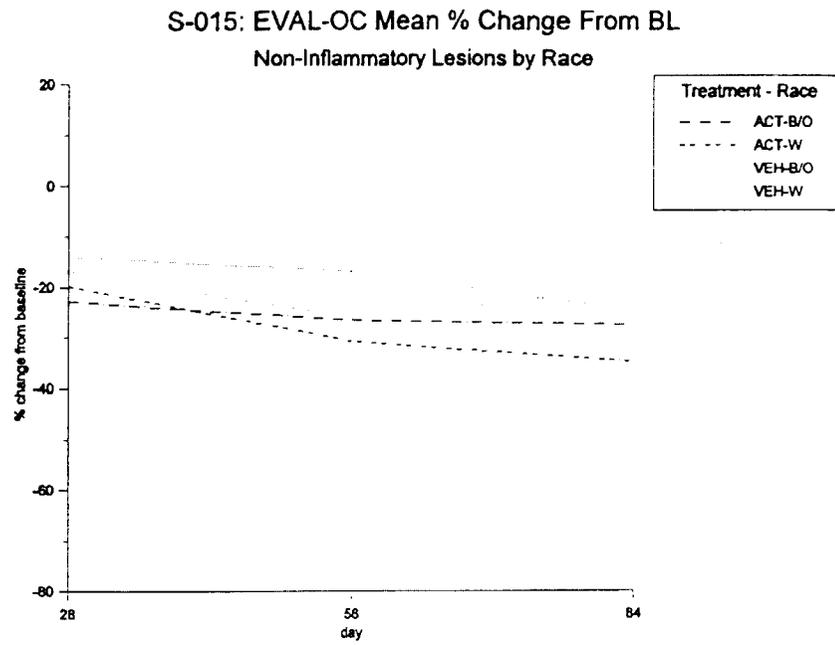


FIGURE 11: Study 015 Lesion Counts by Age

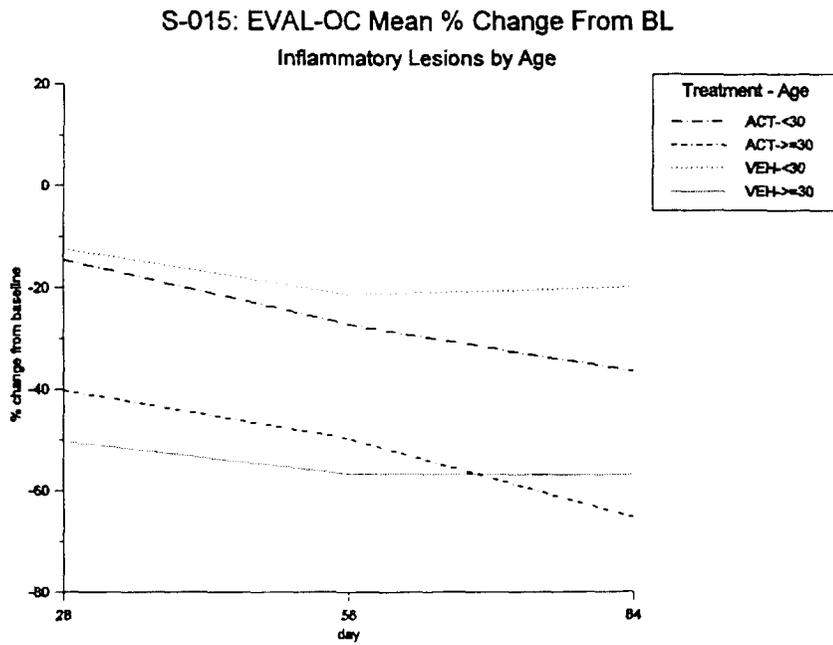
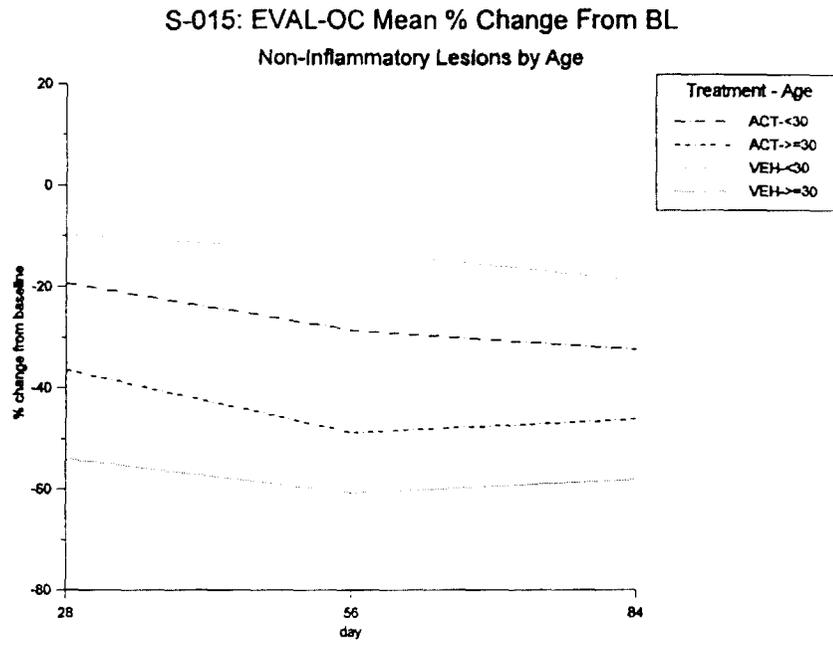


