

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:** 75 213

**MEDICAL REVIEW(S)**

Medical Officer Review  
November 24, 1998

ANDA 75-213

Drug Product: Tretinoin Cream USP 0.1%

Sponsor: Spear Pharmaceuticals, Inc.

The Medical Officer Review, Statistical Review and Secondary Medical Review have been completed. The Spear Tretinoin Cream USP 0.1% has been found to be bioequivalent to the Retin-A product, its reference listed drug. Safety is also comparable. The biostatistician pointed out that there was a discrepancy between the observed body as a whole and infection symptoms in the two treatment groups which were statistically significant.

	Retin-A	Tretinoin Cream	p
Body as a whole	36%	49%	0.012
Headache	8.52%(15)	15.34%(27)	
Infection	24%	35%	0.024

These findings are not clinically significant in that they are very unlikely to be attributable to the medications.

Recommendation: This study has been found to show bioequivalence between the reference listed drug and the Spear Tretinoin Cream USP, 0.1%. Therefore, the product can be approved from this point of view provided that all other relevant aspects of the application are also approvable.

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**Enrollment:**

Study subjects were enrolled between November 14, 1996 and December 16, 1996. The study was completed March 10, 1997. Four hundred and thirty-six (436) prospective study patients were screened and signed informed consent forms. The IND for the original study conducted on the 0.05% strength, which is identical to this study, was approved by the Division of Bioequivalence. Of the 436 subjects eligible for the study, only 398 were randomized to a treatment group. No information is given on the reasons for withdrawal or disqualification of the 38 subjects who did not proceed to randomization.

Three-hundred and ninety-eight (398) normal male and female subjects (children and adults age 12 to 40) with at least Grade 2 acne vulgaris were assigned sequential numbers and stratified by acne severity and gender into 6 groups: 1-[mild acne, male], 2-[mild acne, female], 3-[moderate acne, male], 4-[moderate acne, female], 5-[severe acne, male], 6-[severe acne, female]. Study subjects had to have at least 10 inflammatory and 10 non-inflammatory lesions with a maximum of 3 nodulocystic lesions on the face. A restricted randomization procedure was used to balance the treatment groups in a 3:3:1 ratio. Accrual of subjects to the three treatment groups follows:

- 1. Tretinoin Cream, 0.1% - 168
- 2. Retin-A Cream, 0.1% - 174
- 3. Cream Vehicle - 56

**Study Conduct:**

Subjects were instructed to apply the assigned cream to the full face daily for 84 days.

A single, blinded, trained observer graded and counted acne lesions using the design described by Chalker, et.al., 1987 at screening and at study weeks 0, 2, 4, 8 and 12. Patient outcomes were determined by doing counts of inflammatory lesions, counts of non-inflammatory lesions and then determining a global severity scale, using the Global Severity Scale designed by Cook, et.al., 1979 as used and described by Allen and Smith, 1982 :

**GRADING SCALE FOR OVERALL SEVERITY\***

Grade 0 - Facial skin need not be perfectly clear. A few scattered comedones or papules may be present, but these should be visible only on close exam.

Grade 2 - About one fourth of the facial area is involved, with small papules (about six to 12) and comedones (a few pustules or large prominent papules may be present).

Grade 4 - About half of the facial area is involved, with small papules (about six to 12) and large or small comedones. A few pustules and large prominent papules are usually present. (If lesions are generally large, subject may have "grade 4" severity, although less than half of facial area is involved).

Grade 6 - About three fourths of facial area is involved, with papules and/or large open comedones. (Lesser facial area of involvement is permissible if inflammatory lesions are large.) Numerous pustules are usually present, some of which may be large.

Grade 8 - Practically all of facial area is involved, with lesions. Large prominent pustules are usually visible. Lesions are usually highly inflammatory. Other types of acne (such as conglobata, including sinus and cystic types) may be present.

\* Taken from Allen, B.S., Jr. & Smith, G, Jr.: Various parameters for grading acne vulgaris. Arch Dermatol, 118:23-25, 1982. This is an adaptation of the original Cook scale (1979). The actual instrument used was not provided. The initial Cook paper has two scales. One is from 0 to 9, including all numbers, and it defines facial coverage by lesions on a progressive scale. The other has grades 0 to 8 including only even numbers. It describes the type of lesions which lead to increases in grades. The instrument validated by Allen seems to incorporate the two.

The grading scores were extrapolated to mild, moderate and severe:

MILD	- Grade 2 or 3
MODERATE	- Grade 4 or 5
SEVERE	- Grade 6

Assessment of erythema/peeling was made at each facial examination and was scored from:

0	= none
1	= mild
2	= moderate
3	= moderately severe
4	= severe

Adverse events were elicited by the observer who graded acne lesions. Adverse event reports included the date of onset, severity and the date of resolution. All concomitant medications were recorded.

