MEDICAL OFFICER'S REVIEW OF NDA 20-400

Addendum

NDA 20-400	**Date of original NDA:** 3/28/94
M.O. Review #2	**Date of addendum:** 10/7/94
	Review date: 11/23/94

DRUG NAME:

Generic Name:	Tretinoin
Proposed Trade Name:	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
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 0.025%
Nature of Submission:	Additional information regarding patient racial demographics

8.0 CLINICAL STUDIES

8.1.1 Study #1

Title: A Double-Blind, Parallel, Comparative Efficacy and Safety Study of Two Topical Tretinoin Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris (Protocol PDC 004-003)
(Date Completed: 2/13/91)

8.1.1.4 RESULTS

8.1.1.4.1 Population Enrolled/Analyzed

The racial demographics of all enrolled patients are shown in Table 1.

Table 1 - - Racial Demographics of Enrolled Patients

	Acticin™	Retin-A™	Vehicle
Caucasian	59 (83%)	59 (80%)	58 (83%)
African-American	4 (6%)	8 (11%)	2 (3%)
Hispanic	3 (4%)	1 (1%)	6 (9%)
Asian	2 (3%)	5 (7%)	2 (3%)
Other	0	0	1 (1%)
Unknown	3 (4%)	1 (1%)	1 (1%)
Total	71	74	70

8.1.1.4.4 Safety Outcomes

Investigator and Patient Evaluations:

Investigator and patient evaluations were not analyzed by race.

Adverse Reactions:

Of the 2 patients who withdrew from the study due to an adverse event related to the skin (i.e., facial irritation), both were in the Retin-A™ treatment group. One of these patients was Asian. Of the 13 patients in the Acticin™ treatment group who reported an adverse event related to the skin, 2 were African-American. In the Retin-A™ treatment group, 12 patients experienced an adverse event related to the skin. Of these, 1 patient was Asian (Patient described above) and 1 was African-American. In the vehicle treatment group, there was only 1 adverse event related to the skin; this was in a Caucasian patient. Thus, there was a total of 3 African-American patients (2 in the Acticin™ treatment group and 1 in the Retin-A™ treatment group) and 1 Asian patient (Retin-A™ treatment group) who experienced an adverse reaction related to the skin.

Reviewer's Comment:

1) Overall, there were relatively few non-Caucasian patients represented in the study. Those experiencing an adverse reaction related to the skin are too few to allow statistical comparisons between the treatment groups.

2) The reported adverse events related to the skin in the non-Caucasian patients concerned facial irritation (i.e., peeling and dryness). There were no comments of hypo- or hyperpigmentation as a result of inflammation or as a direct result from the use of tretinoin. However, it may be that pigmentation problems were not specifically examined for and/or there were too few non-Caucasian patients enrolled in the study to detect this potential adverse event. It is recommended that future clinical trials include a sufficient number of non-Caucasian patients in each treatment group to enable a statistically meaningful analysis of adverse reactions related to the skin, including changes in pigmentation. In addition, it is recommended that pigment changes be specifically examined for and commented upon.

8.1.2 Study #2

Title: A Double-Blind, Parallel, Comparative Efficacy and Safety Study of a Topical Retinoic Acid Gel Formulation and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris (Protocol PDC 004-015) (Date completed 1/13/93)

8.1.2.4 RESULTS

8.1.2.4.1 Population Enrolled/Analyzed

The racial demographics of all enrolled patients are shown in Table 2.

Table 2 - - Racial Demographics of Enrolled Patients

	Acticin™	Vehicle
Caucasian	72 (79%)	74 (83%)
Hispanic	14 (15%)	7 (8%)
African-American	3 (3%)	2 (2%)
Asian	1 (1%)	4 (4%)
Other	1 (1%)	2 (2%)
Total	91	89

8.1.2.4.3 Safety Outcomes

Investigator and Patient Evaluations:

As with Study #1, the investigator and patient evaluations were not analyzed by race.

Adverse Reactions:

Of the 5 patients who had an adverse event related to the skin (i.e., facial irritation) in the Acticin™ treatment group, 1 patient was Asian and 1 was Hispanic. In the vehicle treatment group, of the 2 patients who were considered to have had an adverse reaction related to the skin, neither were non-Caucasian. It should be noted that 1 Hispanic patient in the vehicle group was reported as having had an "acne exacerbation" (although this was not considered to be related to the treatment, according to the investigator). Thus, there were 2 Hispanic patients (1 in the Acticin™ treatment group and 1 in the vehicle treatment group) and 1 Asian patient (Acticin™ treatment group) who had adverse reactions related to the skin (including "acne exacerbation").

Reviewer's Comment:

1) As with Study #1, there are too few non-Caucasian patients who experienced an adverse reaction related to the skin to allow statistical comparisons between the treatment groups.

2) As with Study #1, it is possible that the lack of reported adverse reactions related to hypo- or hyperpigmentation may be because patients were not specifically examined for this problem, there were too few non-Caucasian patients enrolled in the study to detect this potential adverse event, or the product does not cause hypo- or hyperpigmentation. It is recommended that future clinical trials include a sufficient number of non-Caucasian patients in each treatment group to enable a statistically meaningful analysis of adverse reactions related to the skin, including changes in pigmentation. In addition, it is recommended that pigment changes be specifically examined for and commented upon.

Nancy Slifman, M.D. 11/23/94 /S/

cc: orig NDA 20-400
HFD-340
HFD-540
HFD-540/Chem/NMokhtari-Rejali
HFD-540/Pharm/HSheevers
HFD-540/MO/RLabib
HFD-540/MO/NSlifman
HFD-710/Biometrics/ETurney
HFD-420/Biopharm/HSun
HFD-540/CSO/KChapman
11/25/94

11/2/94

MEDICAL OFFICER'S REVIEW OF NDA 20-400

NDA 20-400
M.O. Review #1

Submission date: 3/28/94
Review date: 10/7/94

DRUG NAME:

Generic Name:	Tretinoin
Proposed Trade Name:	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
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 0.025%
Related Reviews:	Statistical Review dated: Pharmacology Review dated: 8/2/94 Biopharm Review dated: Microbiology Review dated:
Related Submissions:	IND NDA 20-404 (Acticin™ cream 0.025%, 0.05%, 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.)

Ingredient	Quantity (%w/w)
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

Material Reviewed: Volumes 1.1, 1.11 - 1.17 of the original NDA submission (9/24/93) and volumes 1 - 7 of the resubmission (3/28/94)

Chemistry/Manufacturing Controls: See Chemistry Review

Animal Pharmacology/Toxicology: See Pharm/Tox Review

6. CLINICAL BACKGROUND

6.1 Relevant Human Experience

Retin-A™ gel 0.025% (tretinoin gel 0.025%) was approved for the treatment of acne vulgaris in 1975. Acticin™ gel 0.025% has the same qualitative formulation as Retin-A™ gel 0.025% except for the addition of a new excipient, polyolprepolymer-2. The sponsor feels that this polymer acts as an emollient and, therefore, may reduce some of the known skin irritation associated with the topical use of tretinoin. Polyolprepolymer-2 has not been used in any previously approved prescription topical drug products and thus has not undergone formal NDA review. It should be noted, however, that polyolprepolymer-2 is currently marketed in an over-the-counter sunscreen preparation and in a lotion and cream for dry skin.

6.2 Foreign Experience

Acticin™ gel 0.025% was approved in Canada on January 21, 1994. It has not been approved in any other countries.

6.3 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Previous studies in humans with radioactive tretinoin in a gel formulation indicate minimal systemic absorption following topical administration. In an effort to further characterize the percutaneous absorption of Acticin™ gel 0.025%, the sponsor performed a pharmacokinetic study in which plasma levels of tretinoin and isotretinoin were measured in normal volunteers following multiple applications of Acticin™ gel to the face over a 28-day period (Protocol PDC 004-017). Retin-A™ gel 0.025% was used for comparison in a parallel control group. Eighteen subjects (9 females/9 males; age range years) were enrolled with a total of 9 subjects per treatment group. Application of the test drug was made to the forehead and both cheeks with a target dose of $2mg/cm^2$ of gel to $150cm^2$ of surface area (approximately 300mg of gel/application). Applications were made nightly except on Days 7, 14, and 28 at which time applications were also made in the morning. Multiple blood samples for tretinoin and isotretinoin were obtained on Days 0 (endogenous Baseline levels), 7, 14, and 28. In addition, clinical evaluations of erythema, peeling, and dryness were performed. The results of this study are pending review by the Division of Biopharmaceutics. However, according to the study investigators, there was no statistically significant difference between the Acticin™ and Retin-A™ treatment groups in the AUC or C_{max} for plasma levels of tretinoin or isotretinoin relative to Baseline at any evaluation time. However, the C_{ss} of plasma tretinoin on Day 7 was increased in relation to Baseline for both treatment groups. This value was considered within the "normal" plasma levels of retinoic acid reported by others. By Days 14 and 28, the C_{ss} for tretinoin had decreased to Baseline levels. One possible explanation for the elevation of the C_{ss} seen at Day 7 may be related to decreased barrier function.

6.4 Directions for Use

According to the proposed package insert, "Acticin™ gel should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly....Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen. Once the acne lesions have responded satisfactorily, it may be possible to maintain improvement with less frequent applications."

7. DESCRIPTION OF CLINICAL DATA SOURCES

The data that serve as the basis for this review were obtained from the Sponsor's original NDA submission and resubmission.

Seven clinical studies were conducted to evaluate the safety and efficacy of Acticin™ gel 0.025%. Five of these studies addressed issues of cutaneous safety and clinical pharmacology; 4 of these studies were conducted in normal subjects and 1 study was conducted in subjects with a history of acne. The remaining 2 studies were considered pivotal clinical trials. These include 1 study which used both the innovator drug (Retin-A™ gel 0.025%) and the vehicle as controls and 1 study which was vehicle-controlled only. These studies are listed in the following table:

CLINICAL STUDIES

Study #	Study Description	Subjects	Duration
1. PDC 004-005	Primary irritation		1 day
2. PDC 004-007	Primary irritation		5 days
3. PDC 004-018	Contact Sensitization		22 days
4. PDC 004-001	Retinoid-induced dermatitis		21 days
5. PDC 004-017	Pharmacokinetic study		28 days
6. PDC 004-003	Efficacy study (Retin-A™/Vehicle control)		3 months
7. PDC 004-015	Efficacy study (Vehicle control)		3 months

8. CLINICAL STUDIES

The sponsor has submitted 2 multi-center clinical studies in support of this NDA. Study #1 (Protocol PDC 004-003) utilized a "3-arm" design in which Acticin™ gel 0.025% was compared to its vehicle and to Retin-A™ gel 0.025% (tretinoin gel 0.025%). Study #2 (Protocol PDC 004-015) compared Acticin™ gel 0.025% to its vehicle only. The inclusion/exclusion criteria, study protocols, and efficacy variables were very similar for the 2 studies except where noted.

Inclusion/exclusion criteria:

1) Male or female
2) Age 14 - 40 years for Study #1; Age 13 - 40 years for Study #2
3) Mild to moderate acne (of the face) defined as:
    a. At least 30 open and closed comedones (non-inflammatory lesions)
    b. At least 10 papules and/or pustules (inflammatory lesions)
    c. Fewer than 4 nodules/cysts
    d. Fewer than 200 lesions total count (Study #2 only)
4) Not having obvious skin pathology or condition of the face (including acne conglobata, acne fulminans, secondary acne [drug or chemical-induced]) other than mild to moderate acne
5) Not having a history of sensitivity to any of the study medications
6) Complete disclosure of all prescription and over-the-counter medications
7) Provision of written informed consent; for patients under 18 years of age, provision of written informed consent by a parent or guardian
8) Not having used topical acne treatments, medicated soaps, and/or topical steroids on the face for at least 2 weeks
9) Not having used systemic antibiotics (except penicillin) or steroids for at least 4 weeks
10) Not having used systemic retinoid therapy for at least 6 months
11) Not a participant in a clinical research study for at least 6 weeks
12) Not pregnant or nursing
13) Female patients must be practicing an accepted means of birth control (i.e., oral contraceptives, IUD, barrier methods, tubal ligation, or abstinence, if not sexually active):
    a. Oral contraceptive users must have used the same birth control prescription for at least 3 months prior to entry into the study and must agree not to change contraceptive regimen during the study period
    b. Past oral contraceptive users must have discontinued use for at least 6 months prior to entry into the study
14) Female patients of child-bearing potential must have a negative urine pregnancy test prior to beginning the study

Dosage and Duration of Treatment:

Each patient was instructed to wash his/her face nightly, wait 20 to 30 minutes, and then apply about one-half inch of medication (approximately 0.24 grams) to the forehead, nose, chin, and cheeks for 12 weeks. The patient was not to have applied the medication to any other body area (e.g., the neck). On Day 0, each patient applied the medication under supervision; the remaining applications were done by the patient at home. The treated areas were to be protected from the sun, as much as possible, by the use of protective clothing and hat when outdoors. The use of a provided sunscreen was recommended when sun exposure could not be avoided.