FIGURE 12A: Study 015 Burning/Stinging and Dryness

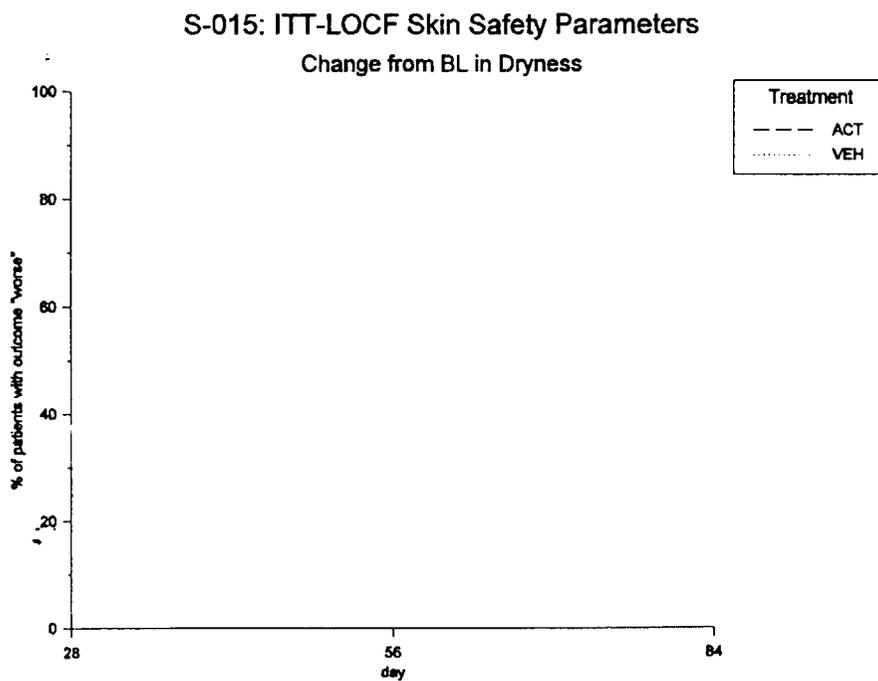
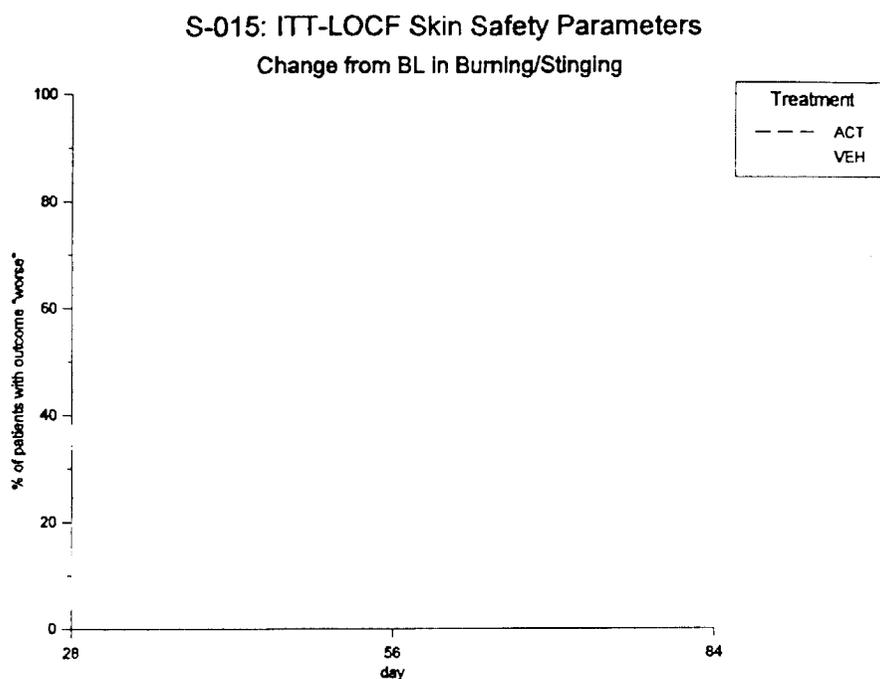
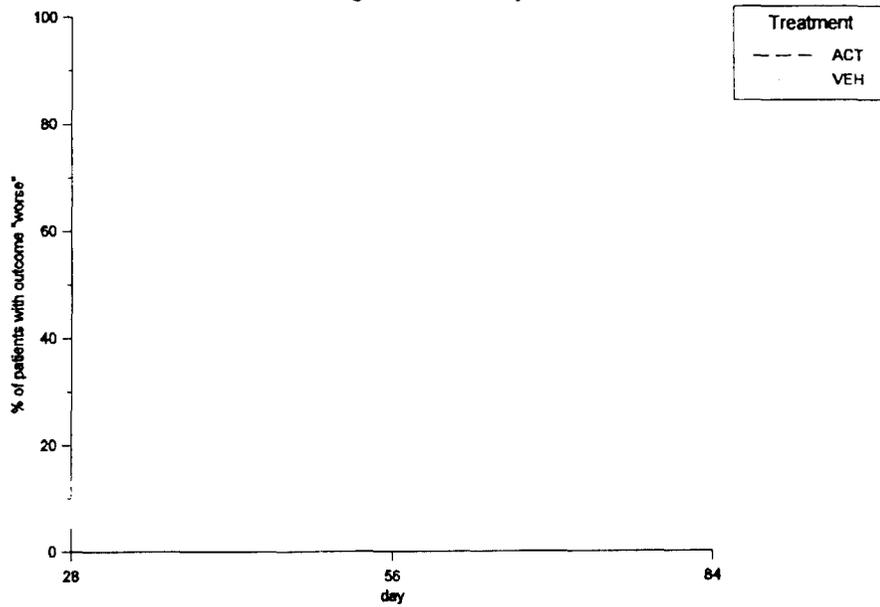


FIGURE 12B: Study 015 Erythema and Itching

S-015: ITT-LOCF Skin Safety Parameters
Change from BL in Erythema



S-015: ITT-LOCF Skin Safety Parameters
Change from BL in Itching

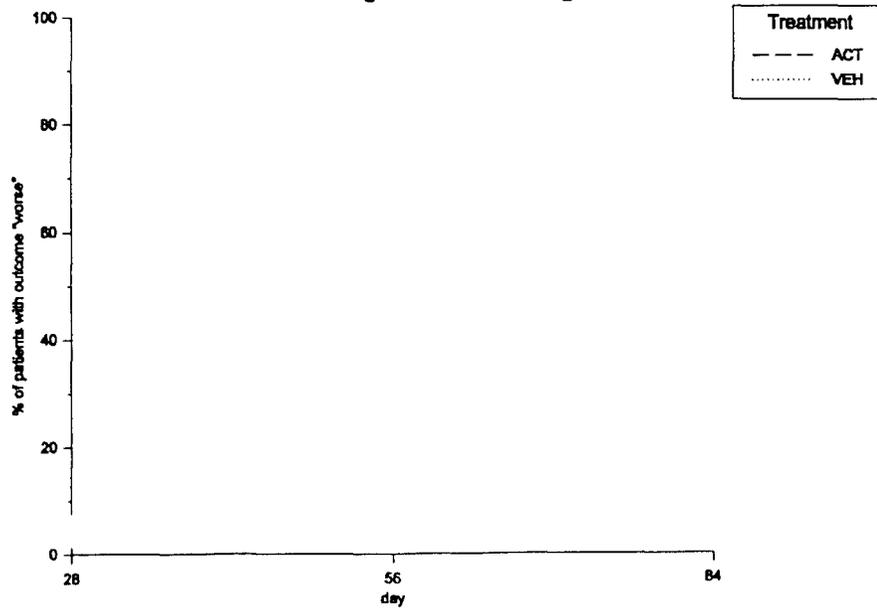
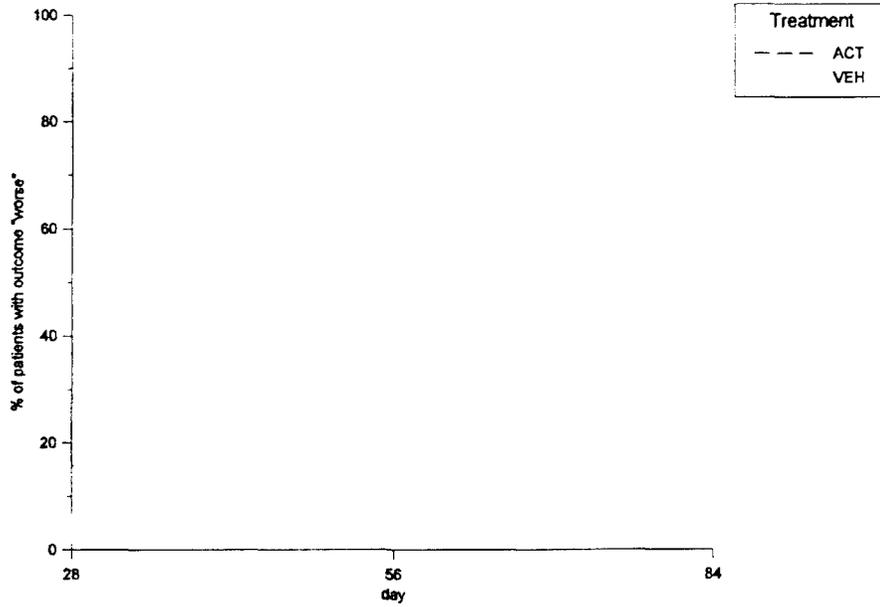
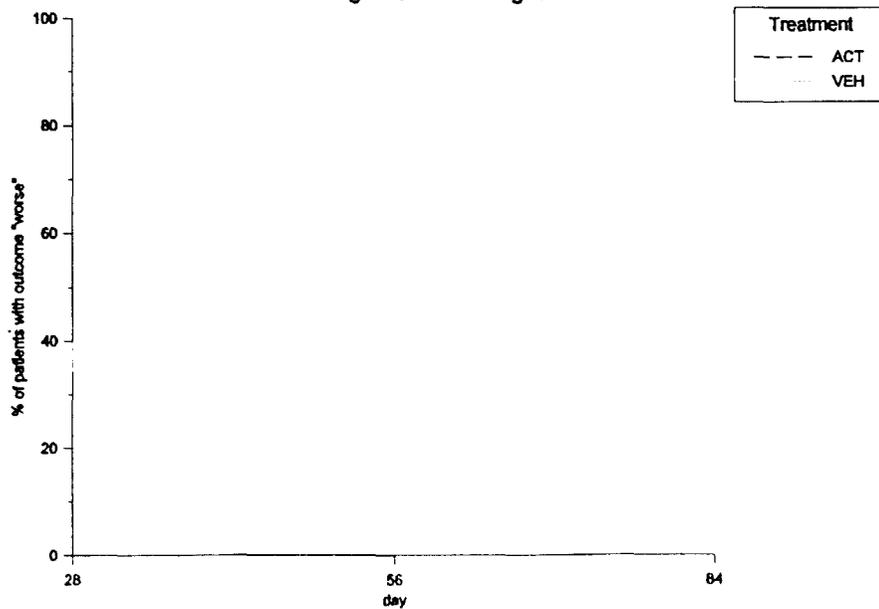


