

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-400

MEDICAL REVIEW(S)

Date of Review : December 17, 1996

Final Review : December 30, 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-400 AMENDMENT

Sponsor: Penederm Inc.
320 Lakeside Drive, Suite A
Foster City, CA 94404

Drug: Avita (Acticin, tretinoin 0.025% gel)

Indication: Acne Vulgaris

Date of Submission: July 12, 1996

Background: Penederm Inc., the sponsor of NDA 20-400, is submitting this new clinical trial of 0.025% tretinoin gel for the treatment of acne vulgaris, in response to the nonapprovable letter of June 26, 1996. The original NDA contained two clinical studies, study #003 and study #015. Study #015 failed to replicate the results of study #003 regarding superiority of tretinoin gel over placebo. The new study (# PDC 004-022) is submitted, as requested by FDA in the nonapprovable letter, to support study #003 in proving the superiority of tretinoin gel over placebo.

REVIEW OF STUDY # PDC 004-022

Introduction:

Study #022 is a randomized, double-blind, vehicle-controlled, parallel-group, multicenter study, consisting of three treatment arms: Avita Gel, Retin-A Gel, and Vehicle. The study is designed to evaluate the efficacy and safety of the two topical tretinoin gels (Avita and Retin-A) in patients with grade II or III acne vulgaris in a 12-week course. It is submitted as a second pivotal study for NDA 20-400.

A total of 747 patients were randomized for this clinical trial. Of these, 675 patients received medication. The sponsor's analysis considered the following three populations.

(1) The safety population: All patients who received study medication and who returned for at least one post-baseline visit. There were 660 in the three arms.

(2) The intent-to-treat (ITT) population: This population consisted of the patients in the safety population that met the study entrance criteria and had no significant protocol violations. Missing visits were replaced by the last visit for which the patient was present (LOCF). No visit windows were applied for the ITT population, but Baseline visits were not carried forward if the patient was not present for the Day 7 visit. The ITT population included **620** patients.

(3) The per protocol (PP) population: All patients included in the ITT population who made their study visits within ± 3 days of the assigned date were also included in the Per Protocol population for those visits, with two exceptions. Patients who used the study medication for more than the number of days allowable by the protocol were not considered in the Per Protocol population. Additionally, patients who were judged non-compliant by the Investigator and terminated early from the study, as well as patients defined as non-compliant by missing 10 or more applications were not included in the Per Protocol analyses. The PP population included **610** patients.

Two additional populations were analyzed by the FDA statistical reviewer. These were:

(1) The FDA-evaluable (FDA-E) population: This population consisted of all randomized patients whose end of treatment lesion count was available. There were **605** patients in this set.

(2) The intent-to-treat (ITT-S) population: In order to maintain the integrity of randomization, the statistical reviewer analyzed this set which consisted of all randomized patients. For the patients who did not have an end of treatment (84th day) visit, the last available evaluation was carried forward to replace the lesion count of the missing 84th day visit. There were **675** patients in this set.

In the present review, unless stated otherwise, all safety data are based on the **safety population**, and all efficacy data are based on the **PP population**. The agreement or disagreement between analyses of the different populations will be discussed in the reviewer's comments as needed.

General study design:

This randomized, double-blind, parallel group, vehicle-controlled, 12-week, multi center trial was conducted in the United States and Canada by Penederm Incorporated, Foster City, CA. Six hundred seventy-five (675) patients were randomized to Avita Gel 0.025%, Retin-A Gel 0.025%, or Vehicle in order to obtain approximately 525 evaluable patients.

Male or female patients, 12 - 40 years of age, who had the following facial lesions, excluding lesions on the nose, were enrolled into the study:

- (1) a minimum of 10, but no more than 30 papules and/or pustules combined
- (2) a minimum of 30, but no more than 95 comedones
- (3) no more than four nodulocystic lesions

The Baseline visit (Visit 1) occurred on the same day that study medication dosing started (Day 1). Patients were scheduled to return at Days 7, 14, 28, 56, and 84 (Visits 2-6). At the Baseline visit, all patients were instructed as to how and when to apply their study medication. Each patient was instructed on the importance of complying with the study medication schedule.

Investigator's clinical assessments and lesion count of facial acne occurred at each visit. The lesion count was divided into the following categories: comedones, papules and/or pustules, and nodulocystic lesions. The clinical assessments consisted of the Investigator's evaluation of the following signs and symptoms: peeling, erythema, and dryness. At all visits subsequent to Baseline (Days 7, 14, 28, 56, and 84), the Investigator additionally made a Global Assessment for overall improvement in the patients acne as compared to Baseline.

At these same visits, patients assessed the following signs and symptoms: burning/stinging, itching, and tightness. The patients also rated their disease condition as compared to Baseline.

The Schedule of Visits and Study Procedures are summarized in the following table:

Schedule of Visits and Study Procedures

| VISIT NUMBER VISIT DAY DAYS FROM BASELINE | 1* Baseline 0 | 2 7 (\pm 3) 4-10 | 3 14 (\pm 3) 11-17 | 4 28 (\pm 3) 25-31 | 5 56 (\pm 3) 53-59 | 6** 84 (\pm 3) 81-87 |
|---|---------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------------------|
| Review Inclusion/Exclusion Criteria | X | | | | | |
| Obtain Written Informed Consent | X | | | | | |
| Obtain Medical History/Acne History | X | | | | | |
| Conduct Physical Examination | X | | | | | |
| Conduct Urine Pregnancy Test | X | | X | X | X | X |
| Assess Adverse Events | | X | X | X | X | X |
| Assess Concomitant Medications | X | X | X | X | X | X |
| Count Lesions | X | X | X | X | X | X |
| Conduct Physician's Global Assessment | | X | X | X | X | X |
| Conduct Patient's Global Assessment | | X | X | X | X | X |
| Medication accountability | X | X | X | X | X | X |
| Schedule Return Appointment | X | X | X | X | X | |

* Disperse study medication at Baseline and then at each visit as needed thereafter. Patients must bring study medication tube(s) to each visit. Empty tubes are to be kept by the Medication Dispensing Staff Member. All study medication must be collected by Day 84 or Discontinuation Visit.

** Procedures to be performed at Day 84 or Discontinuation Visit, if different from Day 84.

Comments:

1- The centers/investigators in this study were 13. None of the investigators was common with study # 003. The 13 principal investigators were : R. Berger (NJ), W. Carey (PQ), D. Crosby (WI), W. G. Danby (Ont), L. Drake (MA), I. Cantor (NY), S. E. Kempers (MN), J. Leyden (PA), D. Lookingbill (PA), S. W. Maddin (BC), R. Savin (CT), D. Stewart (MI), and L. J. Swinyer (UT).

2- The general design of this study is similar to that of study # 003.

Patient populations:

Figure A shows a flowchart for the populations analyzed by the sponsor, their distribution in the three arms of the study, the excluded patients and the reasons for their exclusion. As previously mentioned in the introduction, these populations were the safety population (n=660), ITT population (n=620) and PP population (n=610).

Comments:

1- Figure A is taken from the NDA (p.1.0045). On checking the data in this figure, it was noticed that there were four minor numerical mistakes. The number of patients excluded from efficacy analysis in the Avita arm should be 14 (rather than 13 in Fig. A), and in the Retin-A arm should be 16 (rather than 17 in Fig. A). Also, those excluded for non-compliance with the protocol should be 10 in the Avita arm (rather than 9 as in Fig. A) and 15 in the Retin-A arm (rather than 16 in Fig. A).

2- The number of patients present in the ITT-S population and excluded from the FDA-E population was 70. Those were the patients who did not have day 84 evaluations. They were 24 in each of the Avita and Avita vehicle arms, and 22 in the Retin-A arm.

EFFICACY EVALUATION:

A- Demography and baseline characteristics:

The major demographic and baseline characteristics of the PP population are shown in Table A in the following pages. There were no statistically significant differences between the different arms of the study.

Comment: There were no statistically significant differences in the demographics or baseline characteristics for any of the other populations analysed. The demographics