Endpoints:

1) The following **efficacy** parameters were evaluated by the investigator:

(1) **Lesion counts** consisting of the actual counts of open and closed-comedones (noninflammatory lesions) and papules and pustules (inflammatory lesions) located on the forehead, cheeks, and chin above the jawline (the nose will be excluded from lesion counts). For Study #1, these were obtained at Baseline and at each scheduled follow-up visit (Days 7, 14, 28, 56, and 84). For Study #2, these were obtained at Baseline and at each scheduled follow-up visit (Days 28, 56, and 84).

(2) **Global clinical assessment of overall improvement** of the patient's acne from Baseline obtained at all scheduled follow-up visits using the following grading scale:

Excellent
Good
Fair
No Change
Worse

2) The following **safety parameters were evaluated by the investigator** at Baseline and at each scheduled follow-up visit on a scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe:

Erythema
Peeling
Dryness of the treatment sites

3) The following **safety parameters were evaluated by the patient** at Baseline and each scheduled follow-up visit on a scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe:

Burning/Stinging
Itching
Tightness

4) Patients were considered evaluable for efficacy if they:
   (1) Completed the study according to the protocol
   (2) Did not miss 2 consecutive visits
   (3) If visits scheduled for Day 7 or Day 14 were within ± 2 days
   (4) If visits scheduled for Days 28, 56, or 84 were within ± 7 days

Reviewer's Comments:

1) The scoring system used for the global assessment by the investigator (i.e., excellent, good, fair, no change, and worse) was not defined either in words or photographs in the original study protocols (see resubmission volume 5, p.14C-0001 and 15B-0001). Thus, each investigator was able to use his/her own definition of these parameters during the conduct of the study, which would likely result in inconsistencies between investigators.

2) It should be noted that, according to the sponsor, lesions of the nose were not counted in the evaluations. Although exclusion of the nose is not a recommendation by the FDA for the study of acne vulgaris, there is no objection as long as this is clearly stated in the protocol and on the Case Report Form in order to ensure consistency between investigators.

Statistical Considerations:

For Study #1, according to the sponsor's protocol, the primary efficacy variables were to be the change from Baseline in **total lesion count** (noninflammatory + inflammatory) and the investigator's global assessment. However, efficacy was also assessed by evaluating the mean count, mean percent change in count from Baseline, and "categorical improvement" in count (see below) for total noninflammatory lesions, total inflammatory lesions, and total lesions. Lesion counts and percent change in lesion counts were tested for significant treatment, investigator, and treatment-by-investigator interaction using an analysis of variance model where Y = trt + inv + (trt X inv) + error. The sponsor states that counts of individual lesion types would be similarly analyzed. The investigator global assessment was analyzed using a categorical means score model. In addition, for Study #1, the sponsor proposed a "categorical" analysis in which the percent of patients whose percent change in noninflammatory, inflammatory, and total lesion counts were categorized dichotomously as: 1) any improvement, 2) ≥ 50% improvement, or 3) ≥ 75% improvement, with each category analyzed separately to determine if differences among treatment groups existed.

However, a post-study decision was made to redefine the categories as 1) worse/no change, 2) 1-25% improvement, 3) 26-50% improvement, and 4) 51-100% improvement. These results were analyzed using a categorical means score model.

For Study #2, according to the sponsor, the primary efficacy variable was the change, percent change, and categorical change in **total lesion counts** (noninflammatory + inflammatory) from Baseline to Day 84. **If the assumption of normality was not satisfied, the ANOVA was performed on rank transformed data.** Secondary efficacy variables were changes in noninflammatory and inflammatory lesion counts. For Study #2, it was not stated as to whether the investigator's global assessment would be considered a primary or secondary efficacy variable.

Reviewer's Comment:

1) The usual primary efficacy variables for acne include changes in noninflammatory and inflammatory lesion counts (each analyzed separately) in addition to total lesion counts. A physician's global evaluation is usually considered a primary efficacy variable ***in conjunction with*** *lesion counts.*

2) Subgroup analyses of age, gender, and race are recommended.

8.1.1 **Study #1**

Title: A Double-Blind, Parallel, Comparative Efficacy and Safety Study of Two Topical Tretinoin Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris (Protocol PDC 004-003) (Date Completed: 2/13/91)

Investigators: Stanley I. Cullen, M.D.
Gainesville, FL

Michael Jarratt, M.D.
Pharmaco Health Research Center
Austin, TX

Anne W. Lucky, M.D.
Dermatology Research Associates, Inc,
Cincinnati, OH

8.1.1.1 **Objective/Rationale:**

The objectives of this study were to: 1) compare the safety and efficacy of Acticin™ gel 0.025% (tretinoin gel 0.025%) to its vehicle and 2) evaluate the therapeutic equivalency of Acticin™ gel 0.025% and Retin-A™ gel 0.025% (tretinoin gel 0.025%) in the treatment of mild to moderate acne vulgaris.

8.1.1.2 **Study Design:**

This was a multi-center, randomized, double-blind, vehicle- and active-controlled, parallel group study of 12 weeks duration.

8.1.1.3 **PROTOCOL**

8.1.1.3.1 **Population/Procedures:**

See Section 8.0

A total of 215 patients were enrolled at 3 sites and were randomized to 1 of 3 treatment groups consisting of Acticin™ gel 0.025%, Retin-A™ gel 0.025%, and Acticin™ gel vehicle. After having first washed the face and then waiting 20 to 30 minutes, each patient was instructed to apply about one-half inch of gel over the entire face nightly. The patient was allowed to use his/her regular acne medication on other parts of the body after applying the test material to the face. Soap was provided. Patients were cautioned to avoid the sun and were provided a sunscreen. If a patient developed severe irritation to the test material during the course of the study, the dosage was either reduced by 50% or the dosing frequency was reduced to every-other-night until the irritation decreased. If excessive dryness, peeling, or tightness occurred which did not respond to the above measures, a facial moisturizer was allowed. Follow-up visits were at weeks 1, 2, 4, 8, and 12.

8.1.1.4 RESULTS

8.1.1.4.1 Population Enrolled/Analyzed:

71 patients were enrolled in the Acticin™ treatment group, 74 patients in the Retin-A™ treatment group, and 70 patients in the vehicle group (see Table 1).

Table 1 - - Patients Enrolled (by treatment group)

Treatment Group	# of Patients Enrolled
Acticin™	71
Retin-A™	74
Vehicle	70
TOTAL	215

The demographics of all enrolled patients are shown in Table 2.

Table 2 - - Demographics of Enrolled Patients

	Acticin™	Retin-A™	Vehicle
Total	71	74	70
Male	29 (41%)	34 (46%)	34 (49%)
Female	42 (59%)	40 (54%)	36 (51%)
Age (yrs)*	21.92 ± 6.32 Range:	20.34 ± 5.55 Range:	19.5 ± 5.16 Range:

* Age expressed as mean years ± standard deviation

Race was not included by the sponsor in the characteristics of the study population. According to the sponsor, there was no significant difference in treatment groups with respect to gender. However, comparison of mean age between treatment groups showed a significant difference using a one-way ANOVA.

Reviewer's Comments:

1) Although there is a significant difference with respect to mean age between the treatment groups, it is unlikely to influence the study results because of its small value.

2) In general, race and skin type should be included as demographic factors. It is possible that more darkly pigmented skin may experience either hypo- or hyperpigmentation as an adverse event secondary to the use of this drug product.

The number of evaluable patients (according to the sponsor's criteria under Section 8.0) per investigator and treatment group are shown in Tables 3 and 4.

Table 3 - - Evaluable Patients (by investigator)

Investigator	Treatment Group	# of Patients Enrolled	# Evaluable for Efficacy	% of Total Evaluable Patients (N=190)
Cullen	Acticin™ Retin-A™ Vehicle	5 6 5	5 6 5	
Total		16	16	8%
Jarratt	Acticin™ Retin-A™ Vehicle	42 42 41	36 37 36	
Total		125	109	57%
Lucky	Acticin™ Retin-A™ Vehicle	24 26 24	21 24 20	
Total		74	65	34%
TOTAL		215	190	

Table 4 - - Evaluable Patients (by treatment group)

Treatment Group	# of Patients Enrolled	# Evaluable for Efficacy	# Unevaluable for Efficacy	% Unevaluable for Efficacy
Acticin™	71	62	9	13%
Retin-A™	74	67	7	9%
Vehicle	70	61	9	13%
TOTAL	215	190	25	12%

Reviewer's Comment:

1) Table 3 indicates that Dr. Jarratt contributed the majority of patients to the clinical trial and that Dr. Cullen contributed significantly fewer (8%).

2) The percent of unevaluable patients per treatment group is fairly consistent.

The reasons for unevaluable patients, according to the sponsor's criteria, are shown in Table 5. According to the sponsor, there was only 1 patient Retin-A™) discontinued the study due to an adverse event. (Please see safety evaluation below for more information regarding this patient.)

Table 5

Summary of Reasons for Unevaluable Patients*

	Acticin™	Retin-A™	Vehicle	Total
Lost to Follow-Up	2	1	4	7
Acne Worse	1	0	3	4
Adverse Experience	0	1	0	1
Personal	2	0	1	3
Non-compliant	2	3	1	6†
Protocol Violation	2	1	0	3
Concomitant Illness	0	1	0	1
TOTAL	9	7	9	25

* From vol 1.12, p. 388

† Includes Patient (Retin-A™) who discontinued himself from the study due to an adverse experience of irritation/dryness

Includes Patient (Acticin™) who became pregnant during the study

Includes Patient (Retin-A™) who became pregnant during the study

Reviewer's Comment:

1) It should be noted that the above table lists "Acne "Worse" as a reason for being unevaluable. This is the reason that the patient gave to the investigator (as recorded on the CRF) for wanting to withdraw early from the study. All of these patients had at least 1 post-Baseline follow-up visit and thus their results should be captured in an intent-to-treat/last-observation-carried-forward analysis, which is pending.

2) It should also be noted that there were 2 other patients whose acne worsened, but were categorized as "Lost to Follow-Up" or "Non-Compliant." These include Patient (vehicle) and Patient (Acticin™). If these 2 patients are included with the other 4 patients in the "Acne Worse" category, then 2 Acticin™-treated and 4 vehicle-treated patients would have shown worsening acne at the time of early withdrawal. In addition, Patient (Retin-A™), listed as "Non-Compliant," withdrew from the study due to an adverse event consisting of facial irritation/dryness.

3) It is recommended that the sponsor provide information regarding the pregnancy outcome of the 2 patients who were exposed to topical tretinoin.

4) The categories of "Lost to Follow-Up" and "Non-Compliant" appear to be used interchangeably on the CRF and without definition. For example, Patient was listed as "Non-Compliant" because of missing 2 consecutive visits, even though dates of attempted contact are listed on the CRF. This should be clarified by the sponsor.

Table 6
Unevaluable Patients (by patient number)

Reason	Patient Number
Lost to Follow-Up	
Acne Worse	
Adverse Experience	
Personal	
Non-Compliant	
Protocol Violation	
Concomitant Illness	

* Patients without a post-Baseline follow-up visit: Acticin™), (Retin-A™), and (Vehicle)

Nine additional patients (4 Acticin™, 3 Retin-A™, and 2 vehicle) presented with deviations from the protocol, but were considered evaluable and included in the statistical analyses provided by the sponsor. These include 1 Acticin™ patient who started the study at

age 13 years, but who turned 14 years old after 18 days in the study; 1 Acticin™ patient with only 28 non-inflammatory lesions (instead of the required 30) at the Baseline visit; 1 Acticin™ and 1 Retin-A™ patient respectively) who used moisturizers without first decreasing the dosing frequency of their treatment; 1 vehicle patient who received metronidazole for 10 days; 1 Acticin™ patient who received erythromycin for 10 days and systemic steroids for 6 days; 2 Retin-A™ patients who received erythromycin for 4 and 9 days, respectively; and 1 vehicle patient who received erythromycin for 10 days. In addition to these patients reported by the sponsor, there was 1 Retin-A™ patient who received an unknown antibiotic for 4 days and 1 Retin-A™ patient who received trimethoprim/sulfa for 10 days.