FIGURE 12C: Study 015 Peeling and Tightness

S-015: ITT-LOCF Skin Safety Parameters
Change from BL in Peeling



S-015: ITT-LOCF Skin Safety Parameters
Change from BL in Tightness



Statistical Review and Evaluation
(Amendment)

NDA#: 20-400

JUN 19 1996

Applicant: Penederm Inc.

Name of Drug: Tretinoin Gel 0.025% (Avita [formerly Acticin])

Documents Reviewed: File of prior minutes of meetings, statistical and clinical reviews plus Penederm's supplementary statistical analyses submission received in DBIV in May 1996 conducted in accordance with conversations in November and December 1995 between Ms. Kennerly Chapman, Ms. Beth Turney and Dr. Ralph Harkins of FDA and Mr. Barry Calverese, Dr. David Ng and Dr. Jennings Lin.

Indication: Acne Vulgaris

Type of Review: Clinical

Medical Input: Dr. Nancy Slifman. HFD-540

A. Background:

This application was originally submitted as an ANDA to the Office of Generic Drugs. However, due to the use of an excipient, polyolprepolymer-2, in Acticin™ and not used in Retin-A™ nor in any previously approved prescription drug products, it was withdrawn and submitted as an NDA. Subsequently, the sponsor claimed this retinoic Acid formulation should be considered as a generic drug and requested that the Center consider it as such. The sponsor wanted the Agency to apply the OGD 80/120 rule and 90% CIs rather than the 95% CI required by an NDA submission. They insisted on this even after it was pointed out to them that the 90% CI requirement may be more difficult to meet than the 95% CI. The CI is on the form: $a + Kb$. In the 95% CI $K = 1.96$ and in the 90% CI $K = 1.645$. The 90% CI is shorter than the 95% CI. However, it appears the sponsor believed the 80/120 rule would outweigh this consideration.

As a Generic Drug Product, the sponsor's submission must meet the 80/120 rule based on the use of 90% confidence intervals (CI) for demonstrating therapeutic and related equivalency statements. This is the same as using two-one sided 95% confidence intervals. The 80/120 rule provides an allowable confidence interval length of + and - 20% for cure/failure type trials and within 20% of the active control mean response for other type response variables. Since the concept is that the new agent is neither better than nor worse than the control agent, the 90% CI must contain zero and be completely contained within the -20% and +20% cut-off values.

Therefore, after much urging by the sponsor, the Center took the sponsor's request under advisement. After much due consideration, it was decided at the Center level that this product formulation could be analyzed using the OGD 90% CI methodology based on its unique regulatory history.

Previously, the sponsor submitted two studies in support of their claims. Study PDC 004-003 is a three arm (Avita, Retin-A and Vehicle) trial designed to demonstrate equivalency to Retin-A and superiority to Vehicle. Study PDC 004-015 is a Vehicle controlled trial to demonstrate superiority to Vehicle. It was noted by the prior reviewer and confirmed by this reviewer that statistical analyses in the original submission should be performed using more appropriately center weighted statistical procedures. In addition, we require that the two studies be independent. Dr. Jarrett is a common investigator to the two studies noted above. After discussion with the sponsor, the sponsor decided to remove this investigator from study PDC 004-003 and repeat the analyses using a center weighted method. It was further agreed that the sponsor's reanalyses must demonstrate that Acticin (Avita) is statistically superior to its vehicle at day 84 for the efficacy variables of Physician's Global Assessment, % change from baseline in total Lesions and % change from baseline in Non Inflammatory Lesions. They were to demonstrate therapeutic equivalency to Retin-A at day 84 for these same three efficacy variables in PDC 004-003 with Dr. Jarrett's data removed. The primary analysis would be the LOCF (ITT) analysis. No correction for multiple comparisons was required since all three efficacy variables must be successfully satisfied for approval.

In the reanalyses the OGD 80/120 criteria using 90% CIs were to be used to demonstrate therapeutic equivalency and for the vehicle comparisons the 10% test level was to be used.

The purpose of this amendment is to summarize these supplemental analyses provided by the sponsor.

A. Calculations and Evaluation

All confidence interval results are presented as two-sided 90% confidence intervals in the format $n_t, n_c (CI)_{p_t, p_c}$ where n_t and p_t are respectively the sample size and success rates for the test agent (Penederm's Retinoic Acid product) and n_c and p_c are similarly defined for the control agent (either PBO or an active agent).

I have used the 90% CIs and test results from the sponsor's latest reanalysis submission in the following discussion. Since it was agreed that all conclusions would be based on the LOCF data, only the LOCF results are presented. Also, in Study PDC 004-003 only results with Dr. Jarrett's data removed are given.

Table 1.A presents all results for % reduction from baseline in Total Lesion Counts. For Study PDC 004-003 the 90% CI and p value comparing Vehicle to Avita is $_{29.29}(1.7, 35.1)_{42.8,24.4}$, $p = .036$. For Study PDC 004-015 the 90% CI and p value comparing Vehicle to Avita is $_{89.86}(1.2, 20.9)_{35.0,24.4}$, $p = .028$.

Table 1.B presents all results for % reduction from baseline in Noninflammatory Lesion Counts. For Study PDC 004-003 the 90% CI and p value comparing Vehicle to Avita is $_{29.29}(3.2, 37.8)_{45.7,25.2}$, $p = .021$. For Study PDC 004-015 the 90% CI and p value comparing Vehicle to Avita is $_{89.86}(-1.4, 19.0)_{33.6,24.8}$, $p = .091$.

Table 2.B presents all results for Investigators Global Assessment for improvement from baseline for Study PDC 004-003. The CMH test for improvement gives $p = .004$. I calculated a shift parameter of 0.6, $p = .009$.

Table 2.D presents all Investigator Global Assessment results for Study PDC 004-015. The sponsor's CMH test p value is 0.019 in favor of Avita. I calculated a shift parameter of 0.07, $p = .038$.

These last two comparisons are nonparametric and confidence intervals were not calculated due to lack of a variance estimate.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The December 1995 agreement with the sponsor was that 90% test levels and the OGD 80/120 rule would be applied to their data. The results of the LOCF data reanalyses were to demonstrate that Acticin (Avita) is statistically superior to its vehicle at day 84 for % change from baseline in total Lesions, % change from baseline in Noninflammatory Lesions and Physician's Global Assessment. In addition, Avita was to be therapeutically equivalent to Retin-A at day 84 for these same three efficacy variables in PDC 004-003 with Dr. Jarrett's data removed.

The above analyses support the claim of superiority of Avita to its Vehicle. However, the sponsor failed to perform the required comparisons of Avita to Retin-A to demonstrate therapeutic equivalency.

Based on these analyses, it appears the sponsor can have the claim of superiority but cannot have the generic claim of therapeutic equivalency.

/S/

Ralph Harkins, Ph.D.
Division Director
Biomedical Statistician, DBIV

cc:

Archival: NDA-20-400

HFD-540

HFD-540/Dr. Wilkin

HFD-540/Dr. Katz

HFD-540/Dr. Slifman

HFD-540/Mr. Blay

HFD-725/Dr. Harkins

Chron.