Figure A.
 Population Flowchart

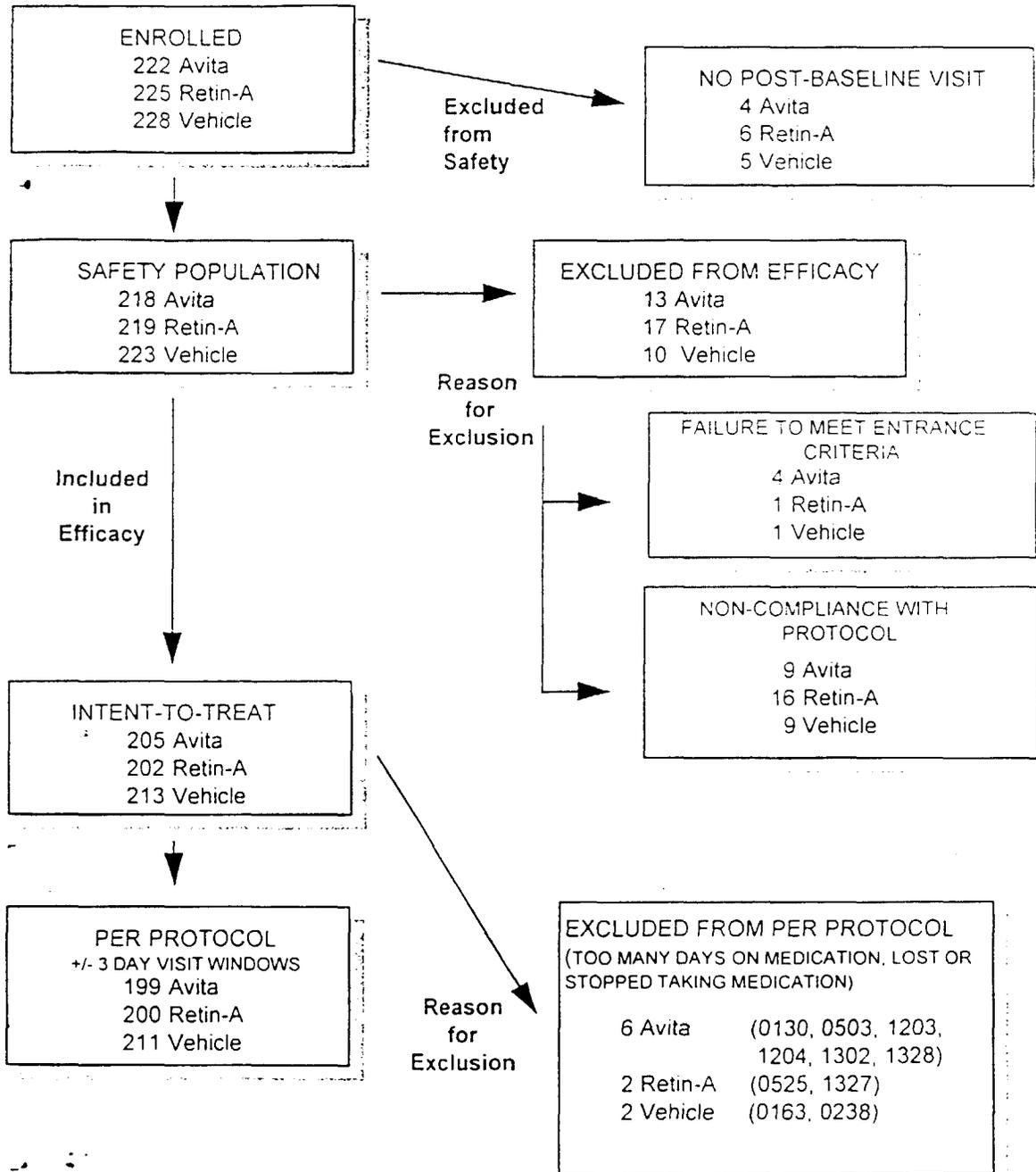


Table A
Patient Baseline Demographics Per Protocol Analysis

| | Avita Gel 0.025% | Retin-A Gel 0.025% | Vehicle |
|------------------------|---------------------|-----------------------|---------|
| Males | 88 | 100 | 107 |
| Females | 111 | 100 | 104 |
| Mean Age (years) | 21.2 | 20.4 | 20.0 |
| Age Range | | | |
| Race | | | |
| Caucasian | 159 | 158 | 176 |
| Hispanic | 12 | 8 | 13 |
| Black | 13 | 17 | 10 |
| Asian | 10 | 10 | 9 |
| Other | 5 | 7 | 3 |
| Fitzpatrick Skin Type | | | |
| Type I | 6 | 8 | 9 |
| Type II | 19 | 30 | 33 |
| Type III | 70 | 58 | 79 |
| Type IV | 73 | 64 | 54 |
| Type V | 19 | 23 | 21 |
| Type VI | 12 | 17 | 15 |
| Baseline Lesion Counts | | | |
| Noninflammatory (mean) | 50.4 | 52.8 | 52.3 |
| Inflammatory (mean) | 18.4 | 18.9 | 19.5 |

Table A
 Patient Baseline Demographics Per Protocol Analysis
 (Continued)

| | Avita Gel 0.025% | Retin-A Gel 0.025% | Vehicle |
|--|---------------------|-----------------------|---------|
| Baseline Sign/Symptom Score | | | |
| Erythema | | | |
| None | 153 | 157 | 159 |
| Mild | 43 | 40 | 48 |
| Moderate | 3 | 3 | 4 |
| Severe | 0 | 0 | 0 |
| Peeling | | | |
| None | 192 | 191 | 201 |
| Mild | 7 | 9 | 8 |
| Moderate | 0 | 0 | 2 |
| Severe | 0 | 0 | 0 |
| Dryness | | | |
| None | 184 | 180 | 195 |
| Mild | 13 | 20 | 14 |
| Moderate | 2 | 0 | 2 |
| Severe | 0 | 0 | 0 |
| Burning/Stinging | | | |
| None | 194 | 198 | 208 |
| Mild | 4 | 2 | 2 |
| Moderate | 1 | 0 | 1 |
| Severe | 0 | 0 | 0 |
| Itching | | | |
| None | 192 | 190 | 190 |
| Mild | 5 | 9 | 18 |
| Moderate | 2 | 1 | 3 |
| Severe | 0 | 0 | 0 |
| Tightness | | | |
| None | 189 | 183 | 195 |
| Mild | 10 | 16 | 13 |
| Moderate | 0 | 1 | 1 |
| Severe | 0 | 0 | 2 |
| Amount of Drug Used in grams (mean) | 29.2 | 25.0 | 28.7 |

and the baseline characteristics of the ITT-S population (all randomized patients given treatment) are shown in Tables B, C, respectively (from the FDA statistical review).

Table B
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 C
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 |

B- Primary efficacy endpoints:

The primary endpoint variables for this study were:

- 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 the FDA statistical review was 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***

C- Efficacy analysis:

1- Lesion counts throughout treatment:

The number of total lesions at each observation point is shown in Table D.

Table D
Number of total (inflammatory and noninflammatory) lesions

| Day | Avita | | Retin-A | | Vehicle | |
|-----|-------|--------------|---------|--------------|---------|--------------|
| | n | Mean (SEM) | n | Mean (SEM) | n | Mean (SEM) |
| 1 | 199 | 68.59 (1.22) | 200 | 71.72 (1.38) | 211 | 71.81 (1.35) |
| 7 | 190 | 61.23 (1.75) | 198 | 62.59 (1.70) | 203 | 67.99 (1.82) |
| 14 | 191 | 58.73 (2.07) | 187 | 58.88 (1.89) | 197 | 63.99 (1.77) |
| 28 | 168 | 52.89 (1.96) | 178 | 53.46 (2.13) | 184 | 60.89 (1.91) |
| 56 | 159 | 48.65 (2.20) | 173 | 45.73 (1.98) | 176 | 57.01 (2.16) |
| 84 | 174 | 43.93 (2.16) | 182 | 39.52 (1.95) | 189 | 52.84 (2.19) |

The changes in the mean total lesion counts during treatment is shown in Table E.

Table E
Changes in the means of total lesion counts every 2 or 4 weeks

| From-To (Days) | Avita | Retin-A | Vehicle |
|----------------|-------|---------|---------|
| 1 - 14 | 9.86 | 12.84 | 7.84 |
| 14 - 28 | 5.84 | 5.42 | 3.10 |
| 28 - 56 | 4.24 | 7.73 | 3.88 |
| 56 - 84 | 4.72 | 6.21 | 4.17 |

Comments:

1- The data in Tables D, E show that, numerically, the reduction in total lesions was greater in Avita and Retin-A arms than in the vehicle arm for all 4 time intervals, was greater in the first two weeks in all arms in comparison to the other 3 subsequent time intervals, and was greater in the Retin-A arm than the Avita arm in all time intervals except the second two weeks. The data in these two tables are taken from Table 3b.3 of the NDA (p.1.0133-1.0135), and they describe the PP population.

2- A similar analysis was carried out by the FDA statistical reviewer for the FDA-E population (Table VI in the statistical review). The results of the analysis of this population were in agreement with the results of the PP population mentioned above (in comment no.1) with only one exception: the reduction in the total lesions was greater in the Vehicle arm than in the Avita arm for the period from 56-84 days.

3- Comparison of the changes in the means of total lesion counts over the 84 days of treatment in the FDA-E population showed that both Avita (-24) and Retin-A (-32) were significantly better than placebo (-19), and that Retin-A was significantly better than Avita ($p=0.002$).

2-⁴ Total lesion counts and percent improvement at Day 84:

Tables F and G show the total lesion counts, noninflammatory lesion counts and inflammatory lesion counts, and percent improvements in each at day 84.

**Table F
Avita Gel vs. Vehicle Results**

| EFFICACY OUTCOME | Day 84 (ITT) | | | Day 84 (PP) | | |
|--|--------------|---------|--------------|-------------|---------|--------------|
| | Avita | Vehicle | p-value | Avita | Vehicle | p-value |
| Total Lesion Count (Two-way ANOVA) | 44.9 | 52.6 | p = 0.007 | 43.9 | 52.8 | p = 0.004 |
| Total Noninflammatory Lesion Count (Two-way ANOVA) | 32.3 | 37.3 | p = 0.028 | 32.0 | 37.4 | p = 0.023 |
| Total Inflammatory Lesion Count (Two-way ANOVA) | 12.5 | 15.3 | p = 0.009 | 11.9 | 15.4 | p = 0.005 |
| % Improvement Total Lesion Count (Repeated Measures ANOVA) | 35.7% | 27.6% | p < 0.001 | 37.1% | 27.7% | p < 0.001 |
| % Imp. Noninflammatory Lesion Count (Repeated Measures ANOVA) | 35.8% | 28.4% | p = 0.003 | 37.4% | 28.6% | p < 0.001 |
| % Imp. Inflammatory Lesion Count (Repeated Measures ANOVA) | 33.7% | 23.31% | p = 0.006 | 35.2% | 23.2% | p = 0.008 |

Table G
Retin-A Gel vs. Vehicle Results

| EFFICACY OUTCOME | Day 84 (ITT) | | | Day 84 (PP) | | |
|---|--------------|---------|-----------|-------------|---------|-----------|
| | Retin-A | Vehicle | p-value | Retin-A | Vehicle | p-value |
| Total Lesion Count (Two-way ANOVA) | 40.7 | 52.6 | p = 0.007 | 39.5 | 52.8 | p < 0.001 |
| Total Noninflammatory Lesion Count (Two-way ANOVA) | 29.3 | 37.3 | p < 0.001 | 28.5 | 37.4 | p < 0.001 |
| Total Inflammatory Lesion Count(Two-way ANOVA) | 11.4 | 15.3 | p < 0.001 | 11.0 | 15.4 | p < 0.001 |
| % Improvement Total Lesion Count (Repeated Measures ANOVA) | 43.3% | 27.6% | p < 0.001 | 44.8% | 27.7% | p < 0.001 |
| % Imp. Noninflammatory Lesion Count (Repeated Measures ANOVA) | 43.9% | 28.4% | p < 0.001 | 45.2% | 28.6% | p < 0.001 |
| % Imp. Inflammatory Lesion Count (Repeated Measures ANOVA) | 39.8% | 23.3% | p < 0.001 | 41.5% | 23.2% | p < 0.001 |

Comments:

1- The data in Table F (taken from NDA, p. 1.0068) show that Avita gel was significantly better than placebo in all 6 parameters analyzed at day 84 (end of treatment). Also, Retin-A gel (0.025%) was significantly better than placebo in all 6 parameters (Table G). These conclusions were true for both PP and ITT populations. The sponsor did not compare Avita gel to Retin-A gel.