**Results:**

Of the 398 who received study drug, 68 did not complete the study per protocol. Of these, 29 were in the Tretinoin Cream, 0.1% group, 29 in the Retin-A Cream 0.1% group and 10 in the Placebo group. The reasons for withdrawal were:

	<u>Total</u>	<u>Placebo</u>	<u>Retin-A</u>	<u>Tretinoin</u>
Non-compliant	52	8	24	20
Adverse Events	3	1	0	2
Moved Out of Area	4	0	4	0
Withdrew Consent	8	1	1	6
Pregnant	1	0	0	1

The Intent-to-Treat sample included all 398 subjects who received treatment. The Efficacy Valid Analysis was conducted on the sample of subjects who completed the study (to week 12) per protocol (n=330).

**Efficacy:**

The means and standard deviations of the overall severity grade, the number of inflammatory lesions, the number of non-inflammatory lesions and the total number of lesions were calculated for both the Intent-To-Treat and Efficacy Valid Analysis groups. Differences from baseline values and placebo treatment were confirmed during the course of the study. Mean values for each study evaluation as well as the mean for evaluations done week 2 through week 12 are presented in a series of tables for both analysis groups (Intent-To-Treat and Efficacy Valid Analysis). The data was examined for treatment differences based on least squares means.

Treatment arms vs. Placebo

There were no differences among the test, reference and placebo arms in all the baseline (week 0) variables ( $p \geq 0.116$ ). The reference and test groups differed consistently from placebo with greater improvement noted in the following parameters:

Statistically significant treatment and placebo differences

ASSESSMENT	TEST vs. PLACEBO	REFERENCE vs. PLACEBO	p-value
OVERALL SEVERITY	Week 8 and 12 Average, wk 2-12	Week 8 and 12 Average, wk 2-12	p<0.018 p<0.001
INFLAMMATORY LESIONS	Week 8 and 12 Average, wk 2-12	Week 8 and 12 Average, wk 2-12	p<0.037 p<0.001
NON-INFLAMMATORY LESIONS	Week 12 Average, wk 2-12	Week 12 Average, wk 2-12	p<0.001 p<0.038
TOTAL LESIONS	Week 12 Average, wk 2-12	Week 12 Average, wk 2-12	p<0.001 p<0.001

Test vs. Reference Comparison

A comparison of clinical responses for the group on Tretinoin 0.1% and the group receiving Retin-A shows that they are statistically equivalent and meet Confidence Interval criteria of 80-125%. The data for overall severity is shown below.

Comparison of Test and Reference Products  
Overall Severity  
Intent-to-Treat Analysis

OVERALL SEVERITY	REFERENCE	TEST	CONFIDENCE INTERVAL (%)
WEEK 0	4.46	4.45	98.2 - 101.5
WEEK 2	4.06	4.07	97.0 - 103.3
WEEK 4	3.14	3.13	94.2 - 105.2
WEEK 8	2.02	2.07	93.2 - 111.4
WEEK 12	1.35	1.39	92.2 - 113.3
AVERAGE OF WEEKS 2 - 12	2.67	2.68	95.5 - 105.3

Either treatment led to progressive improvement in acne from moderate to mild, as measured by the Overall Severity Scale, when comparing baseline to week 12 or to the average of weeks 2-12.

**Comparison of Test and Reference Products**  
**Inflammatory Lesions**  
**Intent-to-Treat Analysis**

<b>INFLAMMATORY LESIONS</b>	<b>REFERENCE</b>	<b>TEST</b>	<b>CONFIDENCE INTERVAL (%)</b>
WEEK 0	27.58	27.44	96.1 - 102.9
WEEK 2	21.57	21.98	96.4 - 107.4
WEEK 4	16.07	16.5	94.6 - 110.7
WEEK 8	10.92	11.29	93.4 - 113.6
WEEK 12	7.08	7.41	92.3 - 117.0
AVERAGE OF WEEKS 2 - 12	14.1	14.39	95.4 - 108.8

**Comparison of Test and Reference Products**  
**Non-inflammatory Lesions**  
**Intent-to-Treat Analysis**

<b>NON-INFLAMMATORY LESIONS</b>	<b>REFERENCE</b>	<b>TEST</b>	<b>CONFIDENCE INTERVAL (%)</b>
WEEK 0	29.60	29.96	95.9 - 106.5
WEEK 2	25.51	26.37	97.5 - 109.2
WEEK 4	21.53	22.21	96.2 - 110.1
WEEK 8	15.86	16.76	97.0 - 114.4
WEEK 12	9.44	9.29	87.7 - 109.2
AVERAGE OF WEEKS 2 - 12	18.33	18.77	95.8 - 108.9