This review contains 3 pages.

JUN 26 1988

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Statistical Review and Evaluation
(Amendment No. 2)

NDA#: 20-400

Applicant: Penederm Inc.

Name of Drug: Tretinoin Gel 0.025% (Avita [formerly Acticin])

Indication: Acne Vulgaris

Type of Review: Clinical

Medical Input: Dr. Nancy Slifman. HFD-540

The Center evaluated the sponsor's request that their product formulation be judged using the OGD 90% CI methodology based on its unique regulatory history. To be approved as a Generic Drug Product, the sponsor's submission must meet the 80/120 rule based on the use of 90% confidence intervals (CI) for demonstrating therapeutic equivalency. However, if the product fails to demonstrate therapeutic equivalency to Retin-A, the Agency would consider approval as a new drug if the product demonstrates superiority to its vehicle in both trials using the OGD test level criteria. The Agency has never approved a drug using a more liberal test level than the historical 0.05 level.

Study PDC 004-003 is a three arm (Avita, Retin-A and Vehicle) trial designed to demonstrate equivalency to Retin-A and superiority to Vehicle. Study PDC 004-015 is a Vehicle controlled trial to demonstrate superiority to Vehicle. We require that the two studies be independent. Dr. Jarrett is a common investigator in these two studies. The sponsor agreed to remove this investigator from study PDC 004-003 and keep PDC 004-015 intact in center weighted reanalyses. It was further agreed that the sponsor's reanalyses must demonstrate that Acticin (Avita) is statistically superior to its vehicle at day 84 for the efficacy variables of Physician's Global Assessment, % change from baseline in total Lesions and % change from baseline in Non Inflammatory Lesions. To gain OTC approval, they were to demonstrate therapeutic equivalency to Retin-A at day 84 for these same three efficacy variables in PDC 004-003 with Dr. Jarrett's data removed. The primary analysis would be the LOCF (ITT) analysis. No correction for multiple comparisons was required since all three efficacy variables must be successfully satisfied for approval.

For the Total Lesion comparison, Avita is statistically superior to its vehicle, $p = .036$ in study 003 and $p = .028$ in study 015.

For the Non Inflammatory Lesion comparison, Avita is statistically superior to its vehicle, $p = .021$ in study 003. However, $p = .091$ in study 015. This meets the OGD criteria but fails to meet new drug approval criteria.

For the Physician's Global Evaluation comparison, Avita is statistically superior to its vehicle, $p = .004$ in study 003 and $p = .019$ in study 015.

For approval, the sponsor's reanalyses must demonstrate that Acticin (Avita) is statistically superior to its vehicle at day 84 for the efficacy variables of Physician's Global Assessment, % change from baseline in total Lesions and % change from baseline in Non Inflammatory Lesions in both studies. Study 004-015 fails to support superiority of Avita to its vehicle for Non-Inflammatory lesions using the historical approval test level of 0.05.

/S/

Ralph Harkins, Ph.D.
Division Director
Biomedical Statistician, DBIV

6/26/96

cc:

Archival: NDA-20-400

HFD-540

HFD-540/Dr. Wilkin

HFD-540/Dr. Katz

HFD-540/Dr. Slifman

HFD-540/Mr. Blay

HFD-725/Dr. Harkins

Chron.

This amendment contains 2 pages.

CLINICAL/STATISTICAL REVIEW AND EVALUATION

NDA/Drug Class: 20-400 / 5S SEP 13 1996

APPLICANT: Penederm Incorporated

NAME OF DRUG: Avita (Tretinoin 0.025%)

INDICATION(S): Treatment of Grade II or III Acne Vulgaris

TYPE OF REVIEW: Clinical/Statistical

DOCUMENTS REVIEWED: Volumes 1 through 10, Study# PDC 004-022,
Dated July 15, 1996

CLINICAL INPUT: Ramzy Labib, M.D. (HFD 540)

I. INTRODUCTION

Tretinoin (all-trans-retinoic acid), a natural metabolite of vitamin A (retinol), was first shown to be effective in Keratinization disorders by Stuttgen in 1962. However, the skin irritation was considered too great for chronic use. Kligman, et al., were the first to demonstrate the successful treatment of acne with topical tretinoin, but the alcoholic solution used in the initial clinical trials was associated with severe skin irritation. Subsequently, gel and cream formulation with reduced irritation were developed. However, the irritation associated with these formulation remains severe enough to limit their usage.

Tretinoin's effectiveness in treating acne has been proven; but the benefits of this agent can be improved by reducing its side effects (erythema, edema, blistering, crusting, severe irritation on eczematous skin). In vivo preclinical data has shown that retinoic acid can be formulated such that the irritation from multiple dosing is significantly reduced. The sponsor claims that a study of retinoid-induced dermatitis from nightly dosing in normal adult volunteers has demonstrated a low degree of irritation for Avita Gel 0.025% compared to Retin-A Gel 0.025%.

The sponsor intends to demonstrate: 1) The efficacy of Avita Gel 0.025% and Retin-A Gel 0.025% versus vehicle on day 84, visit 6, 2) To compare the relative incidence of signs and symptoms in the Avita Gel 0.025% and Retin-A Gel 0.025% treatment groups, and 3) To determine the relative safety of Avita Gel 0.025% and Retin-A Gel 0.025% in comparison with vehicle in terms of the safety parameters (signs and symptoms) and adverse events.

The sponsor has submitted the results of one study which would be the basis for the approval of Avita Gel 0.025% for the treatment of grade II or III acne vulgaris.

In order to gain approval for this formulation, the sponsor should show a statistical superiority of the Avita Gel 0.025% to its vehicle at a two-sided, 5% significance level.

In this review, two different approaches were made. First, the analyses were performed on the data set based on all randomized subjects whose end of treatment lesion count was available. This data set will be referred to as FDA-Evaluable (FDA_Eval) data. Second, in order to maintain the integrity of the randomization, an intent-to treat analysis was done. For the subjects who did not finish the 84 day treatment, the last available value was carried forward and replace their missing 84th day lesion count value.

II. REVIEW OF STUDY, **EFFICACY**

Objectives, Design, Patient Enrollment and Statistical Methods:

The objective of this study was to evaluate the safety and efficacy of Avita Gel 0.025%.

This was a randomized, double-blind, parallel group, vehicle-controlled, 12-week, multi center trial which was conducted in the United States and Canada. In order to obtain approximately 525 evaluable patients, six hundred and seventy-five (675) subjects male or female, 12 to 40 years of age, were randomized to Avita Gel 0.025%, Retin-A Gel 0.025% or Vehicle with ratio of 1:1:1. The subjects should have had the following facial lesions, excluding lesions on the nose to be enrolled into the study:

- A minimum of 10, but no more than 30 papules and/or pustules combined
- A minimum of 30, but no more than 95 comedones
- No more than four nodulocystic lesions

Assessment of facial acne vulgaris was done at baseline (Day 1), Days 7, 14, 28, 56 and 84 or at an early discontinuation visit. The baseline lesion counts were performed on the same day that study medication was dispensed.

At each visit, the patient's facial acne vulgaris was assessed by counting the number of facial lesions above the jaw line to the hairline (except the nose) for each of the following categories: comedones (open or closed), papules, pustules, and nodulocystic lesions.

The primary endpoint variables for this study are:

- 1) Percent Change from Baseline in Total Lesion Count for the Combined Number of Inflammatory and Noninflammatory Lesions.
- 2) Percent Change from Baseline in Total Lesion Count for Noninflammatory Lesions.
- 3) Percent Change from Baseline in Total Lesion Count For Inflammatory Lesions.
- 4) Categorical Improvement in the Physician's Global Assessment.