2- Similar analysis of the FDA-E and ITT-S populations (Tables H and I) showed that Avita gel was better than placebo in all of these 6 parameters. Comparison of Avita gel and Retin-A gel showed significantly better responses with Retin-A in most (total lesions and noninflammatory lesions) of the percent improvement parameters as shown in Tables H and I below (marked with *).

3- Statistical analysis for investigator interaction in FDA-E or ITT-S populations did not reveal any significant investigator effects in any of the parameters in Tables H and I.

Table H
Total lesion counts and percent improvement on Day 84 in FDA-E population

| Efficacy Outcome | Avita Gel (n=198) | Retin-A Gel (n=203) | Vehicle (n=204) | P-Value | |
|----------------------|-------------------|---------------------|-----------------|-------------------|-------------------|
| | | | | Avita vs. placebo | Avita vs. Retin-A |
| Total lesions (TL) | 44 | 39 | 53 | 0.001 | 0.1 |
| Noninflamm. lesions | 32 | 28 | 39 | 0.007 | 0.1 |
| Inflammatory lesions | 12 | 11 | 15 | 0.003 | 0.3 |
| % Improvement in TL | 36% | 45% | 27% | 0.006 | 0.006* |
| % Improv. Noninflam. | 36% | 45% | 27% | 0.02 | 0.02* |
| % Improv. Inflamm. | 35% | 42% | 25% | 0.02 | 0.1 |

Table I
Total lesion counts and percent improvement on Day 84 in ITT-S population

| Efficacy Outcome | Avita Gel (n=222) | Retin-A Gel (n=225) | Vehicle (n=228) | P-Value | |
|----------------------|-------------------|---------------------|-----------------|-------------------|-------------------|
| | | | | Avita vs. placebo | Avita vs. Retin-A |
| Total lesions (TL) | 46 | 42 | 54 | 0.004 | 0.2 |
| Noninflamm. lesions | 34 | 31 | 39 | 0.02 | 0.2 |
| Inflammatory lesions | 13 | 11 | 15 | 0.006 | 0.2 |
| % Improvement in TL | 34% | 42% | 26% | 0.01 | 0.01* |
| % Improv. Noninflam. | 35% | 42% | 26% | 0.02 | 0.03* |
| % Improv. Inflamm. | 32% | 39% | 22% | 0.02 | 0.12 |

3- Physician's global assessment:

Table J shows the physician's global evaluations throughout all evaluation visits in PP population. Starting from week 3, both Avita and Retin-A were significantly better than

Table J

Physician's Global Evaluation Per Protocol Population Using 3 Day Windows

| Day | | Avita | Retin-A | Vehicle | Source | p-value[1] |
|-----|-----------|-----------|-----------|------------|--------|------------|
| 7 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.371 |
| | EXCELLENT | 1 (1%) | 0 (0%) | 0 (0%) | A v V | 0.002 |
| | GOOD | 17 (9%) | 10 (5%) | 7 (3%) | R v V | <.001 |
| | FAIR | 33 (17%) | 45 (23%) | 30 (15%) | | |
| | POOR | 51 (27%) | 67 (34%) | 49 (24%) | | |
| | WORSE | 88 (46%) | 76 (38%) | 117 (58%) | | |
| 14 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.387 |
| | EXCELLENT | 2 (1%) | 2 (1%) | 0 (0%) | A v V | 0.005 |
| | GOOD | 19 (10%) | 20 (11%) | 9 (5%) | R v V | <.001 |
| | FAIR | 49 (26%) | 50 (27%) | 40 (20%) | | |
| | POOR | 51 (27%) | 56 (30%) | 62 (31%) | | |
| | WORSE | 70 (37%) | 59 (32%) | 86 (44%) | | |
| 28 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.074 |
| | EXCELLENT | 5 (3%) | 9 (5%) | 2 (1%) | A v V | 0.014 |
| | GOOD | 28 (17%) | 40 (22%) | 12 (7%) | R v V | <.001 |
| | FAIR | 50 (30%) | 38 (21%) | 56 (30%) | | |
| | POOR | 37 (22%) | 60 (34%) | 63 (34%) | | |
| | WORSE | 48 (29%) | 31 (17%) | 51 (28%) | | |
| 56 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.101 |
| | EXCELLENT | 17 (11%) | 21 (12%) | 8 (5%) | A v V | 0.042 |
| | GOOD | 29 (18%) | 41 (24%) | 28 (16%) | R v V | <.001 |
| | FAIR | 50 (31%) | 53 (31%) | 59 (34%) | | |
| | POOR | 38 (24%) | 40 (23%) | 44 (25%) | | |
| | WORSE | 25 (16%) | 18 (10%) | 37 (21%) | | |
| 84 | CLEARED | 1 (1%) | 0 (0%) | 0 (0%) | A v R | <.001 |
| | EXCELLENT | 26 (15%) | 51 (28%) | 17 (9%) | A v V | 0.031 |
| | GOOD | 38 (22%) | 47 (26%) | 43 (23%) | R v V | <.001 |
| | FAIR | 59 (34%) | 45 (25%) | 52 (28%) | | |
| | POOR | 29 (17%) | 25 (14%) | 40 (21%) | | |
| | WORSE | 21 (12%) | 14 (8%) | 37 (20%) | | |

[1] p-values from CMH Test Using Modified Ridits, stratified by investigator.

Physician Global Evaluation: Cleared = 100% improvement over baseline
 Excellent = 75-99% improvement over baseline
 Good = 50-74% improvement over baseline
 Fair = 25-49% improvement over baseline
 Poor = 1-24% improvement over baseline
 Worse = Condition unchanged or worse

placebo. On day 84, Retin-A was significantly better than Avita.

Comments:

1- Analysis of physician's global evaluations for ITT population (Table K) showed similar results as PP population, except that Retin-A was also significantly better than Avita on day 28.

2- Analysis of physician's global evaluations for FDA-E population on day 84 showed that Avita gel was significantly better than placebo ($p < 0.02$). This conclusion was unchanged when results were controlled for center effect ($p < 0.02$, see FDA statistical review).

SAFETY EVALUATION:

A- Adverse events:

Of the 660 patients in the Safety population, 295 patients (102 in the Avita Gel group, 114 in the Retin-A Gel group, and 79 in the Vehicle group) reported adverse events during the study. A total of 704 adverse events were reported, 223/Avita Gel, 318/Retin-A Gel, and 163/Vehicle.

1- SUMMARY OF ADVERSE EVENTS UNRELATED TO STUDY MEDICATION BY BODY SYSTEM

The body system accounting for the most adverse events in any treatment group unrelated to the study medication was "Flu Syndrome". A total of 97 adverse events were reported in this category; 35 from the Avita Gel group, 32 from the Retin-A Gel group, and 30 from the Vehicle group. The category with the second highest incidence of reported adverse events was "Headache", with 51 (not 37 as reported in the final report of the study, NDA p. 1.0071) adverse events reported; 14/Avita Gel, 19/Retin-A Gel, and 18/Vehicle. A summary of Adverse Events by Body System is presented in Table 13a of the NDA (vol. 11.1, pp. 1.0232-0242, reproduced in Appendix).

2- SUMMARY OF ADVERSE EVENTS RELATED TO STUDY MEDICATION BY BODY SYSTEM

If, in the opinion of the Investigator, a patient developed severe irritation, the dosing frequency could be reduced to every other night until the irritation decreased. If a patient's dosage was decreased because of severe irritation, the irritation was recorded as an adverse event.

Table K

Physician's Global Evaluation Intent-to-Treat Population

| Day | | Avita | Retin-A | Vehicle | Source | p-value[1] |
|-----|-----------|-----------|-----------|------------|--------|------------|
| 7 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.399 |
| | EXCELLENT | 1 (0%) | 0 (0%) | 0 (0%) | A v V | 0.004 |
| | GOOD | 18 (9%) | 10 (5%) | 8 (4%) | R v V | <.001 |
| | FAIR | 34 (17%) | 45 (22%) | 34 (16%) | | |
| | POOR | 58 (29%) | 70 (35%) | 50 (24%) | | |
| | WORSE | 91 (45%) | 77 (38%) | 119 (56%) | | |
| 14 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.468 |
| | EXCELLENT | 2 (1%) | 2 (1%) | 0 (0%) | A v V | <.001 |
| | GOOD | 22 (11%) | 22 (11%) | 12 (6%) | R v V | <.001 |
| | FAIR | 54 (26%) | 56 (28%) | 41 (19%) | | |
| | POOR | 55 (27%) | 59 (29%) | 65 (31%) | | |
| | WORSE | 72 (35%) | 63 (31%) | 95 (45%) | | |
| 28 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.025 |
| | EXCELLENT | 6 (3%) | 11 (5%) | 2 (1%) | A v V | 0.017 |
| | GOOD | 34 (17%) | 44 (22%) | 15 (7%) | R v V | <.001 |
| | FAIR | 62 (30%) | 44 (22%) | 66 (31%) | | |
| | POOR | 43 (21%) | 68 (34%) | 69 (32%) | | |
| | WORSE | 59 (29%) | 35 (17%) | 61 (29%) | | |
| 56 | CLEARED | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.087 |
| | EXCELLENT | 24 (12%) | 24 (12%) | 9 (4%) | A v V | 0.002 |
| | GOOD | 39 (19%) | 52 (26%) | 36 (17%) | R v V | <.001 |
| | FAIR | 62 (31%) | 60 (30%) | 65 (31%) | | |
| | POOR | 45 (22%) | 42 (21%) | 52 (24%) | | |
| | WORSE | 33 (16%) | 22 (11%) | 51 (24%) | | |
| 84 | CLEARED | 1 (0%) | 0 (0%) | 0 (0%) | A v R | <.001 |
| | EXCELLENT | 28 (14%) | 53 (27%) | 19 (9%) | A v V | 0.021 |
| | GOOD | 45 (22%) | 51 (26%) | 48 (23%) | R v V | <.001 |
| | FAIR | 66 (33%) | 50 (25%) | 57 (27%) | | |
| | POOR | 35 (17%) | 26 (13%) | 46 (22%) | | |
| | WORSE | 28 (14%) | 20 (10%) | 43 (20%) | | |

[1] p-values from CMH Test Using Modified Ridits, stratified by investigator.