Reviewer's Comment:

1) Five patients received antibiotics for 7 days or longer. These patients were distributed such that 1 was in the Acticin™ treatment group, 2 were in the Retin-A™ treatment group, and 2 were in the vehicle treatment group. Because of this distribution, it would be unlikely that concomitant antibiotic use in these patients might bias the results in favor of Acticin™. If necessary, a statistical analysis will be requested which excludes these 5 patients.

2) As noted in Table 6, there are 4 patients distributed among the 3 treatment groups (2 Acticin™, 1 Retin-A™, and 1 vehicle) who did not have a post-Baseline follow-up visit. In this study, where ***change from Baseline*** *is an efficacy variable, it is preferred that the intent-to-treat population be* ***modified to exclude*** *those patients who did not have at least 1 post-Baseline follow-up visit.*

8.1.1.4.2 Efficacy Endpoint Outcomes

The following results are for evaluable patients (as defined by the sponsor; see section 8.0). The endpoint of the study was Day 84.

Table 7 - - Baseline Lesion Counts (by investigator)

	Acticin™	Retin-A™	Vehicle
Cullen			
Noninflammatory	52.6 ± 13.15 (N=5)	69 ± 17.67 (N=6)	38.2 ± 1.79 (N=5)
Inflammatory	18 ± 4.85	18 ± 5.83	23.6 ± 20.61
Total Lesions	70.6 ± 10.41	87 ± 17.9	61.8 ± 21.82
Jarratt			
Noninflammatory	64.67 ± 39.19 (N=36)	69.05 ± 44 (N=37)	72.56 ± 42.57 (N=36)
Inflammatory	15.36 ± 6.85	15.78 ± 7.76	17.03 ± 8.34
Total Lesions	80.03 ± 42.82	84.84 ± 47.92	89.58 ± 42.92
Lucky			
Noninflammatory	83.76 ± 43.82 (N=21)	92.29 ± 83.92 (N=24)	83.2 ± 56.92 (N=20)
Inflammatory	27.24 ± 17.92	27.29 ± 17.58	25.55 ± 11.81
Total Lesions	111 ± 55.52	119.58 ± 93.61	108.75 ± 61.12
Combined Investigators			
Noninflammatory	70.16 ± 40.36 (N=62)	77.37 ± 60.5 (N=67)	73.23 ± 47.1 (N=61)
Inflammatory	19.6 ± 12.83	20.1 ± 13.14	20.36 ± 11.38
Total Lesions	89.76 ± 48.07	97.48 ± 67.88	93.59 ± 49.6

Reviewer's Comment:

These results indicate that when all investigators were combined, there was not a significant difference in the mean counts of the various types of lesions at Baseline between the 3 treatment groups (for noninflammatory lesions, p=0.55; for inflammatory lesions, p=0.77; for total lesions, p=0.66). However, when each investigator is separately analyzed, there appears to be significant differences in comparability of baseline lesion counts. As shown in a general linear model analysis, there is a significant site/investigator effect for noninflammatory, inflammatory, and total lesion counts at Day 0 (vol. 1.13, pp. 897, 952, and 1007). The large standard deviations may be due to, in part, the variability of lesion counts between investigators. The distribution of lesion counts for each investigator was not submitted.

Efficacy was analyzed for the mean percent change from Baseline at Day 84 for noninflammatory, inflammatory, and total lesion counts for all evaluable patients (as defined by the sponsor). These results are shown in Table 8.

Table 8 - Mean % Change from Baseline*

	Baseline	Day 84	% Reduction	Overall p (Day 84)
Noninflammatory Lesions				
Acticin™	70.16 ± 40.36	42.14 ± 39.47	41.72% ± 30.79	0.4574
Retin-A™	77.37 ± 60.5	43.98 ± 32.96	42.77% ± 30.95	
Vehicle	73.23 ± 47.1	53.87 ± 37.75	25.61% ± 33.92	
Inflammatory Lesions				
Acticin™	19.6 ± 12.83	11.38 ± 8.17	38.33% ± 32.59	0.5954
Retin-A™	20.1 ± 13.14	11.97 ± 11.06	43.34% ± 33.27	
Vehicle	20.36 ± 11.38	15.02 ± 10.97	22.78% ± 47.53	
Total Lesions				
Acticin™	89.76 ± 48.07	53.52 ± 43.16	41.28% ± 26.9	0.583
Retin-A™	97.48 ± 67.88	55.95 ± 38.75	42.4% ± 28.11	
Vehicle	93.59 ± 49.6	68.89 ± 43.46	25.76% ± 32.38	
Number of Patients				
Acticin™	62	58		
Retin-A™	67	58		
Vehicle	61	55		

* From vol. 1.12, pp. 681, 688, 694

Reviewer's Comment:

These findings indicate that at Day 84 (end of treatment) there was no statistical difference between Acticin™, Retin-A™, or vehicle in regard to mean percent change from Baseline of noninflammatory lesions, inflammatory lesions, or total lesions. Although Acticin™ appears to be numerically superior to the vehicle, the variability of the results, as shown by the large standard deviations of the lesion counts and percent change from Baseline, appears to be great enough so that a statistical difference was not found given the number of patients studied. It should also be noted that the sponsor anticipated a mean percent reduction from Baseline of approximately 50% for

the active treatment groups, which was not achieved in this study. Given the variability and the lower than expected mean percent reduction from Baseline, this study probably did not include enough patients to show a statistical difference between the active and vehicle treatment groups. For listing by investigator of mean percent reduction of lesions, see Appendix 1.

The mean lesion counts for evaluable patients over time for all investigators is shown in Table 9.

Table 9 - - Mean Lesion Counts, Combined Investigators*

	Baseline	Day 7	Day 14	Day 28	Day 56	Day 84
Noninflammatory Lesions						
Acticin™	70 (n=62)	63 (n=61)	57 (n=59)	55 (n=62)	47 (n=61)	42 (n=58)
Retin-A™	77 (n=67)	69 (n=66)	61 (n=62)	60 (n=61)	50 (n=59)	44 (n=58)
Vehicle	73 (n=61)	72 (n=56)	62 (n=51)	62 (n=55)	57 (n=56)	53 (n=55)
Inflammatory Lesions						
Acticin™	20	18	16	17	14	11
Retin-A™	20	18	16	15	12	12
Vehicle	20	19	19	17	15	15

* Evaluable patients only, observed at each visit
From vol. 1.12, p.686 and p.692

Reviewer's Comment:

For both types of lesions, there was not a statistical difference between the 3 treatment groups for mean lesion counts at any evaluation timepoint. For noninflammatory lesions, all 3 treatment groups showed improvement throughout the 12-week study period. Both Acticin™ and Retin-A™ had the greatest rate of improvement during the first 14 days of treatment. For inflammatory lesions, the Acticin™ and Retin-A™ treatment groups appear to have shown slow, minimal improvement throughout the 12-week study period. The clinical significance of a decrease of 8 or 9 inflammatory lesions (papules and/or pustules) over 12 weeks of treatment is unclear.

The data were further analyzed by the sponsor by categorizing the data (see Section 8.0, Statistical Considerations). These results are summarized in Table 10. Results are shown for Day 84 only.

Table 10 - Results at Day 84, Categorized

	Worse/No change	1-25% Improvement	26-50% Improvement	51-100% Improvement	p value
Noninflammatory Lesions					Overall p= 0.0401*
Acticin™	8 (14%)	9 (16%)	12 (21%)	29 (50%)	vs.vehicle= 0.0261†
Retin-A™	7 (12%)	8 (14%)	16 (28%)	27 (47%)	vs.vehicle= 0.0287
Vehicle	13 (24%)	10 (18%)	18 (33%)	14 (25%)	
Inflammatory Lesions					Overall p= 0.0637
Acticin™	8 (14%)	9 (16%)	20 (34%)	21 (36%)	
Retin-A™	7 (12%)	8 (14%)	16 (28%)	27 (47%)	
Vehicle	17 (31%)	9 (16%)	10 (18%)	19 (35%)	
Total Lesions					Overall p= 0.0022
Acticin™	5 (9%)	10 (17%)	16 (28%)	27 (47%)	vs.vehicle= 0.0015
Retin-A™	6 (10%)	8 (14%)	18 (31%)	26 (45%)	vs.vehicle= 0.0035
Vehicle	14 (25%)	13 (24%)	16 (29%)	12 (22%)	

* Overall p value refers to the use of a categorical means score model
† Pairwise comparisons

Reviewer's Comment:

These results indicate that for noninflammatory lesions and total lesions (noninflammatory + inflammatory), the active treatment groups were statistically significantly different from vehicle at Day 84 (end of study). The Retin-A™ and Acticin™ treatment groups were not significantly different from each other. When the dichotomous grouping of less than vs. greater than or equal to 50% improvement at Day 84 was used, Acticin™ was significantly different from vehicle for noninflammatory and total lesion counts. The dichotomous category of less than vs. greater than 75% improvement did not show a significant difference between any of the treatment groups at Day 84.

The results of the physician global evaluations for evaluable patients at Day 84 are shown in Table 11.

Table 11 - Physician Global Evaluations, By Individual Investigator and All Investigators Combined, Day 84

	Excellent	Good	Fair	No change	Worse	N
Cullen						
Acticin™	1 (20%)	2 (40%)	1 (20%)	1 (20%)	0	5
Retin-A™	1 (20%)	2 (40%)	1 (20%)	1 (20%)	0	5
Vehicle	0	4 (80%)	1 (20%)	0	0	5
Jarratt						
Acticin™	4 (12%)	13 (38%)	9 (26%)	6 (18%)	2 (6%)	34
Retin-A™	5 (16%)	15 (48%)	6 (19%)	4 (13%)	1 (3%)	31
Vehicle	6 (18%)	5 (15%)	5 (15%)	12 (35%)	6 (18%)	34
Lucky						
Acticin™	4 (21%)	8 (42%)	5 (26%)	1 (5%)	1 (5%)	19
Retin-A™	4 (18%)	7 (32%)	6 (27%)	3 (14%)	2 (9%)	22
Vehicle	0	3 (19%)	8 (50%)	4 (25%)	1 (6%)	16
Combined investigators						
Acticin™	9 (16%)	23 (40%)	15 (26%)	8 (14%)	3 (5%)	58
Retin-A™	10 (17%)	24 (41%)	13 (22%)	8 (14%)	3 (5%)	58
Vehicle	6 (11%)	12 (22%)	14 (25%)	16 (29%)	7 (13%)	55

Reviewer's Comments:

Definitions of the various categories of improvement (i.e., "Excellent," "Good," and "Fair") were not provided in the original protocol, thus making the interpretation of the results difficult. In addition, Dr. Cullen has very few patients in each category. Using a categorical means score model of analysis for combined investigators, there appears to be is a statistical difference between the 3 treatment groups at Day 84 ($p=0.005$). A pairwise analysis at Day 84 showed the Acticin™ treatment group to be significantly different from vehicle ($p=0.0049$), the Retin-A™ treatment group different from vehicle ($p=0.009$), and the Acticin™ treatment group not significantly different from Retin-A™ ($p=0.94$). Adjustments for Baseline lesion count (Dr. Lucky's patients had more lesions at Baseline) may yield additional information.

The last-observation-carried-forward analysis is pending.

Summary of p values - Acticin™ vs. vehicle

	Evaluable/Observed	ITT/Observed	Evaluable/LOCF	ITT/LOCF
Lesion counts: Mean % reduction from baseline, day 84				
Noninflammatory	NS	NS		
Inflammatory	NS	NS		
Total lesions	NS	NS		
Categorical Analysis, Day 84				
Noninflammatory	0.0261	0.0166		
Inflammatory	NS	NS		
Total lesions	0.0015	0.0016		
Physician Global, Day 84	0.005 (overall) Acticin™ vs. vehicle: 0.0049	Not done		

Reviewer's Comment:

The intent-to-treat analysis of the physician global evaluation does not appear to have been submitted.

APPEARS THIS WAY
ON ORIGINAL

8.1.1.4.3 Equivalence

Therapeutic equivalence was assessed by the sponsor by testing for equivalence of mean percent change in **total** lesion counts (inflammatory + noninflammatory) on Day 84. According to the sponsor, using a 2 one-sided t-test, the lower confidence bound on the Acticin™ group fell 22.6% below the Retin-A™ mean, and the upper bound fell 17.34% above the Retin-A™ mean.

Reviewer's Comment:

1) A detailed equivalence analysis will be performed by the Division of Biometrics based on 95% confidence intervals (see Table below). However, it should be noted that, because the lower confidence bound of the Acticin™ group is greater than 20% below the Retin-A™ mean (determined by using a one-sided t-test), the usual standard used by the Office of Generic Drugs to establish equivalence would not be met.