However, the focus of this review is on the:

- **Change** in lesion count for, Inflammatory, Non-Inflammatory and Total Lesions from baseline
- **Percent change** in lesion count for, Inflammatory and Non-Inflammatory and Total Lesions from baseline
- **Investigator's Global Assessment**

In order to gain approval, the sponsor should show statistical significance for all primary endpoints, at a significance level of 0.05. Therefore, no adjustments to the p-value is necessary.

A total of 747 subjects were randomized for this clinical trial, of which 675 subjects ultimately participated in the study. Out of the 675 subjects, 222 were randomized to the Avita Gel, .025% treatment group, 225 to Retin-A Gel, .025%, and 228 to Avita Gel Vehicle, 0%.

A one-way analysis of variance statistical methodology was used to look at the difference in the primary endpoint variables, change and percent change in the number of acnes (inflammatory and noninflammatory) from baseline among the three treatment groups. The contrast method was used for pair wise comparison of the treatments.

In addition, a two-way analysis of variance test was performed with treatment, center and treatment by center interaction.

The investigator's global assessment was evaluated using a Cochran-Mantel-Haenszel test on the 84th day observation.

Randomization:

According to the protocol, due to investigator error at site #Z02, study medication was dispensed out of sequence during the first two weeks of patient enrollment. As result, the first 40 patients enrolled at this site were dispensed medication that was not in keeping with the randomization code. At the remaining sites, there were several instances where individual study medication was dispensed out of sequence.

These errors are considered protocol violations, and there is a possibility of bias in the analysis. For this reason, all the analyses of the "Change in Lesion Count" are reported with and without the center effect. Particularly, the results of the "Investigator's Global Assessment" should be interpreted with caution.

Evaluable Subjects:

Of 675 subjects, a total of 605 completed the study and had the end of treatment data available. Of these 198 (33%) were in the Avita Gel, .025% group, 203 (34%) in the Retin-A Gel, .025%, and 204 (34%) in the Avita Gel Vehicle treatment arm. Table I summarizes

the number of the patients who dropped out of the study, by treatment group.

Table I
Drop-Out Rates Among the Treatment Groups

Treatment N	Avita Gel, .025% 222	Retin-A Gel, .025% 225	Avita Gel Vehicle 228
n (%)	24 (24/222=11%)	22 (22/225=10%)	24 (24/228=11%)

These subjects were eliminated from the FDA_Eval end of treatment analysis of efficacy.

Baseline Comparability:

The distribution of demographic and baseline characteristics were not different among the three treatment groups. A total of 13 sites from the United States and Canada participated in this study.

The demographic and baseline information are summarized in the tables II and III.

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Table II
Demographics of All Randomized Subjects

	Whole Population (N=675)	Avita Gel (n=222, 33%)	Retin-A Gel (n=225, 33%)	Vehicle (n=228, 34%)	P- Value
Age (Mean):	20	21	20	20	0.30
Race (n):					0.75
Caucasian	553 (82%)	182 (82%)	180 (80%)	191 (84%)	
Black	42 (6%)	13 (6%)	19 (8%)	10 (4%)	
Oriental	29 (4%)	10 (5%)	10 (4%)	9 (4%)	
Hispanic	36 (5%)	12 (5%)	9 (4%)	15 (7%)	
Other	15 (2%)	5 (2%)	7 (3%)	3 (1%)	
Gender (n):					0.22
Male	321 (48%)	97 (44%)	111 (49%)	113 (50%)	
Female	354 (52%)	125 (56%)	114 (51%)	115 (50%)	
Investigator (n):					0.92
Berger	72 (10%)	24 (10%)	24 (10%)	24 (10%)	
Carey	51 (7%)	16 (6%)	17 (7%)	18 (7%)	
Crosby	51 (7%)	17 (7%)	17 (7%)	17 (7%)	
Danby	51 (7%)	18 (7%)	16 (6%)	17 (7%)	
Drake	51 (7%)	17 (7%)	17 (7%)	17 (7%)	
Kantor	51 (7%)	16 (6%)	17 (7%)	18 (7%)	
Kempers	72 (10%)	24 (10%)	24 (10%)	24 (10%)	
Leyden	51 (7%)	17 (7%)	16 (6%)	18 (7%)	
Lookingbill	51 (7%)	17 (7%)	17 (7%)	17 (7%)	
Maddin	51 (7%)	17 (7%)	17 (7%)	17 (7%)	
Savin	72 (10%)	24 (10%)	24 (10%)	24 (10%)	
Stewart	72 (10%)	24 (10%)	24 (10%)	24 (10%)	
Swinyer	51 (7%)	17 (7%)	17 (7%)	17 (7%)	

**Table III
Baseline Characteristics of All Randomized Subjects**

	Whole Population (N=675)	Avita Gel (n=222, 33%)	Retin-A Gel (n=225, 33%)	Vehicle (n=228, 34%)	P-Value
Total Inflammatory Lesions (Mean)	19	18	19	19	0.2
Total Non-Inflammatory Lesions (Mean)	52	51	53	53	0.3
Total Inflammatory & Non-Inflammatory Lesions (Mean)	71	69	72	72	0.2

The drop-outs did not change the integrity of the randomization. There was no statistical difference among the treatments in terms of the demographic or baseline characteristic variables after eliminating the drop outs, for the efficacy analysis of FDA_Evaluable subjects ($p > .1$).

Efficacy Analysis:

For our review purposes the primary endpoint variables are as follows:

1) Change in Lesion Count (Inflammatory, Non-inflammatory, and all Lesions combined) from baseline. A one-way analysis of variance test was used to compare the change in lesion count from baseline among the three treatment groups. For pairwise comparison of treatments, the contrast method was applied.

In addition, a two-way analysis of variance test was performed with treatment, center and treatment by center interaction.

2) Percent Change in Lesion Count (Inflammatory, Non-inflammatory, and all Lesions combined) from baseline. A one-way analysis of variance statistical methodology was used to compare the percent change in the lesion count from baseline among the three treatment groups. The contrast method was used for pair wise comparison of the treatments.

In addition, a two-way analysis of variance test was performed with treatment, center and treatment by center interaction.

The analyses for these two primary endpoint variables were performed on FDA_Eval as well as Intent-to-Treat population.

3) Investigator's Global Assessment. Originally, in the protocol, the investigator's assessment was based on a scaling scheme from 0 to 5, 0 being 'Condition Unchanged or Worsened' and 5 as 'Condition Completely Cured'. However, in the analysis, a different scheme was used. The new scoring method was from 1 to 6, 1 being 'Completely Cured' and 6 being 'Worse'. In this review, the second scoring scheme (1 to 6) and a Cochran-Mantel-Haenszel test was used to compare the three treatments at the 84th day.

Separate Mantel-Haenszel tests were performed in order to compare the treatments two at a time.

1. Change in Lesions Count from Baseline

The table IV demonstrates the comparisons of the means for inflammatory lesion counts at baseline, days 7, 14, 28, 56, 84 and the mean changes for each treatment group, using the FDA_Evaluable population.

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Table IV
Comparison of Mean Change in Inflammatory Lesion Count by Treatment Group
(FDA Eval)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	18	19	19	0.2	0.5	0.08
Day7 (n=654)	16	16	18			
Day14 (n=644)	16	16	17			
Day28 (n=624)	14	14	17			
Day56 (n=612)	12	12	16			
Day84 (n=605)	12	11	15	0.0002	0.3	0.003
Day7-Day1	-2	-3	-1			
Day14-Day7	-0.6	-0.2	-0.8			
Day28-Day14	-1.7	-1.6	-0.7			
Day56-Day28	-2	-2.5	-0.6			
Day84-Day56	0.03	-0.9	-0.9			
Day84-Day1	-6	-8	-5	0.001	0.07*	0.06

As it is shown in table IV, the greatest decrease in the inflammatory lesions occurred at day 7. Within the first six days, on average, there was a reduction of 2 lesions. The change in lesion count monotonically decreased. In the last 28 days of the study, a very small change was observed.