Physician Global Evaluation: Cleared = 100% improvement over baseline
 Excellent = 75-99% improvement over baseline
 Good = 50-74% improvement over baseline
 Fair = 25-49% improvement over baseline
 Poor = 1-24% improvement over baseline
 Worse = Condition unchanged or worse

The body system accounting for the most adverse events related to study medication in any treatment group was "Application Site Reaction". A total of 334 adverse events were reported in this category; 99 from the Avita Gel group, 191 from the Retin-A Gel group, and 44 from the Vehicle group. A summary of Adverse Events Related to Study Medication by Body System is presented in Table 13b of the NDA (vol. 11.1, pp. 1.0243-0246, reproduced in Appendix).

3- SUMMARY OF ADVERSE EVENTS BY RACE

Adverse events (AE) as related to race were monitored by comparing AE incidence in a population of all those patients whose race was listed as Caucasian versus a population of all other races combined (non-Caucasian). There were no reports of application site pigmentation changes in any Caucasian or non-Caucasian patients exposed to the active formulations.

In addition, the percent of patients (Caucasian versus non-Caucasian) with adverse events was similar within each treatment group. Forty-eight percent of the Caucasian subjects in the Avita Gel group experienced adverse events versus 40% of the non-Caucasian subjects treated with Avita Gel. Similarly in the Retin-A Gel group, 54% of Caucasians versus 44% of non-Caucasians experienced adverse events. In the Vehicle group, 35% of Caucasians experienced adverse events versus 38% of non-Caucasians. When the incidence of those adverse events categorized as application-site skin reactions was compared for Caucasian and non-Caucasian populations, the following results were reported: Avita Gel, 21%/ Caucasian versus 20%/non-Caucasian; Retin-A Gel, 30% Caucasian versus 26% non-Caucasian; and Vehicle, 7% Caucasian versus 11% non-Caucasian. No difference in incidence of adverse events by race was seen in this study.

4- SERIOUS ADVERSE EVENTS AND WITHDRAWALS DUE TO ADVERSE EVENTS

There was one serious adverse event reported for Patient It was determined that this event (vehicular accident) was not related to study medication and did not affect the subject's study participation.

In the Safety population, a total of 23 adverse events were categorized by the Investigators as "Severe"; seven from the Avita Gel group (4 application site reactions, 1 headache, 1 migraine and 1 rectal disease), 11 from the Retin-A Gel group, and five from the Vehicle group.

A total of five patients withdrew from the study as a result of their Adverse Events; one from the Avita Gel group and four from the Retin-A Gel group. All withdrew for reason related to "Application Site Reaction".

There were two patient withdrawals as a result of "Intercurrent Illness"; one from the Avita Gel group and one from the Retin-A Gel group. All "Intercurrent Illness" adverse events were not due to the study medication.

In addition to this total, seven pregnancies were reported; two from the Avita Gel group (Patients _____, three from the Retin-A Gel group (Patients _____, and two from the Vehicle group (Patients _____). All patients discontinued study medication and were terminated from the study upon receipt of positive pregnancy test results. Patient _____ ended study participation on Day 14. Patients _____ tested positive for pregnancy at their Day 56 visits and were terminated at that time. Patients _____ completed the study but tested positive for pregnancy at the final study visit, Day 84. All subjects reporting pregnancies are followed by the Investigator's site staff with progress reports as needed and a final report at the end of the subject's term. No further information is available at present about any adverse events in these pregnancies.

A summary of Adverse Events Possibly, Probably, or Definitely Related to Study Medication by Body System is presented in Table 13b of the NDA (vol. 11.1, pp. 1.0243-0246, reproduced in Appendix).

B- Cutaneous tolerance:

Erythema increased by Day 7 in all treatment groups, but more in the active treatment groups. At Baseline, erythema was present in 23%, 21%, and 24% of patients in the Avita Gel, Retin-A Gel, and Vehicle groups, respectively. This high Baseline prevalence led to the development of a shift table (Table 12 of the NDA, vol. 11.1, pp. 1.0229-0231, reproduced in Appendix) to assess the number of new cases of erythema that developed after the initiation of treatment. There were significantly more new cases of erythema at Day 28 in the Retin-A Gel group than the Avita Gel group ($p = 0.032$).

The prevalence of peeling at Baseline was very low with 5%, 5%, and 4% of patients in the Avita Gel, Retin-A Gel, and Vehicle groups, respectively, exhibiting peeling. Retin-A patients experienced statistically significantly more peeling than Vehicle control and Avita patients at Days 7, 14, and 28. At Day 84, 23% of Avita patients had peeling compared to 25% of Retin-A patients.

Very few patients (5/218 in the Avita arm, 2/219 in Retin-A arm, and 4/223 in placebo arms) experienced burning/stinging at Baseline but the incidence increased in all treatment groups with the Avita Gel and Retin-A Gel groups being statistically higher than Vehicle at all follow-up visits. The incidence of burning/stinging was significantly lower in the Avita Gel group (91/215, 73/213) than the Retin-A Gel group (112/218, 91/213) at Days 7 and 14.

Itching was not a common complaint in any group and when it did occur it was usually mild. The incidence of itching at Day 14 in the Retin-A Gel group (21%) was statistically worse than Avita Gel group (15%) and Vehicle group (7%).

Tightness occurred more in the active treatment groups and seemed to peak on Day 14. There was significantly less tightness at Day 28 in the Avita Gel group compared to the Retin-A Gel group (p 0.033).

Very few patients reported dryness at Baseline. On Day 7, 54% Avita Gel patients, 57% Retin-A Gel patients, and 29% Vehicle patients presented with dryness. The incidence of dryness peaked at Day 7 and there was statistically significantly more dryness in both active groups than Vehicle at all follow-up visits.

Comments:

The differences in side effects were in favor of Avita gel as compared to 0.025% Retin-A gel. The results of the statistical reviewer's analysis of 6 local adverse events shown in Table L support this conclusion. However, the sponsor is not claiming any comparisons of Avita and Retin-A gels in the proposed labeling. The use of such comparisons of adverse events in labeling is misleading if not accompanied by comparisons of efficacy as well.

CONCLUSIONS:

The results of this clinical study reproduced the results of study # 003 regarding superiority of Avita gel over placebo. The present reviewer recommends approval of this product for the treatment of Acne vulgaris. Labeling was discussed in an internal meeting

Table L
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%) | |

Medical Officer

/S/

Ramzy S. Labib, M.D., Ph. D.

cc: Orig NDA
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
HFD-540
HFD-540/DivDir/Wilkin
HFD-540/SMO/Katz
HFD-540/MO/Labib
HFD-540/Pharm/Jacobs
HFD-540/Chem/DeCamp
HFD-540/CSO/Blay
HFD-710/Biometrics/Harkins

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Table 12
Shift in Erythema Scores
Safety Population

Table 12
 Shift in Erythema Scores
 Safety Population

| Baseline Erythema | Shift | Avita | Retin-A | Vehicle | Source | p-value [1] |
|-------------------|-----------|------------|------------|------------|--------|-------------|
| DAY 7 | | | | | | |
| None | BETTER | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.254 |
| | NO CHANGE | 108 (67%) | 103 (61%) | 138 (84%) | A v V | <.001 |
| | WORSE | 53 (33%) | 66 (39%) | 26 (16%) | R v V | <.001 |
| Mild | BETTER | 4 (8%) | 2 (4%) | 6 (11%) | A v R | 0.264 |
| | NO CHANGE | 35 (71%) | 27 (60%) | 45 (85%) | A v V | 0.031 |
| | WORSE | 10 (20%) | 16 (36%) | 2 (4%) | R v V | <.001 |
| Mod. | BETTER | 2 (40%) | 1 (25%) | 2 (50%) | A v R | 1.000 |
| | NO CHANGE | 3 (60%) | 3 (75%) | 2 (50%) | A v V | 1.000 |
| | WORSE | 0 (0%) | 0 (0%) | 0 (0%) | R v V | 1.000 |
| DAY 14 | | | | | | |
| None | BETTER | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.410 |
| | NO CHANGE | 109 (69%) | 108 (65%) | 130 (80%) | A v V | 0.040 |
| | WORSE | 48 (31%) | 58 (35%) | 33 (20%) | R v V | 0.003 |
| Mild | BETTER | 9 (18%) | 6 (14%) | 7 (14%) | A v R | 0.913 |
| | NO CHANGE | 31 (61%) | 29 (66%) | 40 (78%) | A v V | 0.105 |
| | WORSE | 11 (22%) | 9 (20%) | 4 (8%) | R v V | 0.267 |
| Mod. | BETTER | 3 (60%) | 0 (0%) | 2 (50%) | A v R | 0.250 |
| | NO CHANGE | 2 (40%) | 2 (67%) | 2 (50%) | A v V | 1.000 |
| | WORSE | 0 (0%) | 1 (33%) | 0 (0%) | R v V | 0.429 |
| DAY 28 | | | | | | |
| None | BETTER | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.032 |
| | NO CHANGE | 110 (72%) | 97 (60%) | 128 (81%) | A v V | 0.084 |
| | WORSE | 43 (28%) | 64 (40%) | 31 (19%) | R v V | <.001 |
| Mild | BETTER | 8 (17%) | 7 (17%) | 9 (18%) | A v R | 0.717 |
| | NO CHANGE | 35 (73%) | 28 (67%) | 35 (71%) | A v V | 1.000 |
| | WORSE | 5 (10%) | 7 (17%) | 5 (10%) | R v V | 0.727 |
| Mod. | BETTER | 3 (60%) | 1 (33%) | 3 (75%) | A v R | 1.000 |
| | NO CHANGE | 2 (40%) | 2 (67%) | 1 (25%) | A v V | 1.000 |
| | WORSE | 0 (0%) | 0 (0%) | 0 (0%) | R v V | 0.486 |
| DAY 56 | | | | | | |
| None | BETTER | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.607 |
| | NO CHANGE | 107 (72%) | 120 (75%) | 127 (82%) | A v V | 0.039 |
| | WORSE | 41 (28%) | 40 (25%) | 27 (18%) | R v V | 0.130 |
| Mild | BETTER | 11 (23%) | 12 (29%) | 9 (18%) | A v R | 0.522 |
| | NO CHANGE | 27 (57%) | 19 (45%) | 37 (74%) | A v V | 0.177 |
| | WORSE | 9 (19%) | 11 (26%) | 4 (8%) | R v V | 0.011 |
| Mod. | BETTER | 3 (60%) | 1 (50%) | 2 (50%) | A v R | 1.000 |
| | NO CHANGE | 2 (40%) | 1 (50%) | 2 (50%) | A v V | 1.000 |
| | WORSE | 0 (0%) | 0 (0%) | 0 (0%) | R v V | 1.000 |

[1] p-values from a Fisher's Exact test.