2) The following table summarizes the results of equivalence based on the 95% confidence interval of the difference between the mean percent reduction of lesions of Acticin™ and Retin-A™ at Day 84 for evaluable patients:

	Mean % Reduction	95% CI of difference (Acticin™ - Retin-A™)	20% of Retin-A mean % reduction
Noninflammatory Lesions			
Acticin™	41.72% ± 30.79	(-10.3, 12.4)	-8.55
Retin-A™	42.77% ± 30.95		
Inflammatory Lesions			
Acticin™	38.33% ± 32.59	(-7.1, 17.1)	-8.67
Retin-A™	43.34% ± 33.27		
Total Lesions			
Acticin™	41.28% ± 26.9	(-9.0, 11.2)	-8.48
Retin-A™	42.4 ± 28.11		

These results indicate that the lower bound of the Acticin™ group is greater than 20% of the mean percent reduction of Retin-A™ for noninflammatory lesions and total lesions. Based on this method of determining equivalence, Acticin™ and Retin-A™ would not be considered statistically equivalent in the mean percent reduction of noninflammatory lesions and total lesions (noninflammatory + inflammatory).

8.1.1.4.4 Safety Outcomes

Investigator and Patient Evaluations:

Erythema, peeling, and dryness were evaluated at each visit by the investigator on a scale of 0 (none) to 3 (severe). The percent of patients in each treatment group exhibiting the given parameter at each visit (regardless of the severity) is shown in Table 12.

Table 12 - - Investigator's Evaluation of Erythema, Peeling, and Dryness (expressed as % of patients)

	Acticin™	Retin-A™	Vehicle
Erythema			
Baseline	6% (4/71)	5% (4/74)	4% (3/70)
Day 7	*35% (24/68)	*49% (35/72)	15% (9/61)
Day 14	29% (19/66)	*38% (27/71)	21% (13/62)
Day 28	27% (17/63)	38% (26/68)	21% (13/61)
Day 56	19% (12/63)	22% (18/64)	11% (6/57)
Day 84	13% (8/62)	21% (14/67)	8% (5/61)
Peeling			
Baseline	0% (0/71)	0% (0/74)	1% (1/70)
Day 7	*31% (21/68)	*50% (36/72)	8% (5/61)
Day 14	*29% (19/66)	*38% (27/71)	10% (6/62)
Day 28	*19% (12/63)	*35% (24/68)	7% (4/61)
Day 56	8% (5/63)	*27% (17/64)	5% (3/57)
Day 84	8% (5/62)	*22% (15/67)	3% (2/61)
Dryness			
Baseline	0% (0/71)	0% (0/74)	0% (0/70)
Day 7	*35% (24/68)	*40% (29/72)	7% (4/61)
Day 14	27% (18/66)	*31% (22/71)	15% (9/62)
Day 28	18% (11/63)	27% (18/68)	15% (9/61)
Day 56	14% (9/63)	22% (14/64)	9% (5/57)
Day 84	10% (6/62)	*22% (15/67)	8% (5/61)

* Statistically different from vehicle

Reviewer's Comment:

1) Overall, approximately 30% of the Acticin™ patients experienced erythema, peeling, or dryness. These were most commonly seen within the first 28 days of treatment and then declined until the end of the study. The Retin-A™ patients showed a similar pattern except that the percent of patients experiencing peeling and/or dryness continued to be significantly different from the vehicle treatment group even at the end of the study (Day 84). For all 3 safety parameters, the majority of patients were scored as being "mild." However, for erythema, 5 patients were classified as "severe" (1 Acticin™ and 4 Retin-A™); for peeling, 4 patients (Retin-A™) were classified as "severe;" and for dryness, 3 patients (Retin-A™) were "severe."

2) For peeling, the Acticin™ and Retin-A™ treatment groups were statistically significantly different from each other on days 28, 56, and 84.

3) The vehicle treatment group showed a similar time course of worsening and improvement of symptoms as that of the active treatment groups, indicating that the vehicle itself may be responsible for some of the side effects of the drug product.

4) It is recommended that these results be analyzed by age, gender, and race.

Safety parameters evaluated by the patient were burning/stinging, itching, and tightness. These results are shown in Table 13.

Table 13 - - Patient Evaluation of Burning/Stinging, Itching, and Tightness (expressed as % of patients)

	Acticin™	Retin-A™	Vehicle
Burning/Stinging			
Baseline	0% (0/71)	1% (1/74)	0% (0/70)
Day 7	*43% (29/68)	*49% (35/72)	5% (3/61)
Day 14	*23% (15/66)	*25% (18/71)	5% (3/62)
Day 28	11% (7/64)	15% (10/68)	5% (3/61)
Day 56	8% (6/63)	*16% (10/64)	0% (0/57)
Day 84	6% (4/62)	10% (7/67)	2% (1/61)
Itching			
Baseline	0% (0/71)	0% (0/74)	0% (0/70)
Day 7	*24% (16/68)	*21% (15/72)	5% (3/61)
Day 14	9% (6/66)	*21% (15/71)	3% (2/62)
Day 28	19% (12/64)	12% (8/68)	7% (4/61)
Day 56	*13% (8/63)	*12% (8/64)	2% (1/57)
Day 84	6% (4/62)	*10% (7/67)	0% (0/61)
Tightness			
Baseline	0% (0/71)	1% (1/74)	1% (1/70)
Day 7	*43% (29/68)	*40% (29/72)	16% (10/61)
Day 14	*33% (22/66)	*32% (23/71)	16% (10/62)
Day 28	22% (14/64)	21% (14/68)	11% (7/61)
Day 56	21% (13/63)	22% (14/64)	12% (7/57)
Day 84	10% (6/62)	15% (10/67)	10% (6/61)

* Statistically different from vehicle

Reviewer's Comment:

1) Overall, approximately 40% of the Acticin™ patients showed burning/stinging or tightness. Itching was reported in approximately 25% of the Acticin™ patients and 20% of the Retin-A™ patients. The majority of patients were scored as being "mild" for the 3 safety parameters. However, there were 2 patients (1 Acticin™ and 1 Retin-A™) who were scored as "severe" for burning/stinging and 4 patients (1 Acticin™ and 3 Retin-A™) who were scored as "severe" for tightness. As with erythema, peeling, and dryness, the percent of patients experiencing the symptoms of burning/stinging, itching, or tightness peaked at 7 days and began to decrease by day 28.

2) It is recommended that these results be analyzed by age, gender, and race.

Adverse Reactions:

According to the sponsor, there were 2 patients (Retin-A™) who were withdrawn from the study due to adverse events. These include Patient who was withdrawn from the study after 8 weeks because of persistent irritation (erythema) and peeling even after decreasing the application of medication to every-other-day and Patient (listed in Tables 5 and 6 as "Concurrent Illness") who was withdrawn from the study because of the diagnosis of breast cancer. In addition, Patient (Retin-A™), classified by the sponsor as "Non-Compliant," withdrew from the study at Day 28 due to facial irritation/dryness. Thus, there were 2 patients who withdrew from the study due to an adverse event related to the skin, both of whom received Retin-A™ treatment. There were no patients who received Acticin™ or vehicle who withdrew from the study due to an adverse event.

All of the reported adverse events are presented in Table 14.

Table 14 - - Adverse Events (expressed as number of patients and percent of patients)

Event	Acticin™ N=71		Retin-A™ N=74		Vehicle N=70	
	N	%	N	%	N	%
Rash*	**8**	**(11%)**	**9**	**(12%)**	**2**	**(3%)**
Headache	5	(7%)	1	(1%)	2	(3%)
Allergic Reaction	4	(6%)	3	(4%)	3	(4%)
Dysmenorrhea	3	(4%)	2	(3%)	2	(3%)
Flu Syndrome	3	(4%)	4	(5%)	6	(9%)
Pain‡	**3**	**(4%)**	**3**	**(4%)**	**0**	
Path. Fracture	2	(3%)	0		2	(3%)
Paresthesia.§	**2**	**(3%)**	**1**	**(1%)**	**0**	
Sinusitis	2	(3%)	0		1	(1%)
Abdominal Pain	1	(1%)	0		0	
Accidental Injury	1	(1%)	0		0	
Back Pain	1	(1%)	0		0	
Cyst	1	(1%)	0		0	
Myalgia	1	(1%)	0		0	
Insomnia	1	(1%)	0		0	
Bronchitis	1	(1%)	0		0	
Cough Increased	1	(1%)	0		0	
Pharyngitis	1	(1%)	2	(3%)	0	
Rhinitis	1	(1%)	1	(1%)	3	(4%)
Dry Skin	**1**	**(1%)**	**6**	**(8%)**	**0**	
Eczema	1	(1%)	0		0	
Exfoliative Dermatitis†	**1**	**(1%)**	**3**	**(4%)**	**0**	
Carcinoma	0		1	(1%)	0	
Fever	0		1	(1%)	0	
Infection	0		2	(3%)	1	(1%)

Mouth Ulceration	0	1	(1%)	0	
Lymphadenopathy	0	0		1	(1%)
Arthralgia	0	1	(1%)	0	
Depression	0	1	(1%)	1	(1%)
Pruritus	0	1	(1%)	0	
Conjunctivitis	0	1	(1%)	0	
Otitis media	0	1	(1%)	1	(1%)
Pyelonephritis	0	1	(1%)	0	
Menstrual Disorder	0	0		1	(1%)
Vaginitis	0	0		1	(1%)

* Includes erythema and facial irritation (unspecified)
‡ Includes burning
§ Includes tightness and stinging
† Includes peeling

The majority of the adverse reactions related to the skin were scored by the physician and/or the patient as moderate or severe. There were 13 patients who were felt to have had a severe skin reaction as determined by **either the physician or the patient. (It should be noted that if the physician evaluation of intensity was moderate, but the evaluation by the patient was severe, then this reviewer classified the adverse event as severe).** Of these, 8 were in the Acticin™ treatment group, 4 in the Retin-A™ treatment group, and 1 in the vehicle group. These 13 patients included 9 females and 4 males. There were 10 Acticin™ patients, 10 Retin-A™ patients, and 1 vehicle patient who required reduction of their medication to every-other-day because of erythema, dryness, peeling, etc. In addition, 2 patients (1 Acticin™ and 1 Retin-A™) received a moisturizer due to facial "tightness" and skin dryness, respectively.

Reviewer's Comment:

1) It is recommended that the patients experiencing an adverse event related to the skin be analyzed by age, gender, and race. For example, of the 13 patients who experienced a severe adverse event related to the skin, there appears to be a slight excess of females (70% female vs. 30% male) in comparison to their proportion enrolled in the study (55% female vs. 45% male).

2) Because racial demographics are pending, adverse events specifically related to pigment have not been determined.

8.1.1.5 Reviewer's Conclusions Regarding Efficacy Data

This study was unable to demonstrate a statistically significant difference between Acticin™ gel 0.025%, Retin-A™ gel 0.025%, and vehicle at Day 84 (end of study) as measured by percent reduction of lesion counts from Baseline for noninflammatory, inflammatory, or total lesions. Similarly, this study failed to demonstrate a statistically significant difference between Acticin™, Retin-A™, and vehicle for mean counts of noninflammatory and inflammatory lesions at any evaluation timepoint during the study. The lack of statistical significance may be the result of the large variability seen in the lesion counts and/or an inadequate sample size based on the anticipated efficacy of Acticin™. Although the sponsor was able to demonstrate a statistical difference between Acticin™ and vehicle for noninflammatory and inflammatory lesions by categorizing the percent change from Baseline, this is considered a less than optimal method of analysis because of the loss of primary information. The physician global evaluation at Day 84 showed Acticin™ (and Retin-A™) to be statistically significantly different from vehicle. Unfortunately, the definitions of the various categories (Excellent, Good, and Fair) had not been stated before the study began. In any case, I would consider the physician global evaluation to be confirmatory rather than sufficient by itself to demonstrate efficacy.

This study failed to demonstrate equivalence between Acticin™ gel 0.025% and Retin-A™ gel 0.025% in the mean percent reduction of noninflammatory lesions and total lesions based on the lower bound of Acticin™ gel being greater than 20% outside the 95% confidence interval of Retin-A™ gel. This is the preferred analysis. An alternative analysis using 2 one-sided t-tests of mean percent change of total lesions, provided by the sponsor, also showed that the lower bound of the Acticin™ gel was greater than 20% below the Retin-A™ gel mean.