The decrease in inflammatory lesions were border line significant, when Avita Gel was compared to the vehicle (p=.06).

* Retin-A showed a border-line statistical significant superiority to Avita in inflammatory lesions count (p=0.07).

Table V demonstrates the comparison of the means for non-inflammatory lesion counts at baseline, days 7, 14, 28, 56, 84 and the mean changes for each treatment group, using the FDA-Evaluable subjects.

Table V
Comparison of Mean Change in Non-Inflammatory Lesion Count by Treatment Group
(FDA Eval)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	51	53	53	0.3	0.1	0.3
Day7 (n=654)	45	47	50			
Day14 (n=644)	43	43	47			
Day28 (n=624)	39	39	44			
Day56 (n=612)	35	32	42			
Day84 (n=605)	32	28	39	0.0001	0.1	0.007
Day7-Day1	-5	-6	-3			
Day14-Day7	-2	-4	-2			
Day28-Day14	-4	-4	-3			
Day56-Day28	-4	-6	-2			
Day84-Day56	-3	-4	-4			
Day84-Day1	-18	-24	-14	0.0001	0.004*	0.08

As it is shown in table V, the greatest decrease in the non-inflammatory lesions occurred at day 7. Within the first six days, on average, there was a reduction of 5 lesions. The change in lesion count monotonically decreased. In the last 28 days of the study, a very small change was observed.

* Retin-A showed a statistically significant superiority to Avita in noninflammatory lesions ($p < 0.004$).

The decrease in non-inflammatory lesions was not statistically significant, when Avita Gel was compared to the vehicle (p=.08).

Table VI demonstrates the comparison of the means for inflammatory and noninflammatory lesion counts combined, at baseline, days 7, 14, 28, 56, 84 and the mean changes for each treatment group, using the FDA-Evaluable population.

Table VI
Comparison of Mean Change in Inflammatory and Non-Inflammatory Lesion Count by Treatment Group (FDA_Eval)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	69	72	72	0.2	0.1	0.1
Day7 (n=654)	62	63	68			
Day14 (n=644)	59	59	65			
Day28 (n=624)	53	54	61			
Day56 (n=612)	47	44	58			
Day84 (n=605)	44	39	53	0.0001	0.1	0.001
Day7-Day1	-7	-9	-4			
Day14-Day7	-3	-4	-3			
Day28-Day14	-6	-5	-4			
Day56-Day28	-6	-9	-3			
Day84-Day56	-3	-5	-5			
Day84-Day1	-24	-32	-19	0.0001	0.002*	0.03

* Retin-A showed a statistically significant superiority to Avita in total lesion count (p<0.002).

From tables IV, V, and VI it can be observed that Avita Gel produced statistically significant greater reduction in total lesion (inflammatory and noninflammatory lesions combined) than did vehicle. Yet, these results were only border line significant when inflammatory and noninflammatory lesions were analyzed separately ($p=0.06$ and $p=.08$ respectively).

Change from baseline at 84th day in inflammatory, noninflammatory and total lesion count were also analyzed using a two-way analysis of variance with treatment by investigator interaction, for the FDA_Eval population. The results of the inflammatory and non-inflammatory lesion count were not statistically significant ($p>0.1$), and for total lesion count border-line significance was observed ($p=0.09$).

Table VII demonstrates the comparison of the means for inflammatory lesion counts at baseline and day 84 and the mean change from baseline for each treatment group, for intent-to-treat population.

Table VII
Comparison of Mean Change in Inflammatory Lesion Count by Treatment Group
(Intent-to-Treat)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	18	19	19	0.2	0.5	0.8
Day84 (n=675)	13	11	15	0.0002	0.2	0.006
Day84-Day1	-6	-7	-4	0.0008	0.07*	0.06

Table VIII shows the comparison of the means for non-inflammatory lesion counts at baseline and day 84 and the mean change from baseline to day 84 for each treatment group, for intent-to-treat population.

Table VIII
Comparison of Mean Change in Non-Inflammatory Lesion Count by Treatment Group
(Intent-to-Treat)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	51	53	53	0.3	0.1	0.3
Day84 (n=675)	34	31	39	0.001	0.2	0.02
Day84-Day1	-17	-22	-14	0.0001	0.006*	0.08

Table IX shows the comparison of the means for inflammatory and non-inflammatory lesion counts (Total Lesion Count) at baseline and day 84 and the mean change from baseline at day 84 for each treatment group, for intent-to-treat population.

Table IX
Comparison of Mean Change in Inflammatory and Non-Inflammatory Lesion Count by Treatment Group (Intent-to-Treat)

	Avita Gel	Retin-A Gel	Vehicle	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Day1 (n=675)	69	72	72	0.2	0.1	0.1
Day84 (n=675)	46	42	54	0.0001	0.2	0.004
Day84-Day1	-23	-30	-18	0.0001	0.003*	0.03

From tables VII, VIII and IX it can be observed that the results of the Intent-to-Treat analyses are very similar to that of evaluable subject analyses. The Avita Gel had a statistically significant greater reduction in total lesion (inflammatory and noninflammatory lesions combined) than did the vehicle ($p=0.03$). Yet, these results were only border line significant when inflammatory and noninflammatory lesions were analyzed separately ($p>0.06$ and $p>0.08$ respectively).

* Retin-A showed a statistically significant superiority to Avita in noninflammatory ($p<0.006$) and total lesion count ($p<0.003$) and border line significance in inflammatory lesions count ($p=0.07$).

Change from baseline at 84th day in total inflammatory, noninflammatory and total lesions were also analyzed using a two-way analysis of variance with treatment by investigator interaction, for the Intent-to-Treat population. These results were not statistically significant ($p > 0.1$).

2. Percent Change in Lesions Count from Baseline

In order to further reduce the variation within each treatment group, the percent change at day 84 from baseline was calculated and used to detect a difference among treatments.

Table X demonstrates the comparison of the mean percent change from baseline for inflammatory, non-inflammatory and total lesion counts for each treatment group, based on FDA_Eval population.

Table X
Comparison of Mean Percent Change in Inflammatory, Non-Inflammatory and Total Lesion Count by Treatment Group (FDA_Eval)

	Avita Gel (n=198)	Retin-A Gel (n=203)	Vehicle (N=204)	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Inflammatory	-35%	-42%	-25%	0.0008	0.1	0.02
Non-Inflammatory	-36%	-45%	-27%	0.0001	0.02*	0.02
Total Lesions	-36%	-45%	-27%	0.0001	0.006*	0.006

These results showed that there was a statistically significant superiority in percent reduction in regards to inflammatory, non-inflammatory and combined total lesions, when Avita Gel was compared to its Vehicle ($p < .02$).

Percent change from baseline at 84th day in total inflammatory, noninflammatory and total lesions were also analyzed using a two-way analysis of variance with treatment by investigator interaction, for the FDA_Eval population. The results were not statistically significant ($p > .1$).

Table XI shows the comparison of the mean percent change from baseline for inflammatory, non-inflammatory and total lesion counts for each treatment group, based on Intent-to-Treat population.

* Patients who were treated with Retin-A Gel had a significantly higher lesion reduction than the subjects who used Avita Gel, in regards to non-inflammatory and total lesions ($p < .02$).

Table XI
Comparison of Mean Percent Change in Inflammatory, Non-Inflammatory and Total Lesion Count by Treatment Group (Intent-to-Treat)

	Avita Gel (n=222)	Retin-A Gel (n=225)	Vehicle (N=228)	P-Value		
				Avita vs. Retin-A vs. PBO	Avita vs. Retin-A	Avita vs. PBO
Inflammatory	-32%	-39%	-22%	0.0005	0.12	0.02
Non- Inflammatory	-35%	-42%	-26%	0.0001	0.03	0.02
Total Lesions	-34%	-42%	-26%	0.0001	0.01	0.01

The results of the intent-to-treat analysis were not different from the results presented for the evaluable subjects. Statistically significant results were observed for all lesion categories when Avita Gel was compared to the vehicle ($p < 0.02$).