Table 12 (Continued)
 Shift in Erythema Scores
 Safety Population

| Baseline Erythema | Shift | Avita | Retin-A | Vehicle | Source | p-value[1] |
|-------------------|-----------|------------|------------|------------|--------|------------|
| DAY 84 | | | | | | |
| None | BETTER | 0 (0%) | 0 (0%) | 0 (0%) | A v R | 0.895 |
| | NO CHANGE | 111 (76%) | 118 (74%) | 128 (83%) | A v V | 0.118 |
| | WORSE | 36 (24%) | 41 (26%) | 26 (17%) | R v V | 0.073 |
| Mild | BETTER | 14 (30%) | 11 (26%) | 10 (22%) | A v R | 0.470 |
| | NO CHANGE | 30 (65%) | 26 (62%) | 35 (76%) | A v V | 0.505 |
| | WORSE | 2 (4%) | 5 (12%) | 1 (2%) | R v V | 0.154 |
| Mod. | BETTER | 4 (80%) | 2 (100%) | 3 (75%) | A v R | 1.000 |
| | NO CHANGE | 1 (20%) | 0 (0%) | 1 (25%) | A v V | 1.000 |
| | WORSE | 0 (0%) | 0 (0%) | 0 (0%) | R v V | 1.000 |

[1] p-values from a Fisher's Exact test.

Table 13a

Summary of Adverse Events
Number of Patients, Number of Times Reported
Safety Population

Table 13a
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|---------------------------------|-----------|----------------|------------------|----------------|--------------------|-----------|---------|
| | | | | | Mild | Moderate | Severe |
| Total (Any Body System) | Avita | 218 | 102 (47%) | 223 | 97 (43%) | 119 (53%) | 7 (3%) |
| | Retin-A | 219 | 114 (52%) | 318 | 147 (46%) | 160 (50%) | 11 (3%) |
| | Vehicle | 223 | 79 (35%) | 163 | 97 (60%) | 61 (37%) | 5 (3%) |
| BODY AS A WHOLE ALLERG REACT | Avita | 218 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| | Retin-A | 219 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| | Vehicle | 223 | 2 (1%) | 2 | 0 (0%) | 1 (50%) | 1 (50%) |
| CYST | Avita | 218 | 2 (1%) | 2 | 0 (0%) | 2 (100%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| FEVER | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| FLU SYND | Avita | 218 | 31 (14%) | 35 | 28 (80%) | 7 (20%) | 0 (0%) |
| | Retin-A | 219 | 30 (14%) | 32 | 25 (78%) | 6 (19%) | 1 (3%) |
| | Vehicle | 223 | 28 (13%) | 30 | 25 (83%) | 5 (17%) | 0 (0%) |
| HANGOVER | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1
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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|-------------------------|-----------|----------------|------------------|----------------|--------------------|----------|---------|
| | | | | | Mild | Moderate | Severe |
| BODY AS A WHOLE (cont.) | | | | | | | |
| HEADACHE | Avita | 218 | 13 (6%) | 14 | 9 (64%) | 4 (29%) | 1 (7%) |
| | Retin-A | 219 | 13 (6%) | 19 | 13 (68%) | 5 (26%) | 1 (5%) |
| | Vehicle | 223 | 14 (6%) | 18 | 15 (83%) | 3 (17%) | 0 (0%) |
| INFECT | Avita | 218 | 11 (5%) | 11 | 8 (73%) | 3 (27%) | 0 (0%) |
| | Retin-A | 219 | 18 (8%) | 21 | 14 (67%) | 6 (29%) | 1 (5%) |
| | Vehicle | 223 | 5 (2%) | 6 | 4 (67%) | 2 (33%) | 0 (0%) |
| INJURY ACCID | Avita | 218 | 6 (3%) | 6 | 2 (33%) | 4 (67%) | 0 (0%) |
| | Retin-A | 219 | 5 (2%) | 5 | 1 (20%) | 4 (80%) | 0 (0%) |
| | Vehicle | 223 | 7 (3%) | 8 | 3 (38%) | 4 (50%) | 1 (13%) |
| PAIN | Avita | 218 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| PAIN BACK | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1
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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|-----------------|-----------|----------------|------------------|----------------|--------------------|----------|---------|
| | | | | | Mild | Moderate | Severe |
| CV | | | | | | | |
| MIGRAINE | Avita | 218 | 1 (0%) | 2 | 0 (0%) | 1 (50%) | 1 (50%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| DIGESTIVE | | | | | | | |
| DIARRHEA | Avita | 218 | 2 (1%) | 3 | 2 (67%) | 1 (33%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| GASTRITIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| GASTROENTERITIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| GI DIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| GINGIVITIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931

Avita v Vehicle: p = 0.0158

Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1

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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|-------------------|-----------|----------------|------------------|----------------|--------------------|----------|----------|
| | | | | | Mild | Moderate | Severe |
| DIGESTIVE (cont.) | | | | | | | |
| NAUSEA | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| NAUSEA VOMIT | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| RECTAL DIS | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 0 (0%) | 1 (100%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| STOMATITIS APHTH | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| STOMATITIS ULCER | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| TOOTH CARIES | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1

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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|-----------------------------|-----------|----------------|------------------|----------------|--------------------|----------|---------|
| | | | | | Mild | Moderate | Severe |
| DIGESTIVE (cont.) | | | | | | | |
| TOOTH DIS | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| MUSCULOSKELETAL BONE DIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| JOINT DIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| MYALGIA | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| TENDON DIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 0 (0%) | 1 (50%) | 1 (50%) |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

1 0237

0 0224

Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|------------------------------|-----------|----------------|------------------|----------------|--------------------|----------|--------|
| | | | | | Mild | Moderate | Severe |
| NERVOUS DEPRESSION | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| VERTIGO | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| RESPIRATORY SYSTEM ASTHMA | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| BRONCHITIS | Avita | 218 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| | Retin-A | 219 | 3 (1%) | 3 | 3 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 3 (1%) | 3 | 2 (67%) | 1 (33%) | 0 (0%) |
| COUGH INC | Avita | 218 | 4 (2%) | 4 | 4 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 4 (2%) | 4 | 4 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| EPISTAXIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1

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FINAL

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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|----------------------------|-----------|----------------|------------------|----------------|--------------------|----------|---------|
| | | | | | Mild | Moderate | Severe |
| RESPIRATORY SYSTEM (cont.) | | | | | | | |
| PHARYNGITIS | Avita | 218 | 6 (3%) | 6 | 4 (67%) | 2 (33%) | 0 (0%) |
| | Retin-A | 219 | 7 (3%) | 7 | 5 (71%) | 2 (29%) | 0 (0%) |
| | Vehicle | 223 | 7 (3%) | 8 | 5 (63%) | 2 (25%) | 1 (13%) |
| RESPIRAT DIS | Avita | 218 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| RHINITIS | Avita | 218 | 4 (2%) | 4 | 3 (75%) | 1 (25%) | 0 (0%) |
| | Retin-A | 219 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| SINUSITIS | Avita | 218 | 3 (1%) | 3 | 2 (67%) | 1 (33%) | 0 (0%) |
| | Retin-A | 219 | 9 (4%) | 9 | 6 (67%) | 3 (33%) | 0 (0%) |
| | Vehicle | 223 | 8 (4%) | 9 | 5 (56%) | 4 (44%) | 0 (0%) |
| SKIN AND APPENDAGES | | | | | | | |
| ACNE | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1
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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | | |
|-----------------------------|-----------|----------------|------------------|----------------|--------------------|-----------|--------|--|
| | | | | | Mild | Moderate | Severe | |
| SKIN AND APPENDAGES (cont.) | | | | | | | | |
| ANGIOEDEMA | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 0 | 0 | | | | |
| APPLICAT SITE RE | Avita | 218 | 45 (21%) | 99 | 17 (17%) | 78 (79%) | 4 (4%) | |
| | Retin-A | 219 | 63 (29%) | 191 | 57 (30%) | 126 (66%) | 8 (4%) | |
| | Vehicle | 223 | 17 (8%) | 45 | 18 (40%) | 27 (60%) | 0 (0%) | |
| DERM CONTACT | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 0 | 0 | | | | |
| ECZEMA | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| HERPES ZOSTER | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) | |
| NAIL DIS | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Vehicle | 223 | 0 | 0 | | | | |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

Source Data: Appendix A.11 and B.1

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FINAL

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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | | |
|-----------------------------|-----------|----------------|------------------|----------------|--------------------|----------|--------|--|
| | | | | | Mild | Moderate | Severe | |
| SKIN AND APPENDAGES (cont.) | | | | | | | | |
| SKIN DIS | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) | |
| SKIN DRY | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| SS BLEPHARITIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 0 | 0 | | | | |
| CONJUNCTIVITIS | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 1 (50%) | 1 (50%) | 0 (0%) | |
| OTITIS MED | Avita | 218 | 5 (2%) | 5 | 3 (60%) | 2 (40%) | 0 (0%) | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Vehicle | 223 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