8.1.2 Study #2

Title: A Double-Blind, Parallel, Comparative Efficacy and Safety Study of a Topical Retinoic Acid Gel Formulation and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris (Protocol PDC 004-015) (Date completed 1/13/93)

Investigators: Michael Jarratt, M.D.
Pharmaco Health Research Center
Austin, TX

Terry M. Jones, M.D.
V.I.P. Research, Inc.
Bryan, TX

Reviewer's Comment:
It should be noted that Dr. Jarratt was an investigator in Study #1.

8.1.2.1 **Objective/Rationale:**

The objective of this study was to compare the safety and efficacy of Acticin™ gel 0.025% (tretinoin gel 0.025%) to its vehicle in the treatment of mild to moderate acne vulgaris.

8.1.2.2 **Study Design:**

This was a study involving 2 centers using a randomized, double-blind, vehicle-controlled, parallel group study design for 12 weeks.

8.1.2.3 **PROTOCOL**

8.1.2.3.1 **Population/Procedures**

See Section 8.0 for protocol and endpoints

A total of 180 patients were enrolled at 2 centers and were randomized to either vehicle or active treatment. As in Study #1, patients were instructed to apply about one-half inch of gel to the entire face every evening for 12 weeks, after having first washed the face with provided soap and waiting 20-30 minutes. Patients were to refrain form using moisturizers, aftershave lotions, astringents, and perfumed toiletries, but could continue his/her regular topical acne medication on other areas of the body. The patients were to be protected from the sun by using protective clothing and a hat outdoors. Follow-up visits were at days 28, 56, and 84.

8.1.2.4 RESULTS

8.1.2.4.1 Population Enrolled/Analyzed

91 patients were enrolled in the Acticin™ treatment group and 89 in the vehicle group (see Table 15).

Table 15 - - Patients Enrolled (by treatment group)

Treatment Group	# of Patients Enrolled
Acticin™	91
Vehicle	89
TOTAL	180

The demographics of all enrolled patients are shown in Table 16.

Table 16 - - Demographics of Enrolled Patients

	Acticin™	Vehicle
Total	91	89
Male	49 (54%)	50 (56%)
Female	42 (46%)	39 (44%)
Age (yrs)*	19.7 ± 5.2 Range:	20.2 ± 6.1 Range:

* Age expressed as mean years ± standard deviation

Reviewer's Comment:

As with Study 004-003, race was not included as a demographic factor. The sponsor has been requested to submit this information.

The number of evaluable patients (according to the sponsor's criteria under Section 8.0) per investigator and treatment group are shown in Tables 17 and 18.

Table 17 - - Evaluable Patients (by investigator)

Investigator	Treatment Group	# of Patients Enrolled	# Evaluable for Efficacy	% of Total Evaluable Patients (N = 168)
Jarratt	Acticin™ Vehicle	45 45	42 40	
Total		90	82	49%
Jones	Acticin™ Vehicle	46 44	44 42	
Total		90	86	51%
	TOTAL	180	168	

Table 18 - - Evaluable Patients (by treatment group)

Treatment Group	# of Patients Enrolled	# Evaluable for Efficacy	# Unevaluable for Efficacy	% Unevaluable for Efficacy
Acticin™	91	86	5	5.6%
Vehicle	89	82	7	7.9%
TOTAL	180	168	12	6.7%

The reasons for unevaluable patients are shown in Table 19. According to the sponsor, there were 8 patients (3 Acticin™ and 5 vehicle) who did not complete the study. In addition, 4 completed patients (2 Acticin™ and 2 vehicle) were excluded from efficacy analysis because of a window violation at Day 84.

Table 19

Summary of Reasons for Unevaluable Patients†

	Acticin™	Vehicle	Total
Lost to Follow-Up	1	4	5
Personal	0	1	1
Other	2‡	0	2
Window Violation*	2	2	4
TOTAL	5	7	12

† From vol. 1.15, p. 1753

‡ Includes 1 patient unable to continue because of a new job and 1 patient who moved out-of-state

* Includes 1 patient (Acticin™) who is considered an early window violation rather than lost to follow-up, i.e., the patient completed 72 days of the study rather than 84

Table 20

Unevaluable Patients (by patient number)

Reason	Patient Number
Lost to Follow-Up	
Personal	
Other	
Window Violation	

* Patients without a post-Baseline follow-up visit: (vehicle), (vehicle), (vehicle), (Acticin™), (Acticin™)

Five additional patients (2 Acticin™ and 3 vehicle) violated protocol entrance criteria, but were considered evaluable and included in the statistical analyses. These include 2 Acticin™ patients who did not have parental consent until Day 28, 1 vehicle patient who had participated in a headache research study 5 weeks prior to enrollment instead of the minimum

6 weeks, and 2 vehicle patients who used topical anti-acne products within 2 weeks of starting the study. Three patients (all Acticin™) were allowed to use a moisturizer concomitant with or prior to reducing the dosing frequency of the medication (the protocol stated that the dosing frequency should be reduced prior to using a facial moisturizer for dryness, peeling, or tightness). These patients were considered evaluable. One Acticin™ patient and 1 vehicle patient each received antibiotics during the study. Patient received erythromycin for 5 days near the end of the study; patient received trimethoprim/sulfa for 13 days mid-way through the study.

Reviewer's Comment:

1) It should be noted that 3 patients in study PDC 004-015 had been previous participants in study PDC 004-003. These include patients (Acticin™), (Acticin™), and (vehicle). These patients correspond to patients in study PDC (vehicle), (Retin-A™), and (vehicle), respectively.

2) It is unlikely that the use of erythromycin for 5 days in Patient Acticin™) would bias the results of the study in favor of Acticin™.

*3) As noted in Table 20, there are 5 patients (2 Acticin™ and 3 vehicle) who did not have a post-Baseline follow-up visit. In this study, as in Study #1, where **change from Baseline** is an efficacy variable, it is preferred that the intent-to-treat population be **modified to exclude** those patients who did not have at least 1 post-Baseline follow-up visit. These patients are fairly-well distributed between the 2 treatment groups and would not be expected to bias the results.*

8.1.2.4.2 Efficacy Endpoint Outcomes

The following results are for evaluable patients. Patients were considered evaluable for efficacy if he/she had not violated the protocol and attended each study visit within 7 days of the scheduled visit on days 28, 56, and 84. The endpoint of the study was Day 84.

Efficacy was analyzed for the mean percent change from Baseline at Day 84 for noninflammatory, inflammatory, and total lesion counts for all evaluable patients (as defined by the sponsor). These results are shown in Table 21.

Table 21 - - Mean % Change from Baseline†

	Baseline	Day 84	% Reduction	*p (day 84)
Noninflammatory Lesions				
Acticin™	57.3 ± 29.5	40.3 ± 37.2	33.2% ± 31.2	0.1234
Vehicle	60.3 ± 26.5	49.2 ± 39.6	24% ± 37.4	
Inflammatory Lesions				
Acticin™	16.2 ± 5.1	10.3 ± 9.8	38.1% ± 41.5	0.0648
Vehicle	16.9 ± 6.4	14 ± 12.4	23.3% ± 53.5	
Total Lesions				
Acticin™	73.5 ± 29.8	50.6 ± 42	34.6% ± 29.7	0.0576
Vehicle	77.2 ± 29.2	63.2 ± 47	23.5% ± 36.5	
Number of Patients				
Acticin™	86	86		
Vehicle	82	82		

† From vol. 1.16, pp. 1952, 1970, and 1946
* Analysis performed on rank transformed data

Reviewer's Comment:

1) The mean lesion counts appear comparable at Baseline. In contrast to study 004-003, there does not appear to be an investigator effect at Baseline (data not shown). However, it should be noted that the mean Baseline counts of study 004-015 are much lower than those of study 004-003.

2) These results indicate that at Day 84 (end of treatment), there was no statistical difference between the Acticin™ and vehicle treatment groups in regard to percent change from Baseline for noninflammatory, inflammatory, and total lesion counts. It should be noted that the mean percent change from Baseline for the Acticin™ treatment group is only approximately 35% for each type of lesion, which is lower than anticipated by the sponsor and lower than that found in Study #1.

It should also be noted that although a treatment-by-investigator interaction was not found at day 84 for percent change from Baseline, nonetheless it appears that the 2 investigators have very different study results. For example, for noninflammatory lesions, Dr. Jarratt's patients showed a mean percent reduction of 32.5% for Acticin™ vs. 16.8% for vehicle whereas Dr. Jones' patients showed a 33.8% mean percent reduction for Acticin™ vs. 30.8% mean percent reduction for the vehicle. For a listing of mean percent reduction of lesion counts by investigator, see Appendix 2.

3) The sponsor should be asked to comment on the necessity of using rank transformed data for the analyses.

Table 22 - - Mean Lesion Counts, Combined Investigators*

	Baseline	Day 28	Day 56	Day 84
Noninflammatory Lesions				
Acticin™	57 (n=86)	48 (n=88)	43 (n=85)	40 (n=86)
Vehicle	60 (n=82)	54 (n=84)	52 (n=84)	49 (n=82)
Inflammatory Lesions				
Acticin™	16	13	12	10
Vehicle	17	15	13	14

* Evaluable patients only, observed at each visit

Reviewer's Comment:

For both types of lesions, at Day 84, there was not a statistical difference between the 2 treatment groups in the observed change in number of lesions. It should be noted that ***for noninflammatory lesions, the treatment-by-investigator effect was statistically significant (p=0.0253), with the 2 investigators having opposite results.*** *When both investigators are combined, for noninflammatory lesions, both the Acticin™ and vehicle treatment groups showed improvement throughout the study, with the greatest improvement seen in the first 28 days. For inflammatory lesions, the change in the number of lesions over the course of the study was small. As with study 004-003, the clinical significance of a mean change of 6 papules/pustules over a 12-week period is unclear.*

The results were further analyzed by categorizing the data (see Section 8.0, Statistical Considerations). These results are summarized in Table 23. Results are shown for Day 84 only.

Table 23 - Results at Day 84, Categorized

	Worse/No change	1-25% Improvement	26-50% Improvement	51-100% Improvement	p value
Noninflammatory Lesions					
Acticin™	15 (17%)	15 (17%)	25 (29%)	**31 (36%)**	p=0.092
Vehicle	22 (27%)	16 (20%)	21 (26%)	**23 (28%)**	
Inflammatory Lesions					
Acticin™	13 (15%)	15 (17%)	17 (20%)	**41 (48%)**	p=0.088
Vehicle	21 (27%)	12 (15%)	20 (24%)	**29 (35%)**	
Total Lesions					
Acticin™	12 (14%)	13 (15%)	30 (35%)	**31 (36%)**	p=0.009
Vehicle	23 (28%)	15 (18%)	24 (29%)	**20 (24%)**	

Reviewer's Comment:

These results by categorization indicate that for both noninflammatory and inflammatory lesions there is not a statistically significant difference between the Acticin™ and vehicle treatment groups at day 84.

An analysis using dichotomous grouping of this data was not submitted by the sponsor.

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The results of the physician global evaluations for evaluable patients at Day 84 are shown in Table 24.

Table 24 - - Physician Global Evaluations, By Individual Investigator and Combined Investigators, Day 84

	Excellent	Good	Fair	No change	Worse	N
Jarratt						
Acticin™	4 (10%)	17 (40%)	10 (24%)	7 (17%)	4 (10%)	42
Vehicle	3 (8%)	10 (25%)	9 (23%)	9 (23%)	9 (23%)	40
Jones						
Acticin™	8 (18%)	16 (36%)	6 (14%)	13 (30%)	1 (2%)	44
Vehicle	4 (10%)	14 (33%)	5 (12%)	19 (45%)	0	42
Combined investigators						
Acticin™	12 (14%)	33 (38%)	16 (19%)	20 (23%)	5 (6%)	86
Vehicle	7 (9%)	24 (30%)	14 (17%)	28 (34%)	9 (11%)	82

Reviewer's Comment:

As with Study #1, definitions of the various categories of improvement were not defined prior to the study. When the results of both investigators are combined, there is a statistical difference between the Acticin™ and vehicle treatment groups ($p=0.02$).

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ON ORIGINAL

Summary of p values - Acticin™ vs. vehicle

	Evaluable/Observed	ITT/Observed	Evaluable/LOCF	ITT/LOCF
Lesion counts: Mean % reduction from baseline, Day 84				
Noninflammatory	NS	NS		
Inflammatory	NS	0.0422		
Total lesions	NS	0.0448		
Categorical Analysis, Day 84				
Noninflammatory	NS	NS		
Inflammatory	NS	NS		
Total lesions	0.0092	0.0061		
Physician Global, Day 84	0.0208	0.0160		

8.1.2.4.3 Safety Outcomes

Investigator and Patient Evaluations:

Erythema, peeling, and dryness were evaluated at each visit by the investigator on a scale of 0 (none) to 3 (severe). The percent of patients exhibiting the given parameter at each visit (regardless of the severity) is shown in Table 25.