Percent change from baseline at 84th day in total inflammatory, noninflammatory and total lesions were also analyzed using a two-way analysis of variance with treatment by investigator interaction, for the Intent-to-Treat population. The results were not statistically significant ($p > 0.3$).

3. Physician's Global Assessment

The investigator's global assessment was evaluated based on 1 to 6 scoring schedule, with 1 being 'Completely Cured' and 6 being 'Worse' on subjects who had the end of treatment data available (n=605).

A statistically significant difference was observed in the investigator's global assessment among the three treatments ($p < 0.02$). Investigators rated change in lesion count for patients in the Avita Gel group more favorably than the vehicle group at the end of the treatment period ($p < 0.02$).

In order to detect an investigator bias in this analysis, another test was run controlling for the investigator effect. The physician's global assessment yielded a statistically significant results after controlling for the center effect ($p < 0.02$).

SAFETY

All of the subjects who had data available were included in the safety analysis. Six adverse events were looked at: Dryness, Erythema, Peeling, Burning, Itching and Tightness.

These adverse events were compared among the three treatments, after the baseline visit, using a Cochran Mantel Haenzel test. Highly statistically differences were observed ($p < .002$).

All six adverse events were compared between Avita Gel and Retin-A Gel. Table XII demonstrates these results of these comparisons.

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Table XII
Adverse Events Between Avita Gel and Retin-A
Visit One Excluded

	Avita Gel (n=218)	Retin-A Gel (n=219)	P-Value
Dryness			0.1
None	49 (22%)	43 (20%)	
Mild	110 (50%)	99 (45%)	
Moderate	58 (27%)	74 (34%)	
Severe	1 (.5%)	3 (1%)	
Erythema			0.1
None	70 (32%)	64 (29%)	
Mild	102 (47%)	93 (42%)	
Moderate	46 (21%)	58 (26%)	
Severe	0 (0%)	4 (2%)	
Peeling			0.001
None	99 (45%)	67 (31%)	
Mild	69 (32%)	76 (35%)	
Moderate	50 (23%)	70 (32%)	
Severe	0 (0%)	6 (3%)	
Burning			0.005
None	93 (43%)	74 (34%)	
Mild	76 (35%)	66 (30%)	
Moderate	40 (18%)	65 (30%)	
Severe	9 (4%)	14 (6%)	
Itching			0.1
None	147 (67%)	129 (59%)	
Mild	52 (24%)	65 (30%)	
Moderate	17 (8%)	23 (11%)	
Severe	2 (1%)	2 (1%)	
Tightness			0.4
None	106 (49%)	94 (43%)	
Mild	70 (32%)	81 (37%)	
Moderate	37 (17%)	38 (17%)	
Severe	5 (2%)	6 (3%)	

Patients who were treated with Avita Gel 0.025% had statistically significantly less peeling and burning than subjects who used Retin-A. In regards to dryness, erythema, Itching and tightness, even though the results were not statistically significant, yet a higher percent of Avita Gel group had none or mild events.

III. RESULTS

The results of this study indicated the superiority of Avita Gel to its Vehicle in both FDA_Evaluable and Intend-to-Treat populations in regards to reduction in the non-inflammatory and combined inflammatory and noninflammatory lesion count, at the end of the 84th day ($p < .05$). Inflammatory lesion count, however, showed only a borderline significance in both of the populations ($p = .07$).

Results of the percent decrease in the number of lesions between Avita Gel and Vehicle were significant in both evaluable and ITT populations ($p < 0.02$).

The investigators noticed a significantly higher change in lesion reduction at day 84 from baseline with Avita Gel than the Vehicle ($p < .05$).

There were fewer adverse events in Avita Gel 0.025% group vs. Retin-A Gel 0.025% treatment group.

IV. CONCLUSIONS (which may be conveyed to the sponsor):

Study PDC 004-022 provides an evidence for the applicant's claim that Avita Gel demonstrates a statistically higher reduction in the mean percent lesion count in 84 days than its vehicle. However, it is not clear whether or not this reduction effect will remain after the 84 day period.

The findings of the investigator's global assessment concurred with the above results. Investigators believed that Avita Gel causes more lesion reduction than the Vehicle.

This study showed a statistical superiority of Retin-A Gel .025% to Avita Gel .025% in regards to lesion reduction. However, less adverse events were observed in the Avita Gel group.

Thus, this study demonstrates that Avita Gel is statistically superior to its Vehicle and has a better safety profile than Retin-A.

ISI

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics IV

9/24/96

Sept 24, 1996

/S/

concur: R. Srinivasan, Ph.D.
Acting Group Leader, Biometrics IV

cc:

Archival NDA 20-400
HFD-540
HFD-540/Dr. Labib
HFD-540/Dr. Blay
HFD-725/Ms. Farr
HFD-725/Dr. Srinivasan
HFD-725/Dr. Harkins
HFD-540/Dr. Katz
HFD-540/Dr. Wilkin
Chron.

This review contains 18 pages.

Farr\X7-2037\wpfiles\srini\nda20400.avi Dated 9/11/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-400

MICROBIOLOGY REVIEW(S)

00-1

CONSULTATIVE REVIEW FOR TOPICAL DRUG PRODUCTS
(HFD-540)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiological Review of Manufacturing and Controls

Requestor: Kennerly Chapman

Reason for Request: Microbiology Review of Manufacturing and Controls

NDA #: 20-400 MICRO.REVIEW #: 1 REVIEW DATE: 5-AUG-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT/AC	28-MAR-94	29-MAR-94	5-JUL-94

NAME & ADDRESS OF APPLICANT: PENEDERM INCORPORATED
320 Lakeside Drive, Suite A
Foster City, CA 94404

DRUG PRODUCT NAME

Proprietary: ACTICIN Gel
Nonproprietary/USAN: Tretinoin
Code Names/ #'s: CAS-302-79-4
Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION: Keratolytic agent in an ethanolic gel for the topical treatment of acne vulgaris.

DOŠAGE FORM: GEL
STRENGTHS: 0.025%
ROUTE OF ADMINISTRATION: TOPICAL
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

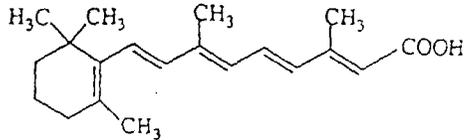
Chemical Name:

Tretinoin, also known as retinoic acid, all-trans-retinoic acid, and vitamin A acid, in a gel vehicle of butylated hydroxytoluene, hydroxypropyl cellulose, polyolprepolymer-2 and denatured 95% ethanol.

NDA 20-400
PENEDERM
ACTICIN GEL

2

Structural Formula:



Molecular Formula: C₂₀H₂₈O₂

Molecular Weight: 300.44

SUPPORTING DOCUMENTS:

Initial submission: 20-400

Received by CDER: September 24, 1993

Not acceptable for filing: November 23, 1993

Abbreviated New Drug Application: 74-071

Not acceptable for filing: February 11, 1993

Application withdrawn: April 2, 1993

Investigational New Drug Application: 34,462

Drug Master File: DMF , for Penederm, Inc.;
reference authorized by letter dated June 11,
1993,

DMF for Penederm, Inc.; reference
authorized by letter dated June 4, 1993,

DMF for Penederm, Inc.;
reference authorized by letter dated June 7, 1993,

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

Tretinoin, also known as vitamin A acid, is a derivative of retinol (vitamin A) and is an endogenous substance in humans. Tretinoin and retinol are necessary for the growth and differentiation of epithelial tissue and skin. Topical tretinoin acts through a reduction in

keratinization, an increase in basal cell proliferation, and an increase in the desquamation of the epidermis.