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Table 13a (Continued)
 Summary of Adverse Events
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | | |
|-------------------|-----------|----------------|------------------|----------------|--------------------|----------|---------|--|
| | | | | | Mild | Moderate | Severe | |
| UROGENITAL SYSTEM | | | | | | | | |
| DYSMENORRHEA | | | | | | | | |
| | Avita | 218 | 3 (1%) | 5 | 1 (20%) | 4 (80%) | 0 (0%) | |
| | Retin-A | 219 | 3 (1%) | 5 | 4 (80%) | 1 (20%) | 0 (0%) | |
| | Vehicle | 223 | 4 (2%) | 5 | 2 (40%) | 2 (40%) | 1 (20%) | |
| INFECT URIN TRAC | | | | | | | | |
| | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Vehicle | 223 | 0 | 0 | | | | |
| PAIN KIDNEY | | | | | | | | |
| | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Vehicle | 223 | 0 | 0 | | | | |
| VAGINITIS | | | | | | | | |
| | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Vehicle | 223 | 0 | 0 | | | | |
| VULVOVAGINAL DIS | | | | | | | | |
| | Avita | 218 | 0 | 0 | | | | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) | |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.2931
 Avita v Vehicle: p = 0.0158
 Retin-A v Vehicle: p = 0.0005

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Table 13b

Summary of Adverse Events
Possibly, Probably, or Definitely Related to Treatment

Number of Patients, Number of Times Reported
Safety Population

Table 13b
 Summary of Adverse Events Possibly, Probably, or Definitely Related to Treatment
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|---------------------------------|-----------|----------------|------------------|----------------|--------------------|-----------|---------|
| | | | | | Mild | Moderate | Severe |
| Total (Any Body System) | Avita | 218 | 46 (21%) | 102 | 19 (19%) | 79 (77%) | 4 (4%) |
| | Retin-A | 219 | 64 (29%) | 195 | 60 (31%) | 126 (65%) | 9 (5%) |
| | Vehicle | 223 | 18 (8%) | 52 | 26 (50%) | 26 (50%) | 0 (0%) |
| BODY AS A WHOLE ALLERG REACT | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| CYST | Avita | 218 | 1 (0%) | 1 | 0 (0%) | 1 (100%) | 0 (0%) |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 0 | 0 | | | |
| HEADACHE | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 2 (1%) | 2 | 1 (50%) | 0 (0%) | 1 (50%) |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| PAIN BACK | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.0608
 Avita v Vehicle: p = 0.0001
 Retin-A v Vehicle: p = <.0001

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Table 13b (Continued)
 Summary of Adverse Events Possibly, Probably, or Definitely Related to Treatment
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | |
|---|-----------|----------------|------------------|----------------|--------------------|-----------|--------|
| | | | | | Mild | Moderate | Severe |
| DIGESTIVE GI DIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| NAUSEA | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| NAUSEA VOMIT | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 0 | 0 | | | |
| | Vehicle | 223 | 2 (1%) | 2 | 2 (100%) | 0 (0%) | 0 (0%) |
| RESPIRATORY SYSTEM SINUSITIS | Avita | 218 | 0 | 0 | | | |
| | Retin-A | 219 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| | Vehicle | 223 | 0 | 0 | | | |
| SKIN AND APPENDAGES APPLICAT SITE RE | Avita | 218 | 45 (21%) | 99 | 17 (17%) | 78 (79%) | 4 (4%) |
| | Retin-A | 219 | 63 (29%) | 191 | 57 (30%) | 126 (66%) | 8 (4%) |
| | Vehicle | 223 | 16 (7%) | 44 | 18 (41%) | 26 (59%) | 0 (0%) |

Fisher's Exact p-values comparing total number of subjects with any event:

Avita v Retin-A: p = 0.0608
 Avita v Vehicle: p = 0.0001
 Retin-A v Vehicle: p = <.0001

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Table 13b (Continued)
 Summary of Adverse Events Possibly, Probably, or Definitely Related to Treatment
 Number of Patients, Number of Times Reported
 Safety Population

| Event | Treatment | Total # Pts | # Pts w/Event | # of Events | -----Severity----- | | | |
|-----------------------------|-----------|----------------|------------------|----------------|--------------------|----------|--------|--|
| | | | | | Mild | Moderate | Severe | |
| SKIN AND APPENDAGES (cont.) | | | | | | | | |
| DERM CONTACT | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 0 | 0 | | | | |
| SS BLEPHARITIS | Avita | 218 | 1 (0%) | 1 | 1 (100%) | 0 (0%) | 0 (0%) | |
| | Retin-A | 219 | 0 | 0 | | | | |
| | Vehicle | 223 | 0 | 0 | | | | |

Fisher's Exact p-values comparing total number of subjects with any event:
 Avita v Retin-A: p = 0.0608
 Avita v Vehicle: p = 0.0001
 Retin-A v Vehicle: p = <.0001

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Supervisory Medical Officer Review

NDA 20-400

DRUG NAME:

Generic Name: Tretinoin gel
Proposed Trade Name: Avita™ (formerly Acticin™)
Chemical Name: All-trans-retinoic acid
Alternative Chemical Names: Vitamin A acid
Retinoic acid

SPONSOR:

Penederm Incorporated
Foster City, Ca

Pharmacologic Category:

Retinoid

Proposed Indication:

Treatment of acne vulgaris

Dosage Form and

Route of Administration:

0.025% gel; topical

NDA Classification:

3S

Related Drugs:

Retin-A™ (tretinoin gel) gel
0.025%

Date of Submission:

12/22/95

Refer to Medical Officer Review by Nancy Slifman, MD dated 5/8/96 and the Statistical Review by Ralph Harkins, Ph.D. for detailed discussion of results.

BACKGROUND:

The application for Penederm's tretinoin gel 0.025% (Avita (formerly Acticin)) was originally submitted as an ANDA to the Office of Generic Drugs in 1993. the application was withdrawn

The application was subsequently submitted and accepted for filing as a NDA on March 28, 1994. Of note, a letter, dated February 10, 1993, from the Division of Anti-Infective Drugs was sent to Penederm recommending that additional data, from two independent vehicle-control clinical trials, be submitted in order to establish clinical effectiveness and safety of the gel formulation. Although not addressed in the letter, an alternative method for gaining approval would be to compare the new drug product (Avita) to the original drug product (Retin-A) and the vehicle if the following conditions are met: 1) the new drug contains the same active ingredient as the original product; 2) the new drug is for the same indication as the original product; and 3) the new drug differs from the original product only in the dosage form. In this situation, Avita 0.025% gel would need to demonstrate superiority over its vehicle and be equivalent to Retin-A (the original drug). A 2-sided 95% confidence interval is used to evaluate a new drug; whereas, a 2-sided 90% confidence interval is used by the Office of Generics in order to determine equivalency. In this case, because Penederm originally sought advice from the Office of Generics with regard to trial design issues, it was decided at the Center level analysis of equivalency between this product and Retin-A could employ a 2-sided 90% confidence interval.

A further complicating issue was the presence of a common investigator (Jarrett) in the two pivotal trials. During discussions with the sponsor it was agreed that Jarrett's data would be removed from Study PDC 004-003, rather than PDC 004-015; even though more appropriate weighting may have existed if Jarrett was removed from PDC 004-015.

CONCLUSIONS:

Attached is the table of the **Summary of Statistics**, analyzed by both the 95% and 90% confidence intervals.

When analyzed by the 95% confidence interval, the results of Study PDC 004-003 showed statistically significant results favoring Avita over the vehicle for all efficacy variables using all centers. When Jarrett was excluded statistical significance remained in the intent-to-treat analysis but not for the

evaluable patient population. Study PDC 004-015 revealed statistically significant results for the total lesion counts in both the evaluable and intent-to-treat populations when all centers were included. When Jarrett was excluded none of the results were statistically significant.

When the 90% confidence interval was used to look for equivalency, only total lesion count for the evaluable population demonstrated equivalence.

Thus, Penederm has been unable to demonstrate that Avita is superior to vehicle by two independent trials or that Avita is equivalent to Retin-A, making this application non-approvable.

ISI

(Linda M. Katz, M.D., M.P.H.
Deputy Director

cc: orig NDA 20-400
HFD-340
HFD-540
HFD-540/DivDir/JWilkin
HFD-540/DepDir/LKatz (6/24/96
HFD-540/Chem/NMokhtari-Rejali
HFD-540/Pharm/HSheevers
HFD-540/MO/RLabib
HFD-540/MO/Nslifman
HFD-540/Biometrics/RHarkins
HFD-540/CSO/RBlay

Summary of Statistics

| | STUDY #003 | | | | STUDY #015 | |
|-------------------------|------------------------|----------------|----------------|----------------|-----------------------|---------------|
| | Avita™ versus Vehicle | | | | Avita™ versus Vehicle | |
| | All Centers | | Excl. Jarratt | | All Centers | Excl. Jarratt |
| Total Lesions | | | | | | |
| Eval | p = 0.003 | | p = 0.0739 | | p = 0.032 | p = >0.05 |
| ITT-LOCF | p = 0.0024 | | p = 0.0316 | | p = 0.0276 | p = >0.05 |
| Noninflammatory Lesions | | | | | | |
| Eval | p = 0.005 | | p = 0.0638 | | p = 0.0818 | p = >0.05 |
| ITT-LOCF | p = 0.003 | | p = 0.0211 | | p = 0.0906 | p = >0.05 |
| | Avita™ versus Retin-A™ | | | | | |
| | All Centers | | Excl. Jarratt | | | |
| | Equiv. 95% CI? | Equiv. 90% CI? | Equiv. 95% CI? | Equiv. 90% CI? | | |
| Total Lesions | | | | | | |
| Eval | No | Yes | No | Yes | | |
| ITT-LOCF | No | No | No | No | | |
| Noninflammatory Lesions | | | | | | |
| Eval | No | Borderline | No | No | | |
| ITT-LOCF | No | No | No | No | | |

JUN 21 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-400

Original Amendment

NDA 20-400
NDA Original Amendment
M.O. Review #1

Submission date: 12/22/95
Received date: 1/5/96
Review date: 5/8/96

DRUG NAME:

Generic Name: Tretinoin gel
Proposed Trade Name: Avita™ (formerly Acticin™)
Chemical Name: All-*trans*-retinoic acid
Alternative Chemical Names: Vitamin A acid
Retinoic acid

Sponsor:

Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
(415) 358-0100

Pharmacologic Category:

Retinoid

Proposed Indication:

Treatment of acne vulgaris

**Dosage Form and
Route of Administration:**

0.025% gel; topical

NDA Drug Classification:

3S

Related Drugs:

Retin-A™ (tretinoin gel) gel 0.025%

Nature of Submission:

Amendment to address the deficiencies cited in
the NDA nonapproval letter dated 3/29/95

Material Reviewed:

Amendment dated 12/22/95 (vol. 9.1)

Related Reviews:

Statistical Review dated: Pending
Chemistry Review dated: Pending
Pharmacology Review dated: Pending

Related Submissions:

IND

NDA 20-404 (Acticin™ cream 0.025%, 0.05%, and 0.1%)

Formulation:

Penederm formulation PDT 004-002 (see IND submissions dated 9/12/90 and 9/23/92; NDA vol. 1.1, p.41.)

| <u>Ingredient</u> | <u>Quantity (%w/w)</u> |
|---|------------------------|
| /Tretinoin, USP | |
| /Ethanol, 95%, denatured | |
| /Polyolprepolymer-2 Poly[oxy(methyl-1,2-ethanediyl)], α -hydro- ω -hydroxy polymer with 1,1'-methylene-bis-[4, isocyanatocyclohexane] | |
| /Hydroxypropyl cellulose, NF | |
| /Butylated hydroxytoluene, NF or F.C.C. | |
| * 10% overage | |

Chemistry/Manufacturing Controls:

See Chemistry Review

Animal Pharmacology/Toxicology:

See Pharm/Tox Review

BACKGROUND

NDA 20-400 was accepted for filing on March 28, 1994, for the treatment of mild to moderate acne vulgaris. The application had been originally submitted as an ANDA to the Office of Generic Drugs,

According to the letter sent from the Division of Anti-Infective Drug Products to Penederm, Incorporated (signed February 10, 1993), it was recommended that additional data be submitted to establish the clinical effectiveness and safety of the gel formulation. It was stated that: "Clinical studies for this dosage form may be vehicle-controlled (no active control is necessary). Two independent studies are needed." Although not indicated in that letter, if the new drug product (1) contains the same active ingredient as the original product, (2) is for the same indication as the original product, and (3) differs from the original product only in the dosage form, an alternative means of gaining marketing approval would be to compare the new drug product to the original drug product and vehicle. In this case, Retin-A™ gel 0.025% would be considered the original drug product and Avita™ (Acticin™) gel 0.025% the new drug product because of the presence of the excipient, polyolprepolymer-2, in Avita™ (Acticin™), which is not found in Retin-A™. Under these circumstances, the efficacy criteria for approval of Avita™ (Acticin™) gel would be that Avita™ (Acticin™) must be superior to its vehicle and "equivalent" to the original drug (i.e., Retin-A™). A 2-sided **95% confidence interval** is usually used to evaluate a "new drug"; the statistical confidence interval usually used by the Office of Generic Drugs to assess "equivalence" of a generic drug product is based on a 2-sided **90% confidence interval**.

RESULTS

In support of the original NDA 20-400, the results of 2 clinical trials were submitted. These included Study #004-003 and Study #004-015. Study #003 consisted of a 3-arm study in which Avita™ (Acticin™) gel 0.025% was compared to Retin-A™ gel 0.025% and vehicle; Study #015 consisted of a 2-arm study in which Avita™ (Acticin™) gel 0.025% was compared to vehicle. The primary efficacy variables were considered to be: (1) percent change from baseline in total lesion count and (2) percent change from baseline in noninflammatory lesion count (or inflammatory lesion count, depending on the target lesion) at day 84 (end of treatment). The Physician Global Evaluation was considered supportive. The following methodologic problems were noted:

- (1) The presence of an investigator (Dr. Jarratt) who was common to both studies. Dr. Jarratt contributed 57% of the patients in Study #003 and 49% of the patients in Study #015.
- (2) The lack of definitions of the terms used in the grading scale used in the Physician Global Evaluation, thus making it of doubtful value as a primary efficacy variable.

Based on the sponsor's statistical analysis submitted in the original NDA, for Study #003, using the evaluable population/observed cases, there was not a statistically significant difference in mean percent reduction from baseline at day 84 (end of study) for total lesion counts, noninflammatory lesion counts, and inflammatory lesion counts between the Avita™ (Acticin™), Retin-A™, and vehicle treatment groups. For Study #015, using the evaluable population/observed cases, there was not a statistically significant difference in mean percent reduction from baseline at day 84 (end of study) for total lesion counts, noninflammatory lesions count, and inflammatory lesion counts between the Avita™ (Acticin™) and vehicle treatment groups.

Since the time of the non-approval letter, the results of these 2 studies have been re-analyzed numerous times with the following revisions:

- (1) Weighting of the study centers to account for the few, but highly influential vehicle patients of Dr. Cullen in Study #003
- (2) Re-definition of the "evaluable" population to include patients who were evaluated at day 84 (end of study), but who may have missed or were late for an earlier visit
- (3) Exclusion of Dr. Jarratt from Study #003 **only**, in order to account for him being an investigator in both of the clinical trials.

The data were analyzed using center-weighted confidence intervals in which 2-sided, 95% confidence intervals were calculated around the difference between the Avita™ (Acticin™) and the vehicle treatment groups in the mean percent change from baseline to day 84 for each of the primary efficacy parameters. The results for total lesions are shown in Table 1 and for noninflammatory lesions in Table 2 in the Evaluable (Eval) population and the Intent-to-Treat Last-Observation-Carried-Forward (ITT-LOCF) population.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1: Center-Weighted Comparisons of Avita™ versus Vehicle
Mean Percent Change from Baseline to Day 84 in Total Lesion Counts†

| Protocol | Analysis | Avita™ | | Vehicle | | Difference | | 2-sided 95% CI of difference | p- value |
|----------------------|-----------|--------|------------------|---------|------------------|------------------|----------------|------------------------------------|-------------|
| | | N | Weighted Mean | N | Weighted Mean | Weighted Mean | Weighted SE | | |
| 003 All centers | Evaluable | 60 | 41.3 | 62 | 23.9 | 17.4 | 5.8 | (6.0, 28.9) | 0.003 |
| | ITT-LOCF | 69 | 37.5 | 69 | 20.2 | 17.4 | 5.6 | (6.3, 28.5) | 0.0024 |
| 003 Excl. Jarratt | Evaluable | 25 | 44.8 | 27 | 28.7 | 16.1 | 8.8 | (-1.6, 33.7) | 0.0739 |
| | ITT-LOCF | 29 | 42.8 | 29 | 24.4 | 18.4 | 8.3 | (1.7, 35.1) | 0.0316 |
| 015 All Centers | Evaluable | 86 | 34.6 | 82 | 23.5 | 11.1 | 5.1 | (1.0, 21.1) | 0.032 |
| | ITT-LOCF | 89 | 35.0 | 86 | 24.0 | 11.0 | 5.0 | (1.2, 20.9) | 0.0276 |
| 015 Excl. Jarratt | Evaluable | 44 | 35.5 | 42 | 29.8 | 5.7 | 6.9 | (-8.0,19.4)* | >0.05 |
| | ITT-LOCF | 45 | 36.2 | 44 | 30.2 | 6.0 | 6.7 | (-7.3,19.3)* | >0.05 |

† Based on Table 1.A (vol. 9.1, p.17)

* Analysis performed by Beth Turney, Division of Biometrics of FDA

Table 2: Center-Weighted Comparisons of Avita™ versus Vehicle
Mean Percent Change from Baseline to Day 84 in Noninflammatory
Counts†

| Protocol | Analysis | Avita™ | | Vehicle | | Difference | | 2-sided 95% CI of difference | p- value |
|----------------------|-----------|--------|------------------|---------|------------------|------------------|----------------|------------------------------------|-------------|
| | | N | Weighted Mean | N | Weighted Mean | Weighted Mean | Weighted SE | | |
| 003 All centers | Evaluable | 60 | 41.8 | 62 | 24.2 | 17.6 | 6.2 | (5.4, 29.8) | 0.005 |
| | ITT-LOCF | 69 | 38.5 | 69 | 20.4 | 18.1 | 6.0 | (6.3, 30.0) | 0.003 |
| 003 Excl. Jarratt | Evaluable | 25 | 46.7 | 27 | 29.5 | 17.1 | 9.0 | (-1.0, 35.3) | 0.0638 |
| | ITT-LOCF | 29 | 45.7 | 29 | 25.2 | 20.5 | 8.6 | (3.2, 37.8) | 0.0211 |
| 015 All Centers | Evaluable | 86 | 33.2 | 82 | 24.0 | 9.2 | 5.3 | (-1.2, 19.7) | 0.0818 |
| | ITT-LOCF | 89 | 33.6 | 86 | 24.8 | 8.8 | 5.2 | (-1.4, 19.0) | 0.0906 |
| 015 Excl. Jarratt | Evaluable | 44 | 33.8 | 42 | 30.8 | 3.0 | 7.0 | (-11.0,17.0)* | >0.05 |
| | ITT-LOCF | 45 | 34.5 | 44 | 31.9 | 2.6 | 6.9 | (-11.0,16.3)* | >0.05 |

† Based on Table 1.B (vol. 9.1, p.19)

* Analysis performed by Beth Turney, Division of Biometrics of FDA

Equivalence between Retin-A™ gel and Avita™ (Acticin™) gel was tested by using a confidence interval approach in which a center-weighted 2-sided 95% confidence interval was calculated around the Avita™ (Acticin™) minus Retin-A™ difference in the mean percent lesion count. To be considered equivalent, the lower and upper bound of this interval must not exceed 20% of the Retin-A™ mean in absolute value. Since Avita™ (Acticin™) is considered a new drug, a 95% confidence interval was used. However, for purposes of comparison, a 2-sided 90% confidence interval is also shown in the following tables.