Table 25 - - Investigator's Evaluation of Erythema, Peeling, and Dryness (expressed as % of patients)

	Acticin™	Vehicle
Erythema		
Baseline	15% (14/91)	15% (13/89)
Day 28	37% (31/88)	27% (23/86)
Day 56	33% (30/87)	24% (20/84)
Day 84	*32% (28/88)	17% (14/84)
Peeling		
Baseline	0% (0/91)	0% (0/89)
Day 28	*16% (14/88)	3% (3/86)
Day 56	*12% (10/87)	2% (2/84)
Day 84	9% (8/88)	4% (3/84)
Dryness		
Baseline	12% (11/91)	17% (15/89)
Day 28	33% (29/88)	23% (20/86)
Day 56	*36% (31/87)	19% (16/84)
Day 84	26% (23/88)	19% (16/84)

* Statistically different from vehicle

Reviewer's Comment:

Overall, approximately 35% of the Acticin™ patients experienced erythema or dryness. The percent of patients affected remained increased even at day 84. For all 3 safety parameters, the majority of patients were scored as "mild." There were no patients who were scored as "severe."

Safety parameters evaluated by the patient were burning/stinging, itching, and tightness. These results are shown in Table 26.

Table 26 - - Patient Evaluation of Burning/Stinging, Itching, and Tightness (expressed as % of patients)

	Acticin™	Vehicle
Burning/Stinging		
Baseline	0% (0/91)	1% (1/89)
Day 28	*25% (22/88)	10% (9/86)
Day 56	10% (9/88)	2% (2/85)
Day 84	*13% (11/88)	1% (1/84)
Itching		
Baseline	4% (4/91)	3% (3/89)
Day 28	9% (8/88)	6% (5/86)
Day 56	9% (8/88)	6% (5/85)
Day 84	6% (5/88)	5% (4/84)
Tightness		
Baseline	5% (5/91)	3% (3/89)
Day 28	*36% (32/88)	14% (12/86)
Day 56	24% (21/88)	11% (9/85)
Day 84	28% (25/88)	14% (12/84)

* Statistically different from vehicle

Reviewer's Comment:

Tightness was reported by approximately 35% of the Acticin™ patients by Day 28 and remained increased at 28% at Day 84 (although this was not statistically different from vehicle; p=0.06). Burning/stinging was reported by approximately 25% of the Acticin™ patients by Day 28 and remained increased at 13% at Day 84 (statistically different from vehicle). Itching seemed to affect fewer patients (overall, approximately 10%), and the 2 treatment groups were not statistically different from each other at any time point. For all 3 parameters, the majority of patients reported their symptom as "mild." There were no reported scores of "severe."

Adverse Reactions:

There were no patients in either treatment group who discontinued therapy due to an adverse event. All of the reported adverse reactions are listed in Table 27.

Table 27 - - Adverse Events (expressed as number of patients and percent of patients)

Event	Acticin™ N=91		Vehicle N=89	
	N	%	N	%
Flu syndrome	12	(13%)	10	(11%)
Pharyngitis	10	(11%)	5	(6%)
Headache	7	(8%)	3	(3%)
Bone Fracture	4	(4%)	0	
Dry skin	**4**	**(4%)**	**2**	**(2%)**
Diarrhea	3	(3%)	1	(1%)
Rhinitis	3	(3%)	7	(8%)
Pain‡	**2**	**(2%)**	**1**	**(1%)**
Paresthesia§	**2**	**(2%)**	**1**	**(1%)**
Cough	2	(2%)	2	(2%)
Exfoliative dermatitis†	**2**	**(2%)**	**0**	
Rash*	**2**	**(2%)**	**2**	**(2%)**
Dysmenorrhea	2	(2%)	0	
Asthenia (fatigue)	1	(1%)	0	
Fever	1	(1%)	1	(1%)
Accidental injury	1	(1%)	1	(1%)
Back pain	1	(1%)	1	(1%)
Nausea	1	(1%)	2	(2%)
Vomiting	1	(1%)	1	(1%)
Facial paralysis (Bell's palsy)	1	(1%)	0	
Bronchitis	1	(1%)	0	
Pleurisy	1	(1%)	0	
Sinusitis	1	(1%)	0	
Nail disease (ingrown nail)	1	(1%)	0	
Pregnancy	1	(1%)	0	
Uterine disease	1	(1%)	0	
Abdominal pain	0		2	(2%)
Migraine	0		1	(1%)
GI disease	0		1	(1%)
Aphthous stomatitis	0		1	(1%)
Pneumonia	0		1	(1%)
Acne	**0**		**1**	**(1%)**
Pruritus	**0**		**1**	**(1%)**
Conjunctivitis	0		1	(1%)

‡ Includes burning
§ Includes stinging and tightness
† Includes peeling
* Includes erythema

The majority of the adverse reactions related to the skin were scored by the physician as moderate. However, two patients were scored as having had a severe reaction related to the skin (peeling, burning, stinging, erythema); both of these patients were in the Acticin™ treatment group and both were females. There were 4 Acticin™ patients and 2 vehicle patients who required decreasing the application of medication to every-other-day. In addition, 1 Acticin™ patient required temporarily discontinuing the medication followed by the use of a moisturizer.

Reviewer's Comment:

1) It should be noted that the number of patients in the Acticin™ treatment group who were reported as having experienced an adverse event related to the skin in this study is lower than that reported in Study #1 (5.5% vs. 18%).

2) All of the patients who experienced an adverse effect related to the skin were females, clearly in excess of the proportion enrolled in the study. As with Study #1, it is recommended that the patients experiencing an adverse event related to the skin be statistically analyzed by age, gender, and race. It might be useful to compare the results of the gender analysis of adverse events to the results of the gender analysis of the physician and patient skin safety parameters to determine if gender effect is a consistent finding.

3) As with Study #1, racial demographics are pending in order to evaluate the occurrence of adverse events specifically related to pigmentation.

8.1.2.5 Reviewer's Conclusions Regarding Efficacy Data

This study was unable to demonstrate a statistically significant difference between Acticin™ gel 0.025% and vehicle in mean percent reduction of noninflammatory, inflammatory, or total lesions at Day 84 (end of study). Similarly, there was not a statistical difference between Acticin™ and vehicle in the change in the number of noninflammatory or inflammatory lesions at Day 84. Furthermore, when the percent change from Baseline was categorized, a less desirable method of analysis, there was no statistically significant difference between the Acticin™ and vehicle groups for noninflammatory or inflammatory lesions. The physician global evaluation showed Acticin™ to be statistically significantly different from vehicle. However, as noted for Study #1, the definitions of "Excellent," "Good," and "Fair" had not been stated before the study had begun. In addition, as with Study #1, I would consider the physician global evaluation as confirmatory but not sufficient by itself to demonstrate efficacy.

9. OVERVIEW OF EFFICACY

In support of this NDA, the sponsor has performed 2 clinical trials. The first of these, Study #1, was a 3-arm study in which Acticin™ gel 0.025% was compared to Retin-A™ gel 0.025% (the innovator drug) and vehicle in the treatment of mild to moderate acne vulgaris. The second study, Study #2, was a 2-arm study in which Acticin™ gel 0.025% was compared to vehicle. It should be noted that Study #1 and Study #2 have a common investigator (Dr. Jarratt) and, therefore, would not necessarily be considered independent trials. This is of particular concern since Dr. Jarratt contributed the majority of patients to Study #1 and approximately 50% of the patients to Study #2.

If Acticin™ gel 0.025% were to be considered a line extension of Retin-A™ gel 0.025%, then the accepted criteria for approval would be 1 study showing that Acticin™ is superior to the vehicle and equivalent to Retin-A™ gel. Statistical equivalence was determined by calculating the 95% confidence interval of the difference between the mean percent reduction of each lesion type of Acticin™ and Retin-A™. From the results of Study #1, the lower bound of the Acticin™ treatment group was greater than 20% of the mean percent reduction of Retin-A™ for both noninflammatory and total lesions. Based on this method, Acticin™ gel 0.025% **would not** be considered statistically equivalent to Retin-A™ gel 0.025%. In addition, when the results were analyzed for equivalence using the method of 2 one-sided t-tests, as submitted by the sponsor, the lower confidence bound on the Acticin™ treatment group for mean percent change of total lesions was greater than 20% of the Retin-A™ treatment group. Even though this is considered a less stringent method of analysis for equivalence, based on these results, Acticin™ gel 0.025% still would not be considered statistically equivalent to Retin-A™ gel 0.025%. In regard to efficacy, for evaluable patients, Study #1 was unable to demonstrate a statistically significant difference between Acticin™ gel and vehicle in the mean percent reduction of noninflammatory, inflammatory, or total lesions at Day 84 (end of study). When these results were reanalyzed by categorizing the data by percent reduction from Baseline, then Acticin™ gel was statistically different from vehicle at Day 84 for noninflammatory lesions and total lesions. In my opinion, categorizing the data results in loss of information and would not be considered a primary method of analysis in support of demonstrating efficacy. Finally, the physician global evaluation showed that the Acticin™ treatment group was statistically different from the vehicle. However, as previously noted, the categories of "Excellent," "Good," and "Fair" had not been defined before the study had been initiated. Moreover, in my opinion, the physician global evaluation should be considered **in conjunction with** the results of the mean percent reduction of lesion counts and would not be considered sufficient by itself to demonstrate efficacy. In summary, this study was unable to demonstrate equivalence between Acticin™ gel 0.025% and Retin-A™ gel 0.025%. At best, marginal efficacy was shown. Therefore, Acticin™ gel 0.025% does not meet the criteria for approval based on its being a line extension of Retin-A™ gel 0.025%.

Alternatively, if Acticin™ were to be considered a new drug without reference to Retin-A™, then efficacy would need to be demonstrated in 2 well-controlled, independent trials. The results of Study #2 were unable to demonstrate a statistical difference between Acticin™ gel and vehicle in mean percent reduction of noninflammatory, inflammatory, or

total lesion counts at Day 84 (end of study) for evaluable patients. Even when these results were reanalyzed by categorizing the data by percent reduction from Baseline, the sponsor was unable to demonstrate a statistically significant difference between the Acticin™ gel and vehicle treatment groups for noninflammatory or inflammatory lesions (although it was significant for total lesions). The physician global evaluation showed a statistically significant difference between Acticin™ gel and vehicle at Day 84. In summary, neither Study #1 nor Study #2 demonstrated efficacy in comparison to vehicle when the accepted primary efficacy variables of mean percent reduction of noninflammatory, inflammatory, and total lesions were analyzed in evaluable patients. In addition, as noted above, this study had an investigator who was common to Study #1, and thus the independence of these 2 trials would be questioned. Based on these results, Acticin™ gel 0.025% does not meet the criteria of approval based on the demonstration of efficacy in 2 well-controlled, independent clinical trials.

10. OVERVIEW OF SAFETY

The major safety issues of Acticin™ gel 0.025% are those of tretinoin and the new excipient, polyolprepolymer-2, which has not yet been approved as a constituent of any prescription topical drug products. As expected with a drug product containing tretinoin, a significant percent of patients using Acticin™ gel 0.025% during the clinical trials experienced skin irritation as evidenced by the physician evaluation of safety parameters (erythema, peeling, and dryness), the patient evaluation of safety parameters (burning/stinging, itching, and tightness), and the reports of adverse events related to the skin. For Study #1, this was as high as 35% of patients who experienced erythema or dryness and 43% who experienced burning/stinging or tightness. Results from Study #2 were similar in that approximately 35% of patients experienced erythema or dryness, and 36% of patients experienced tightness. These local effects tended to occur more frequently in the first 28 days of treatment. However, the results of Study 004-015 showed that erythema remained statistically significantly different from vehicle at Day 84 (32% vs. 17%) as well as burning/stinging (13% vs. 1%). The majority of patients were scored as "mild," although there was an occasional Acticin™-treated patient who had a "severe" score. However, the majority of those patients who were scored as "severe" were in the Retin-A™ treatment group. The reports of adverse events related to the skin were usually moderate or severe, and were treated by temporarily reducing the frequency of medication to every-other-night and/or the application of a moisturizer. Of the patients who received Acticin™ gel 0.025% in the 2 clinical trials, there were no patients who withdrew from the studies due to an adverse event related to the skin.