An application, submitted by another sponsor, for the drug substance tretinoin in a different vehicle was approved and is marketed as Retin-A. Penederm Incorporated submitted an abbreviated application for tretinoin in a different gel vehicle containing polyolprepolymer-2, hydroxypropyl cellulose, butylated hydroxytoluene and % ethanol, which was determined to be unfileable because of the inclusion of the unapproved inactive ingredient polyolprepolymer-2. The subsequent NDA submission was found to be incomplete and not acceptable for filing. This amended submission is for tretinoin for use as a topical agent in the treatment of acne vulgaris with no microbiological indications.

In the Manufacturing and Controls section, the Certificate of Analysis (volume 1.2.2, page 2-0235) states that the microbial limits specification is <1000 cfu/g. This value is not consistent with the Quality Standard Finished Product Release stability specifications (volume 1.2.2, page 2-0151). The Certificate of Analysis should be changed to total aerobic counts of ≤ 100 cfu per gram and total yeast and mold counts of ≤ 10 cfu per gram. The following table summarizes the results of the microbial limits test on tubes stored at the recommended temperature of below 30°C. The sponsor states that these lots passed the microbial limits specification, but did not submit the actual data. The actual data and protocol for the microbial limits test should be submitted.

MICROBIAL LIMITS TEST			
Lot number	Tube size (g)	Temperature	Time (months)
73026	2	30°C	3, 6, 9, 12, 18, 24
73026	20	30°C	3, 6, 9, 12, 18, 24
73026	45	30°C	3, 6, 9, 12, 18, 24
73798	20	30°C	3, 6
		27°C	9, 12, 18
73798	30	30°C	3, 6, 9
		27°C	12, 18
73798	45	30°C	3, 6

		27°C	9,12,18
75735	20	4°C, 27°C	12
57-2290-020	2	ambient	3,6
57-2290-020	45	ambient	3,6,12,24
58-2750-075	20	ambient	3,12,24
69-3200-069	2	ambient	3,6,12,24
69-3200-069	20	ambient	3,6,12,24
69-3200-069	45	ambient	3,6,12,24
52-2390-017	30	ambient	3
Placebo 52-2390-015	30	ambient	3
Vehicle 75620	20	4°C, 30°C/27°C	5

The preservative effectiveness test was used to test the effectiveness of the 95% ethanol. The protocol submitted was similar to that recommended by USP and the following table indicates the lots tested. The bacterial counts were equal to the initial concentration at 7 days and $\leq 0.1\%$ of the initial concentration at 14, 21 and 28 days and the yeast and mold counts were less than or equal to the initial concentration at 7, 14, 21 and 28 days, which are within acceptable range.

PRESERVATIVE EFFECTIVENESS TEST		
Lot number	Tube size (grams)	Time (months) Initial point (I)
73026	45	I, 3, 9, 12, 18, 24
73798	30	I, 3, 6, 12, 24
73798	45	I, 3, 6
69-3200-069	45	I, 12, 24, 36
57-2290-020	45	24, 36
58-2750-075	20	24, 36

The microbiology portion of the chemistry, manufacturing and controls review is approvable with four deficiencies which need to be corrected by the sponsor.

CONCLUSIONS & RECOMMENDATIONS:

From a microbiological perspective, this application is approvable with the following four deficiencies to be corrected by the sponsor. 1) The microbial limits specification on the Certificate of Analysis should be consistent with the Quality Standard Finished Product Release stability specification which is total aerobic counts of cfu per gram and total yeast and mold counts of cfu per gram. 2) The microbial limits protocol should be submitted. 3) Actual microbial limits test results on the following three lots should be submitted: Lot # 73026, 2 gram tube; Lot # 73798, 45 gram tube; Lot # 75735, 20 gram tube. 4) Since there will be a change in the manufacturing facility, stability data including microbial limits and preservative effectiveness testing on the first three lots will need to be submitted (Please refer to the chemistry review).

/S/

LINDA J. UTRUP, PH.D.
Review Microbiologist

cc: - Orig. NDA 20-400
HFD-540/Division File
HFD-520/Micro/LUtrup/8-5-94
HFD-540/MO/NSlifman
HFD-540/Pharm/HSheevers
HFD-540/Chem/M-Rejali
HFD-540/CSO/KChapman
HFD-520/SMicro/ATSheldon
R/D Init by: SUPERVISOR 9/19/94 10/13/94ATS *B 10/13/94*
filename:20-400.FIN

cc 10/21/94

MAY 13 1996
Blair
540

Microbiologist's Review to HFD-540
Office of New Drug Chemistry
Microbiology Staff

May 13, 1996

- A. 1. **Application Number:** NDA 20-400
- Applicant:** Penederm Incorporated
Foster City, CA 94404
2. **Product Name:** Tretinoin Gel, 0.025%
3. **Dosage Form:** Non-sterile topical
4. **Method of Sterilization:** N/A
5. **Pharmacological Category and/or Principle Indication:**
Topical application in the treatment of acne vulgaris
6. **Drug Priority Classification:** 5 S
- B. 1. **Initial Submission:** Unknown
2. **Amendments:** AZ: December 22, 1995 (Subject of this Review)
3. **Supporting Documents:** N/A
- C. **Remarks:**

The subject NDA has apparently been previously reviewed by microbiologists in HFD-520. The current amendment (12/22/95) is submitted in response to the Agency NA letter of March 29, 1995. This review covers only the response to the outstanding micro question(s), and does not infer knowledge of previous microbiology reviews since only the 12/22/95 amendment was sent for consult.

Questions 2(g) and 2(h) of the March 29, 1995 NA letter concern microbiology issues. The questions are repeated below in small type followed by comments on the applicant's response.

FDA Comment:

- 2.g. An explanation of why the microbial limits specification on the Certificate of Analysis is not consistent with the Quality Standard for the finished product stability specification (total aerobic count of cfu per gram and a total yeast and mold count of cfu per gram).

Applicant's Response:

The applicant states that the finished product quality standard of cfu for TAC and cfu for yeasts and molds was adopted after the date of the Certificate of Analysis. The Quality Standard is stated to have been revised on July 9, 1993 to tighten the specification. This was after the issuance of the Certificate of Analysis which was issued on June 30, 1993. The revised Quality Standard appears adequate.

SATISFACTORY

FDA Comment:

2.h. The microbial limits protocol and the actual microbial limits test results on the following lots:

1. Lot 73798, 45 gram tube
2. Lot 75735, 20 gram tube
3. Lot 73026, 2 gram tube

Applicant's Response:

The applicant states that the tests were carried out according to the USP Microbial Limits Tests. Results from each of the three lots in stability trials are presented. The tests were apparently carried out at multiple time points during the shelf life. Results, however, are expressed as
is defined as

Unfortunately, there are no USP criteria for this product specified in the monograph (USP 23, p. 1573). The production dates for these three stability batches was 11/18/91 (Lot 73798), 8/10/92 (Lot 75735), and 5/13/91 (Lot 73026). The Quality Standard for finished drug was stated to have been revised on July 9, 1993 (see comments above). All of these lots preceded that date. Therefore, which set of standards refers to are unknown.

The applicant has responded to a telephone inquiry about this matter in a submission dated May 9, 1996 (FAX received same day). The actual numerical results of the Microbial Limits tests for the three requested lots are provided. In all cases for all three lots, the Total Aerobic Count and the Total Yeast and Mold Count were CFU/g. The tests for the USP indicator organisms (*S. aureus*, *Salmonella*, *Ps. aeruginosa*, *E. coli*) were reported as "negative". The results, therefore; for these lots indicate that the samples were well below the most recent specification of CFU/g for TAC, and within the most recent specification for yeasts and molds of CFU/g. The response to this question is therefore satisfactory.

SATISFACTORY

D. **Conclusions:** Recommend approval based on microbial quality of the subject drug product.

5/13/96 **/S/**
Peter H. Cooney, PhD
Chief, Microbiology Staff
ONDC

cc: NDA 20-400
HFD-540/Blay
HFD-160/Consult File
HFD-805/Cooney