**Comparison of Test and Reference Products  
Total Lesions  
Intent-to-Treat Analysis**

TOTAL LESIONS	REFERENCE	TEST	CONFIDENCE INTERVAL (%)
WEEK 0	57.18	57.40	97.3 - 103.5
WEEK 2	25.51	26.37	98.3 - 107.1
WEEK 4	21.53	22.21	96.9 - 109.1
WEEK 8	15.86	16.76	96.9 - 112.7
WEEK 12	9.44	9.29	91.6 - 110.6
AVERAGE OF WEEKS 2 - 12	18.33	18.77	96.6 - 107.8

All of the clinical assessments (number of inflammatory lesions, number of non-inflammatory lesions and total lesions) followed the same pattern. A one-sided t-test procedure was used to evaluate whether the treatments were statistically significant for bioequivalence. All measurements per time of observation (test vs. reference) were found to be bioequivalent.

Generally, the test and reference arms had no differences in any of the parameters measured for either analysis group (Intent-to-Treat or Efficacy Valid Analyses) considered.

**Side Effects:**

Erythema/Peeling

Erythema and/or peeling were expected outcomes of the application of both tretinoin products. Therefore, they were not considered to be adverse events whose relationship to the treatment had to be established. They were included in the efficacy results section by the sponsor as Side Effects.

**Erythema and/or Peeling  
Intent-to-Treat Analysis**

Erythema /Peeling	Test	Reference	Placebo	Overall Treatment Effect p-value*	Placebo vs. Reference p-value	Placebo vs. Test Drug p-value	Reference vs. Test p-value
Mean +/- Standard Deviation							
WEEK 0	0.17+/- 0.42	0.22+/- 0.42	0.11+/- 0.41	0.133	0.063	0.366	0.176
WEEK 2	1.79+/- 0.90	2.07+/- 0.91	1.06+/- 0.88	<0.001	<0.001	<0.001	0.008
WEEK 4	1.63+/- 0.69	1.74+/- 0.71	0.91+/- 0.68	<0.001	<0.001	<0.001	0.179
WEEK 8	1.68+/- 0.87	1.95+/- 0.87	1.02+/- 0.84	<0.001	<0.001	<0.001	0.010
WEEK 12	1.72+/- 0.69	2.06+/- 0.70	0.42+/- 0.67	<0.001	<0.001	<0.001	<0.001

\* P-values form a two-way analysis of variance with initial severity and treatment as factors.

Baseline measures of Erythema/peeling were equal for the three study arms. The overall treatment effect and the individual effect of the test or reference arm on erythema/peeling compared to Placebo are statistically significantly different with treated group(s) experiencing more erythema/peeling than those receiving no active treatment (placebo). The Reference and Test groups also showed differences at Week 2, 8 and 12, with the Reference group experiencing more erythema/peeling at these evaluation times.

**Adverse Events:**

Adverse events occurred in 220 of the subjects; 89 in the Tretinoin arm (133 experiences), 97 in the Retin-A arm (97 experiences) and 34 in the placebo arm (57 experiences). Three Serious Adverse Events occurred which were unrelated to the study treatment; hospitalization following an MVA, hospitalization for treatment of Attention Deficit Disorder and hospitalization for treatment of Chron's Disease with TPN. The majority of experiences were cold symptoms, flu, pharyngitis, non-specific infection and headache. These were equally divided among the

three groups.

**Concomitant Medications:**

Concomitant medications were taken by 194 study subjects. The most common medications taken were analgesics, decongestants and/or expectorants, medications for the respiratory tract and antibiotics. These were taken by 37 subjects; 21 (12.5%) using Tretinoin, 10 (5.8%) using Retin-A and 6 (10.7%) on placebo. A number of expert opinions were sought which confirmed that short-term courses of antibiotics lasting 7-10 days should have little effect on the outcome of a twelve week study.

**Conclusions:**

The study conduct and design are acceptable. Provided the endpoints measured are acceptable to the Division of Dermatologic and Dental Drug Products, the results show that the two treatment products had an effect greater than placebo and that the test and reference drugs were equivalent in therapeutic effect. The reference product was more irritating (erythema/peeling) than the test product at week 2, 8 and 12. However, this outcome is acceptable for a test product, which must be equal to or less irritating than reference. There were no differences noted in other adverse events.

**Recommendation:**

This study demonstrates clinical equivalence between Spear Pharmaceutical's Tretinoin 0.1% Cream and its reference listed drug, Retin-A Cream 0.1%.

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February 10, 1998