Hypo- or hyperpigmentation was not recorded as an adverse event for any patient. However, the racial demographics of the study population is pending. It is possible that not enough patients with darker skin were enrolled in order to detect adverse events specifically related to primary pigment changes and/or as a response to inflammation. In addition, analysis of adverse events by gender would be helpful.

Based on the results of the human pharmacokinetic study of Acticin™ gel 0.025% (the review of which by the Division of Biopharmaceutics is pending), there were no statistically significant changes in the plasma levels of tretinoin or isotretinoin relative to Baseline as measured by AUC, C_{max}, and C_{ss} except for a slight, but statistically significant, increase in tretinoin C_{ss} at Day 7 which resolved by Day 14. In addition, under the conditions of the study, there were no statistical differences between Acticin™ gel and Retin-A™ gel in the plasma pharmacokinetic parameters measured. The results of this study are supported by an *in vitro* study using Franz chambers with human cadaver skin in which the penetration of Acticin™ gel was not any greater than that of Retin-A™ gel. Under the conditions of that study, at 48 hours (end of the study), it was estimated that Acticin™ gel had less than 1% penetration into the epidermis, dermis, and receptor fluid (although complete recovery was not obtained) (see Pharmacology review for additional details).

The issue of teratogenicity was reviewed in the Pharmacology review by Dr. Hilary Sheevers. A segment II teratology study was conducted in New Zealand white female rabbits with a single dose level of Acticin™ gel 0.025% and Retin-A™ gel 0.025%. Both the Acticin™ gel and Retin-A™ gel groups had a higher incidence of domed head, although only the Retin-A™ gel group was statistically different from the control groups. In addition, both the Acticin™ gel and Retin-A™ gel groups had a statistically significant increased frequency of hydrocephaly. Tretinoin plasma levels were not reported. Dr. Sheevers concluded that Acticin™ gel 0.025% is a definite teratogen and a possible feto-toxicant in rabbits. It was recommended that Acticin™ gel 0.025% be labeled as pregnancy category C.

The human use safety studies of polyolprepolymer-2 showed that it was non-irritating and without evidence of contact sensitization. The sponsor performed 2 studies of phototoxicity and photoallergy potential. The first study did not show evidence of phototoxicity or photoallergy potential; the results of the second study appear to be questionable because of an increased number of subjects who showed mild erythema to distilled water. However, because, according to the sponsor, polyolprepolymer-2 does not show significant absorption in the UV and/or visible spectrum (see resubmission volume 3, p.7-0002), it is unlikely to be a phototoxic or photoallergic compound. The preclinical studies were reviewed by Dr. Sheevers. *In vitro* percutaneous absorption studies using human cadaver skin showed low absorption. A dermal teratology pilot study was performed in rabbits using high doses of polyolprepolymer-2 (1000 and 2000mg/kg/day). All fetuses appeared normal by external examination. It was concluded that, under the conditions of the study, polyolprepolymer-2 was not teratogenic. **A one-species dermal carcinogenicity study using the final formulation of Acticin™ gel 0.025% was recommended because of the presence of polyolprepolymer-2** which had not been previously studied in this manner.

10.2.3 Special Studies

Acticin™ gel 0.025%:

Irritation

Two studies of irritation were performed which utilized the final formulation of Acticin™ gel 0.025%. These include a primary irritation study (one single 24-hour application) and a 5-day cumulative irritation study. A standard 21-day cumulative irritancy study was not performed.

Study Title: Evaluation of Primary Irritation Potential in Humans (Single 24-Hour Application) (Protocol PDC 004-005) - Report Number 90-2892-70

Investigator: Lawrence A. Rheins, Ph.D.
Hill Top Research, Inc.
Miamiville, Ohio

Method: This was a study to evaluate the primary irritancy of the following formulations:

Acticin™ gel 0.025% (PDT 004-002)
Retin-A™ gel 0.025%
A prototype tretinoin cream 0.025% (#1)
A prototype tretinoin cream with xanthan gum 0.025% (#2)
Acticin™ gel vehicle (PDT 004-006)

Eighteen subjects (3 males/15 females; age range years) were enrolled. Each test material was evaluated under occlusive and non-occlusive conditions for each subject. For the occluded sites, 200 microliters of each test material was applied to a 25mm Hill Top Chamber containing a Webril pad; this was then applied to the paraspinal region of the back of each subject. For the non-occluded sites, the test material was applied directly to the paraspinal skin of the back of each subject; this was then covered with a gauze pad which was held in place with tape at the corners of the pad. Each patch remained in place for 24 hours. Evaluations were performed within 30 minutes after removal of the patch and at 24 hours after removal of the patch. Scoring was on a scale of 0 = no evidence of irritation to 7=strong reaction spreading beyond the test site. In addition, the appearance of the skin was scored with letters which were then transformed to a numerical score. The reported total score for each patient consists of the irritation score plus the "skin appearance" score at the immediate reading and 24 hours later.

Results: Using the scoring system described above, the sponsor reports the following mean irritation scores:

	Occlusion	Non-Occlusion
Acticin™ gel 0.025%	0.83	0.06
Retin-A™ gel 0.025%	1.44	0
Acticin™ gel vehicle	0.78	0
Tretinoin cream 0.025% (#1)	0.33	0
Tretinoin cream 0.025% (#2)	0.61	0

Reviewer's Comment:

Examination of the raw data shows that for Acticin™ gel 0.025% under occlusion, 2 subjects at the immediate reading and 1 subject at the 24-hour reading had scores of 2 (definite erythema, readily visible; or minimal edema; or minimal papular response). There were no subjects with a score greater than 2. The majority of subjects at the 24-hour reading had a score of 0. For the Acticin™ gel vehicle under occlusion, the majority of subjects had a score of 0 or 1 at the immediate reading except for 1 subject who had a score of 4 (definite edema). For this subject, the 24-hour reading had decreased to a score of 2. Of interest, readings on this subject for the complete formulation (i.e., containing tretinoin) showed only a score of 1 at the immediate and 24-hour readings. For Retin-A™ gel 0.025% under occlusion, a greater number of subjects showed a score of 1 or 2 at the immediate reading in comparison to Acticin™ gel. However, by 24 hours, the readings of these subjects had decreased to 0 or 1. Both of the tretinoin-containing creams showed low irritancy scores.

Presentation of the mean scores in relation to the time of scoring, for evaluable patients only (2 patients were unevaluable due to loss of the Hill Top Chamber for some of the test substances), and excluding the numerical transformation of the "appearance" of the skin is shown below:

	Occlusion		Non-Occlusion	
	Immediate reading	24 hours	Immediate reading	24 hours
Acticin™ gel 0.025%	0.59	0.18	0.06	0
Retin-A™ gel 0.025%	1.0	0.41	0	0
Acticin™ gel vehicle	0.56	0.11	0	0
Tretinoin cream 0.025% (#1)	0.35	0	0	0
Tretinoin cream 0.025% (#2)	0.44	0.11	0	0

In summary, although occlusive conditions resulted in mild irritation, this tended to resolve by 24 hours later. Non-occlusive conditions, as would be expected in actual use, resulted in virtually no irritation for all formulations tested after a single 24-hour application.

Study Title: Evaluation of Primary Irritation Potential in Humans (Three 24-Hour Applications) (Protocol PDC 004-007) - Report 91-1074-70

Investigator: Lawrence A. Rheins, Ph.D.
Hill Top Research, Inc.
Miamiville, Ohio

Method: This was a study to evaluate the irritancy of the following formulations:

Acticin™ gel 0.025% (PDT 004-002)
Retin-A™ gel 0.025%
Retin-A™ cream 0.025%
A prototype tretinoin cream 0.025%
Retin-A™ cream 0.05%
A prototype tretinoin cream 0.05%
Retin-A™ cream 0.1%
A prototype tretinoin cream 0.1% (#1)
A prototype tretinoin cream 0.1% (#2)
A prototype tretinoin cream 0.1% (#3)

Eighteen subjects (18 females; age range years) were enrolled. Two hundred microliters of each test material was applied to a 25mm Hill Top Chamber containing a Webril pad; this was then applied to the paraspinal region of the back of each subject. Each patch remained in place for 24 hours followed by a "rest" of 24 hours prior to the next application. A total of 3 applications were made. Evaluations were performed within 30 minutes of removing the patch and 24 hours after removal of the patch; a total of 6 scorings were performed. The scoring scales used in this study are the same as for the primary irritancy study described above. For each test material, all 6 readings were summed and then averaged for all subjects. These are reported as the group mean score.

Results: The sponsor reports the following mean scores:

Acticin™ gel 0.025% (PDT 004-002)	1.6
Retin-A™ gel 0.025%	15.0
Retin-A™ cream 0.025%	1.1
A prototype tretinoin cream 0.025%	0.22
Retin-A™ cream 0.05%	2.4
A prototype tretinoin cream 0.05%	0.56
Retin-A™ cream 0.1%	3.6
A prototype tretinoin cream 0.1% (#1)	1.2
A prototype tretinoin cream 0.1% (#2)	0.67
A prototype tretinoin cream 0.1% (#3)	1.1

Reviewer's Comment:

1) It should be noted that the Acticin™ gel vehicle was not included in this study for comparison.

2) Examination of the data shows that for Acticin™ gel 0.025%, only 1 subject had a score of 3 (erythema and papules) at any time during the study. The remainder of the scores were mainly 0 or 1 with an occasional 2. In contrast, for Retin-A™ gel 0.025%, several subjects had scores of 3, and 1 subject had a score of 4. The remainder of the scores were 1 or 2 with very few subjects receiving 0. Several scores from the last application of drug material (days 6 and 7) also had an appended "skin appearance" score, reflecting to some degree the intensity of the skin reaction. In order to compare the Acticin™ and Retin-A™ gels, it might have been useful to have applied each gel directly to the skin and then to have allowed the alcohol to evaporate before applying an occlusive dressing.

3) In summary, Acticin™ gel 0.025% appears to be mildly irritating after three 24-hour applications under occlusion. The vehicle was not tested. Qualitatively, Retin-A™ gel 0.025% appears to be more irritating than Acticin™ gel 0.025% when evaluated on days 5, 6, and 7.

Contact Sensitization Potential

Study Title: Human Repeated Insult Patch Test (Protocol PDC 004-018) - Study Number 93-3596-73A-D

Investigator: Jerold L. Powers, M.D.
Hill Top Research, Inc.
Scottsdale, Arizona

Method: This was a study of the sensitization potential of Acticin™ gel 0.025%. During the same study, Acticin™ cream 0.1% was studied. The Acticin™ gel and cream vehicles were also tested.

Two hundred microliters of each test material was applied to an occlusive patch which was then placed on the paraspinal region of the back. The patches were removed after 24 hours, and each site was evaluated 24 hours later (48 hours after each patch application). A total of 9 patches were applied over a 3 week period (induction phase). The subject was then allowed to "rest" for 10 to 17 days. Patches were then applied to naive sites (challenge phase). The patches were removed after 24 hours, and the sites were evaluated at 48 and 96 hours after application of the patches. Subjects who experienced a reaction of 1+ or greater at the time of challenge were rechallenged. The rechallenge consisted of the application to a naive site of an occlusive patch to which 200 microliters of test material had been applied **and**, at a different naive site, the application of 25 microliters of test material directly to the skin, allowed to evaporate, and then covered with an occlusive patch. The rechallenge patches were removed after 24 hours, and the sites were evaluated at 48 and 96 hours after application of the patches.

Results: Two hundred twenty-five subjects were enrolled. Twenty-three subjects failed to complete the study for reasons felt to be unrelated to the test materials. The demographics of the study population were not provided.

For Acticin™ gel 0.025%, at the time of challenge, there were 4 subjects who exhibited a 1+ reaction at 48 hours and 2 subjects who exhibited a 2+ reaction. For the Acticin™ gel vehicle, there were 3 subjects who had a 1+ reaction (including 1 subject who also reacted to Acticin™ gel 0.025%) and 2 subjects who had a 2+ reaction. Unfortunately, subjects were unavailable for rechallenge. The following table shows the results of the challenge and rechallenge readings (where available):

Subject No.	Challenge		Rechallenge 200 microliters		Rechallenge 25 microliters	
	48 hrs.	96 hrs.	48 hrs	96 hrs.	48 hrs.	96 hrs.
	Gel: 1 P(apules) Vehicle: 1P	0 0	0	0	0	0
	Gel: 2 Vehicle: 2	1 1	Not done			
	Gel: 1 E(dema)	1	1 E(dema)	0	0	0
	Vehicle: 1	0	0	0	0	0
	Vehicle: 1	0	0	0	0	0
	Gel: 1 (peeling)	0 (peeling)	0	0	0	0
	Gel: 2 E(dema), S(preading) Vehicle: 2 ES	2 (peeling) 2	Not done			
	Gel: 1	1	1 P(apules)	0	0	0

Reviewer's Comment:

1) Both subjects had fairly intense reactions to Acticin™ gel 0.025% and vehicle. Without rechallenge, a contact sensitization reaction cannot be excluded.