Table 3: Center-Weighted Comparisons of Avita™ versus Retin-A™ Mean Percent Change from baseline to day 84 in Total Lesion Count Study #003 only†

| Centers Included | Analysis | Avita™ | | Retin-A™ | | Difference | | 2-sided 95% CI of difference | 2-sided 90% CI of difference | 20% of Retin-A mean |
|------------------|----------|--------|---------------|----------|---------------|---------------|-------------|------------------------------|------------------------------|---------------------|
| | | N | Weighted Mean | N | Weighted Mean | Weighted Mean | Weighted SE | | | |
| All centers | Eval | 60 | 41.4 | 64 | 40.7 | 0.7 | 5.1 | (-9.4, 10.9) | (-7.8, 9.3) | 8.1 |
| | ITT-LOCF | 69 | 37.6 | 73 | 38.2 | 0.7 | 5.0 | (-10.6, 9.2)* | (-9.0, 7.6)* | 7.7 |
| Excl. Jarratt | Eval | 25 | 44.7 | 30 | 39.0 | 5.7 | 8.1 | (-10.4, 21.9)* | (-7.7, 19.2)* | 7.8 |
| | ITT-LOCF | 29 | 42.8 | 31 | 38.5 | 4.3 | 7.4 | (-10.6, 19.2)* | (-8.1, 16.7)* | 7.7 |

† Based on Table 3.A (vol. 9.1, p.27)

* Analysis performed by Beth Turney, Division of Biometrics of FDA

APPEARS THIS WAY
ON ORIGINAL

Table 4: Center-Weighted Comparisons of Avita™ versus Retin-A™
 Mean Percent Change from baseline to day 84 in Noninflammatory
 Lesion Count
 Study #003 only†

| Centers Included | Analysis | Avita™ | | Retin-A™ | | Difference | | 2-sided 95% CI of difference | 2-sided 90% CI of difference | 20% of Retin- A mean |
|------------------|--------------|--------|------------------|----------|------------------|------------------|----------------|------------------------------------|------------------------------------|----------------------------------|
| | | N | Weighted Mean | N | Weighted Mean | Weighted Mean | Weighted SE | | | |
| All centers | Eval | 60 | 41.9 | 64 | 40.4 | 1.6 | 5.8 | (-10.0, 13.0) | (-8.1, 11.2) | 8.1 |
| | ITT- LOCF | 69 | 38.5 | 73 | 37.2 | 1.2 | 5.8 | (-10.1, 12.6)* | (-8.3, 10.8)* | 7.4 |
| Excl. Jarratt | Eval | 25 | 46.6 | 30 | 41.1 | 5.6 | 8.9 | (-12.3, 23.5)* | (-9.4, 20.5)* | 8.2 |
| | ITT- LOCF | 29 | 45.6 | 31 | 40.5 | 5.2 | 8.3 | (-11.4, 21.7)* | (-8.6, 19.0)* | 8.1 |

† Based on Table 3.B (vol. 9.1, p.28)

* Analysis performed by Beth Turney, Division of Biometrics of FDA

APPEARS THIS WAY
 ON ORIGINAL

Summary of Statistics

| | STUDY #003 | | | | STUDY #015 | |
|-------------------------|------------------------|----------------|----------------|----------------|-----------------------|---------------|
| | Avita™ versus Vehicle | | | | Avita™ versus Vehicle | |
| | All Centers | | Excl. Jarratt | | All Centers | Excl. Jarratt |
| Total Lesions | | | | | | |
| Eval | p = 0.003 | | p = 0.0739 | | p = 0.032 | p = >0.05 |
| ITT-LOCF | p = 0.0024 | | p = 0.0316 | | p = 0.0276 | p = >0.05 |
| Noninflammatory Lesions | | | | | | |
| Eval | p = 0.005 | | p = 0.0638 | | p = 0.0818 | p = >0.05 |
| ITT-LOCF | p = 0.003 | | p = 0.0211 | | p = 0.0906 | p = >0.05 |
| | Avita™ versus Retin-A™ | | | | | |
| | All Centers | | Excl. Jarratt | | | |
| | Equiv. 95% CI? | Equiv. 90% CI? | Equiv. 95% CI? | Equiv. 90% CI? | | |
| Total Lesions | | | | | | |
| Eval | No | Yes | No | Yes | | |
| ITT-LOCF | No | No | No | No | | |
| Noninflammatory Lesions | | | | | | |
| Eval | No | Borderline | No | No | | |
| ITT-LOCF | No | No | No | No | | |

Reviewer's Comments:

(1) In study #003, when all centers are included, and regardless of the statistical population analyzed, for mean percent change from baseline in total lesion counts and noninflammatory lesion counts, Avita™ (Acticin™) was superior to the vehicle. In study #015, Avita™ (Acticin™) was superior to the vehicle for mean percent change from baseline in total lesion counts, but not in noninflammatory lesion counts.

(2) When Dr. Jarratt was excluded from Study #003, Avita™ (Acticin™) was superior to the vehicle in the ITT-LOCF population **only**, but not the Evaluable population. When Dr. Jarratt was excluded from Study #015, Avita™ (Acticin™) was not statistically significantly different from the vehicle in either the Evaluable or the ITT-LOCF statistical populations.

(3) In regard to "equivalence," Avita™ (Acticin™) was equivalent to Retin-A™ at the 2-sided 90% confidence interval in the Evaluable population **only** (but not in the ITT-LOCF population) for total lesions and borderline for noninflammatory lesions. Based on the 2-sided 95% confidence interval, Avita™ (Acticin™) was not equivalent to Retin-A™ for either total lesions or noninflammatory lesions in either the Evaluable or the ITT-LOCF statistical populations. When Dr. Jarratt was excluded from Study #003, "equivalence" was no longer statistically demonstrable using a 90% confidence interval for noninflammatory lesions in either the Evaluable or ITT-LOCF populations.

CONCLUSIONS

In determining the approvability of a "new drug" product, there must be 2 adequate, well-controlled, and independent clinical trials showing safety and efficacy. The purpose of the second clinical trial is to show reproducibility of the results from the first trial. The usual level of statistical significance for a new drug is at the 2-sided 95% level. In the case of Avita™ (Acticin™) gel, it was agreed that the sponsor could potentially gain approval by performing a second clinical trial in which Avita™ (Acticin™) gel was shown to be superior to vehicle. Alternatively, one adequate clinical trial in which Avita™ (Acticin™) gel 0.025% was shown to be "equivalent" to Retin-A™ gel 0.025% and superior to vehicle may have been sufficient to substantiate the safety and efficacy of the new drug product. In that case, conceptually, the previously performed clinical trials submitted to support the safety and efficacy of Retin-A™ gel might be considered one of the clinical trials necessary for approval of Avita™ (Acticin™) gel as long as it could be demonstrated in a separate clinical trial that Avita™ (Acticin™) gel was "equivalent" to Retin-A™ gel and superior to the vehicle.

In my opinion, Study #015 does not replicate the results of Study #003, even when Dr. Jarratt is included in the analysis, since there was not a statistically significant difference between the Avita™ (Acticin™) and vehicle treatment groups in mean percent change from baseline for noninflammatory lesions. Therefore, 2 adequate and well-controlled studies to support the efficacy of the drug were not found in this NDA. Furthermore, when Dr. Jarratt is excluded from Study #003, there is loss of statistical significance between the Avita™ (Acticin™) and vehicle treatment groups in the Evaluable population for total lesions and noninflammatory lesions; when Dr. Jarratt is excluded from Study #015, there is not a statistically significant difference between the Avita™ (Acticin™) and vehicle treatment groups for total lesions and noninflammatory lesions in either the Evaluable or the ITT-LOCF populations.

In Study #003, "equivalence" was established using a 2-sided 90% confidence interval in the Evaluable population only (but not in the ITT-LOCF population). In my opinion, "equivalence," particularly when the less statistically stringent 90% confidence interval is used (as opposed to the usual new drug standard of 95%), should have been demonstrated in both the Evaluable and the ITT-LOCF populations, since, according to the sponsor, the ITT-LOCF population is the most "relevant and least-biased analytical approach." In addition, it should be noted that "equivalence" between Avita™ (Acticin™) and Retin-A™ for noninflammatory lesions was borderline when a 2-sided 90% confidence interval was used. Using the 2-sided 95% confidence interval, "equivalence" was unable to be demonstrated for total lesions or noninflammatory lesions in either the Evaluable or ITT-LOCF populations.

In summary, the results of these clinical trials are inconsistent with each other and, in my opinion, indicate that these studies are flawed. Regardless of whether the 2 trials are considered independent, Study #015 failed to show a statistically significant difference between the Avita™ (Acticin™) and vehicle treatment groups for mean percent change from baseline in noninflammatory lesion counts, a key primary efficacy variable. Similarly, even using the less statistically stringent 2-sided 90% confidence interval (as opposed to a 2-sided 95% confidence interval) for the determination of "equivalence," "equivalence" was established only in the Evaluable population (but not in the ITT-LOCF population) for total lesions and was only borderline in the Evaluable population for noninflammatory lesions. When the data are evaluated *in toto*, it is my opinion that there is not definitive, internally consistent, or reproducible evidence to support the conclusion that efficacy for this new drug product was demonstrated in 2 adequate, well-controlled, and independent clinical trials.

RECOMMENDATIONS

- 1) It is recommended that NDA 20-400 be not approved for the treatment of

- 2) If the sponsor wishes to pursue this application, it is recommended that an additional clinical trial be performed. It is preferred that the clinical trial consist of 3 treatment arms (Avita™ gel 0.025%/Retin-A™ gel 0.025%/vehicle), although a study comparing Avita™ gel to vehicle would be sufficient. As previously recommended, an effort should be made to ascertain adverse events related to race and/or degree of skin pigmentation (i.e., Fitzpatrick skin type).

/S/

6/10/96
Nancy Slifman, M.D.

cc: orig NDA 20-400
HFD-340
HFD-540
HFD-540/DivDir/JWilkin
HFD-540/DepDir/LKatz
HFD-540/Chem/NMokhtari-Rejali
HFD-540/Pharm/HSheevers
HFD-540/MO/RLabib
HFD-540/MO/NSlifman
HFD-540/Biometrics/RHarkins
HFD-540/CSO/RBlay

2/21/96
6/19/96