2) Subjects showed a reaction at the time of rechallenge, but which did not persist at the 96 hour reading. These may represent irritant reactions.

Phototoxicity/Photoallergy Potential

These studies were not performed by the sponsor.

Reviewer's Comment:

For labeling purposes, assuming that the new polymer, polyolprepolymer-2 (PDT 002-002), is not phototoxic or a photosensitizing agent (see section below "Polyolprepolymer-2: Phototoxicity/Photoallergy Potential" for evaluative studies), Acticin™ gel 0.025% would receive the class label for phototoxicity/photoallergy as for the other tretinoin-containing topical drug products.

Other

Study Title: A Double-Blind Comparison Study of Two Topical Retinoic Acid Formulations to Evaluate Retinoid-Induced Dermatitis on the Face and Arms of Human Subjects (Protocol PDC 004-001) - Report No. 90-2216-74

Investigators: Otto H. Mills, Jr., Ph.D.
Hill Top Research, Inc.
East Brunswick, New Jersey

Richard S. Berger, M.D.
University of Medicine and Dentistry of New Jersey
Piscataway, New Jersey

Method: This study was intended to clinically evaluate the dermatitis resulting from the application of 2 retinoic acid formulations (Acticin™ gel 0.025% and Retin-A™ gel 0.025%) to the face and forearms during a 3-week study period. According to the sponsor, this study was aborted before completion because neither treatment group developed dermatitis. Data analysis was not performed and patient line listings were not submitted.

Nine adults with a history of acne (11% male/89% female; age range years) were studied. According to the sponsor, 1 subject did not complete the study for reasons unrelated to the study. This was a bilateral, paired-comparison study in which the right or left side of each subject's face was treated with 1 formulation and the contralateral side treated with the other formulation. In addition, a small area of each forearm was treated with the formulation corresponding to the side of the face. The application of materials was nightly for 21 days.

Results: According to the sponsor, of the 8 subjects who completed the study, there was evidence of little irritation (Day 21 erythema scores ranged from 0.2 to 0.5), and there was no difference between the 2 formulations. In particular, the sponsor felt that the erythema scores were lower than expected from published results of Retin-A™ gel 0.025%.

It was hypothesized that "the warmer weather and higher humidity during the summer months of July and August may have reduced the severity of the retinoid-induced dermatitis." No adverse events were reported.

Polyolprepolymer-2 (PDT 002-002):

The following studies were performed to evaluate polyolprepolymer-2 (PDT 002-002):

Irritation

1. Evaluation of Primary Irritation Potential in Humans (Single 24-Hour Application) (Protocol PDC 002-001)

2. Evaluation of Primary Irritation Potential in Humans (Single 24-Hour Exaggerated Application) (Protocol PDC 002-004)

3. Evaluation of Cumulative Irritation Potential in Humans - 14 Day Test (Protocol PDC 002-003)

4. Evaluation of Cumulative Irritation Potential in Humans - 14 Day Test (Protocol PDC 002-006)

Reviewer's Comment:

Except under conditions of exaggerated irritation in which 0.25% SLS had been previously applied to the skin (Protocol PDC 002-004), polyolprepolymer-2 appears to be minimally irritating, even under occlusion.

Contact Sensitization Potential

1. Repeated Insult Patch Test (Modified Draize Procedure) (Protocol PDC 002-008)

2. Human Repeated Insult Patch Test (Protocol PDC 002-010)

Reviewer's Comment:

1) Both of these studies of contact sensitization potential used the method of 24-hour occlusion followed by a 24-hour "rest" and then reapplication of the test materials for a total of 9 patches over 21 days. It should be noted that for non-irritant substances, it is preferred that each application of test materials remain in place for 48 hours.

2) Protocol PDC 002-008 studied 100 subjects and Protocol PDC 002-010 studied 202 subjects. In Protocol PDC 002-008, 1 subject had a reaction of 1+ at the time of challenge at the 96-hour reading. This subject did not show a reaction at the time of rechallenge. In Protocol PDC 002-010, 1 subject had a 1+ reaction with papules at the time of challenge at the 48-hour reading. This subject did not show a reaction at the time of rechallenge. Based on the results of these studies using the method of a repeated insult patch test, there was no evidence of contact sensitization.

Phototoxicity/Photoallergy Potential

1. Phototoxicity and Photoallergy Test (Protocol PDC 002-002)

2. Human Phototoxicity and Photoallergy (Protocol PDC 002-007)

Reviewer's Comment:

1) Protocol PDC 002-002 evaluated 20 patients for phototoxicity and photosensitization potential using a standard protocol. There was no evidence of phototoxicity or photosensitization based on the results of this study.

2) Protocol PDC 002-007 evaluated 27 subjects for phototoxicity and 27 subjects for photoallergy potential. For phototoxicity, approximately 50% of the subjects exhibited a 1+ reaction (defined as a reaction readily visible but mild. Mild reactions include weak but definite erythema, and weak superficial skin responses such as glazing, cracking, or peeling.) at the 1-hour reading. For 2 subjects, a 1+ reaction persisted to the 72-hour reading. These 2 subjects also showed a 1+ reaction with the distilled water control. The non-irradiated sites did not show erythema. The results of this study are difficult to interpret because of the finding of 1+ erythema with the distilled water patches. Similarly, for photoallergy potential, of the 27 evaluable subjects, 11 subjects had a 1+ reaction at the challenge reading at 72 hours. Some of these subjects, but not all, had a similar reaction to distilled water. However, there remained 6 subjects who had a 1+ reaction to polyolprepolymer-2, but not to distilled water at the 72-hour reading. Two of these subjects had a 1+ reading at the non-irradiated site at 1 hour only (i.e., the erythema did not persist). It should be noted that the challenge irradiation was performed with 16-20 J/cm^2 of UVA, a dose higher than that usually used to elicit a response, but which is considered below the minimal erythema dose for most individuals. However, because so many subjects had a reaction to the distilled water (essentially the same as an untreated control), the results of this study are questionable. It might have been useful to establish the minimal erythema dose of UVA using the light source used in the study. In addition, it would have been useful to have tested the Acticin™ gel vehicle.

3) According to the sponsor, polyolprepolymer-2 does not show significant absorption in the UV and/or visible spectrum (see resubmission volume 3, p.7-0002). In addition, based on the chemical structure of the polymer, UV absorption would not be predicted. However, ***this is pending review by Chemistry.*** *Assuming lack of absorption in the UVB and UVA spectra, it is unlikely that polyolprepolymer-2 would be a phototoxic or photoallergic compound. This is confirmed by the first study (PDC 002-002). The results of the second study (PDC 002-007) are questionable because of the high frequency of 1+ reactions to distilled water.*

12. CONCLUSIONS

The clinical trials submitted in this NDA were unable to demonstrate efficacy for Acticin™ gel 0.025% in comparison to vehicle in the treatment of mild to moderate acne based on the mean percent reduction of noninflammatory, inflammatory, and total lesions in evaluable patients. Furthermore, Study #1 was unable to demonstrate equivalence of Acticin™ gel 0.025% and Retin-A™ gel 0.025% based on the finding that the lower bound of the 95% confidence interval of Acticin™ for noninflammatory and total lesions was greater than 20% of the Retin-A™ gel mean percent reduction for each type of lesion. Side effects related to the skin (erythema, peeling, dryness, burning/stinging, itching, and tightness) occurred as frequently as approximately 40% in the patients receiving Acticin™ (for burning/stinging and tightness) but were usually mild. Of the few patients who were graded as having a "severe" symptom, a greater number were in the Retin-A™ treatment group than the Acticin™ treatment group. In general, for patients with more severe symptoms, temporarily discontinuing the medication, reducing the frequency to every-other-night and/or the addition of a moisturizer was usually sufficient. There were no patients receiving Acticin™ in either clinical trial who withdrew due to an adverse effect related to the skin. Adverse events related to hypo- or hyperpigmentation were not reported. However, the racial demographics of the enrolled patients, and the analysis of adverse events by race are pending. It is possible that not enough patients with darker skin were enrolled in the clinical trials to adequately assess this issue.

As with the other retinoids, Acticin™ gel 0.025% is considered a teratogen and a pregnancy category C label is recommended. A dermal carcinogenicity study is recommended.

13. RECOMMENDATIONS

Pending the statistical review from the Division of Biometrics, from a clinical standpoint, this drug is not approvable. A clinical trial with 3 treatment arms (Acticin™ gel, Retin-A™ gel, and vehicle) with sufficient sample size and careful clinical evaluation of lesions is recommended. In particular, an effort should be made to ascertain adverse events related to race and gender.

Nancy Slifman, M.D. 10/11/94 /S/

cc: orig NDA 20-400
HFD-340
HFD-540
HFD-540/Chem/NMokhtari-Rejali
HFD-540/Pharm/HSheevers
HFD-540/MO/RLabib
HFD-540/MO/NSlifman
HFD-710/Biometrics/ETurney
HFD-420/Biopharm/HSun
HFD-540/CSO/KChapman

10/11/94

10/26/94

/

Appendix 1

Mean % Reduction of Lesions (by investigator)*

	Acticin™	Retin-A™	Vehicle
NONINFLAMMATORY			
Cullen			
Baseline	52.6 ± 13.1	69 ± 17.7	38.2 ± 1.8
% reduction	40.7 ± 35% (N=5)	42.6 ± 38.1% (N=5)	53.7 ± 13.3% (N=5)
Jarratt			
Baseline	64.7 ± 39.2	69.1 ± 44	72.6 ± 42.6
% reduction	37.6 ± 31.5% (N=34)	40.9 ± 29.4% (N=31)	20.3 ± 38.8% (N=34)
Lucky			
Baseline	83.8 ± 43.8	92.3 ± 83.9	83.2 ± 56.9
% reduction	49.4 ± 28.5% (N=19)	45.52 ± 32.9% (N=22)	28.2 ± 21.4% (N=16)
INFLAMMATORY			
Cullen			
Baseline	18 ± 4.9	18 ± 5.3	23.6 ± 20.6
% reduction	49.7 ± 32.2%	52.1 ± 39.5%	71.6 ± 13.1%
Jarratt			
Baseline	15.4 ± 6.9	15.8 ± 7.8	17 ± 8.3
% reduction	42 ± 26.9%	51.3 ± 27.8%	20 ± 52.7
Lucky			
Baseline	27.2 ± 17.9	27.3 ± 17.6	25.6 ± 11.8
% reduction	28.7 ± 40.7%	30.1 ± 36.2%	13.4 ± 32.7%
TOTAL LESIONS			
Cullen			
Baseline	70.6 ± 10.4	87 ± 17.9	61.8 ± 21.8
% reduction	40.6 ± 30.5%	44 ± 37.1%	60.6 ± 7.1%
Jarratt			
Baseline	80 ± 42.8	84.8 ± 47.9	89.6 ± 42.9
% reduction	38.3 ± 28%	42.8 ± 25.1	20.3 ± 36.1%
Lucky			
Baseline	111 ± 55.5	119.6 ± 93.6	108.8 ± 61.1
% reduction	46.8 ± 24.5%	41.4 ± 31.3%	26.4 ± 20.1%

* From vol. 1.13, pp. 795-872

Appendix 2

Mean % Reduction of Lesions (by investigator)*

	Acticin	Vehicle
NONINFLAMMATORY		
Jarratt		
Baseline	66.7 ± 38.6	66.7 ± 34.3
% reduction	32.5 ± 30.6% (N=42)	16.8 ± 40.5% (N=40)
Jones		
Baseline	48.3 ± 11.7	54.2 ± 14.1
% reduction	33.8 ± 32.1% (N=44)	30.8 ± 33.1% (N=42)
INFLAMMATORY		
Jarratt		
Baseline	15.6 ± 4.5	16.5 ± 6.4
% reduction	36.1 ± 43.2%	20.4 ± 58.3%
Jones		
Baseline	16.8 ± 5.7	17.4 ± 6.3
% reduction	40 ± 40.3%	26.1 ± 49.1%
TOTAL LESIONS		
Jarratt		
Baseline	82.4 ± 38.2	83.1 ± 37.7
% reduction	33.6 ± 29.1%	17 ± 39.2%
Jones		
Baseline	65.1 ± 14.8	71.6 ± 16.2
% reduction	35.5 ± 30.7%	29.8 ± 33.1%

* From vol. 1.16, pp. 1948-1974