CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020404

Trade Name : AVITA CREAM 0.025%

Generic Name: Tretinoin Cream

Sponsor :Penederm , Inc.

Approval Date: January 14, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020404

APPROVAL LETTER

NDA 20-404

JAN 14 1997

Penederm Incorporated
Attention: John Quigley, Ph.D.
Senior Vice President, Research and Development
320 Lakeside Drive , Suite A
Foster City, CA 94404

Dear Dr. Quigley:

Please refer your September 29, 1993, new drug application (NDA) and your resubmissions dated March 28, 1994, and July 12, 1996, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avita™ (tretinoin cream) Cream, 0.025%,

Please refer to our not approvable letters dated March 29, 1995, and June 26, 1996.

We acknowledge the receipt of your amendments and additional communications dated May 31, June 3, 13 and 28, July 8, 12 and 30, October 22, November 14 and 20, December 10, 11, 12, 13 and 16, 1996.

This new drug application provides for treatment of acne vulgaris.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling dated January 13, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-404. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in the facsimiles of your letters dated January 13 and 14, 1997. These commitments, along with any completion dates agreed upon, are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville , Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when its available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Olga Cintron, R.Ph.
Consumer Safety Officer
(301) 827-2020

Sincerely yours,

1/14/97

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Original NDA 20-404
HF-2/MedWatch (w/draft labeling)
HFD-2/MLumpkin (w/draft labeling)
HFD-92 (w/draft labeling)
HFD-105/OFFICE DIR/Weintraub (w/draft labeling)
HFD-540/DIV FILE (w/draft labeling)
HFD-540/CSO/Cintron (w/draft labeling)
HFD-540/MO/Labib (w/draft labeling)
HFD-540/CHEM/Mokhtari (w/draft labeling) 1-8-97
HFD-540/PHARM/Alam (w/draft labeling) 1/9/97
HFD-725/STAT/Farr (w/draft labeling) 1/8/97
HFD-880/BIOPHARM/Pelsor (w/draft labeling)
HFD-40 (w/draft labeling)
District Office (w/draft labeling)
HFD-613 (w/draft labeling)
HFD-735 (w/draft labeling)
HFD-005/Axelrad (w/draft labeling)

Concurrence:
HFD-540/PHARM TL/Jacobs (w/draft labeling) 01/8/97
HFD-540/CHEM TL/DeCamp (w/draft labeling) 1/8/97
HFD-540/ACTING SUPV PROJ MGR/Kozma-Fornaro (w/draft labeling)
HFD-880/BIOPHARM TL/Bashaw (w/draft labeling) 1/9/97
HFD-160/MICRO TL/Cooney (w/draft labeling) 1/8/97
HFD-560/Katz (w/draft labeling) 1/10/97
HFD-725/BIOSTAT TL/Srinivasan (w/draft labeling) RS 01/09/97

APPROVAL
PHASE 4 COMMITMENT

Blay
HFD-540
JUN 26 1996

NDA 20-404

Penederm Incorporated
Attention: Barry Calvarese, M.S.
Executive Director, Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Mr. Calvarese:

Please refer to your September 29, 1993, new drug application (NDA) and your resubmission dated March 28, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avita™ (tretinoin cream) Cream, 0.025%.

Please also refer to our not approvable letter dated March 29, 1995. We acknowledge receipt of your additional communications dated April 7 and 17, May 19, September 27, October 13, November 14, December 6, 20, and 28, 1995; and February 22, and May 14, 1996.

We have completed our review of this application, as amended, and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

In addition, although not the basis for the non-approval of this application, the following comments and requests should be addressed in any resubmission of this application:

Chemistry

1. Please revise the assay limits in this drug product to not less than % and not more than % of the labeled amount of tretinoin.

2. Please modify all of the specifications for degradants to the percent of labeled amount of tretinoin.

3. Please submit identical specifications for finished product stability and finished product release.

4. Please submit individual specifications for

5. Please state which tests (in-process and/or regulatory) are performed by as compared to Penederm. Please include timeframes for testing and release.

6. Please submit additional 18 month stability data at room temperature for other batches and strengths of tretinoin cream to support the 24 month expiry date. We recommend that future stability studies be performed at either °C/ambient humidity or % relative humidity.

7. We suggest that a new analytical methodology be developed to identify all impurities. The methodology should include specifications for all products in tretinoin cream.

8. Regarding the environmental assessment (EA), please submit information on the drug substance manufacturing site as described in Format Item 6. Since the manufacturer is foreign, a certification of compliance is sufficient (Please see Industry Guidance for appropriate certification language). The last sentence of page 8 of the EA references a compliance statement for but the statement is not included; please submit this compliance statement. Please note that there are no Format Items 12, 13, or 14 which are required for the abbreviated EA format for topical drugs (21 CFR 25.31a(b)(3)).

Carcinogenicity Advisory Committee (CAC) Recommendations

The high-dose level is approximately equivalent to (and not 150 times greater than) the clinical dose of 0.025%; however, it appears that the dose is at the maximum feasible level given the clinical signs of increasing inflammation in the 90-day study.

1. Please submit data supporting the claim that the dose levels chosen should be compared to the clinical formulation based on a mg/kg (or surface area) basis. The dose levels for the dermal carcinogenicity study (which is primarily concerned about changes in the skin) should be based primarily on a concentration basis, and secondarily, on a volume basis.

2. We suggest that the mid-dose group be 1/3 that of the high dose group (%), and that the low dose group be 1/9 of the high dose %).

3. All formulations should be prepared in the clinically used vehicle (except for the excipient-free control group suggested below).

4. Physical examinations should be performed prior to the initiation of studies.

5. Please clearly state the minimal survival rate needed before the study is terminated early. Please contact the Division pharmacology staff prior to the termination of any group(s).

6. Please consider adding two additional control groups: an untreated vehicle control and a vehicle control group that does not include the previously untested excipient, polyolprepolymer-2. An untreated control group will allow for the clear establishment of the appropriate background skin tumor level. The excipient-free control group may help avoid additional studies, if the vehicle control gel proves to be tumorigenic (i.e., tumors related to the excipient).

7. Since blood samples are being collected, we suggest including clinical pathology parameters for ALT, AST, glucose, and BUN. We recommend that these samples be taken at baseline, 13 weeks, 52 weeks, and at termination. These suggestions are based on the changes seen in the 90-day study and are made with the assumption that the additional tests can be run on the blood already being sampled.

8. As a result of the 90-day study findings, please examine lungs, liver, kidney, heart, thymus, and skin (treated and untreated) from all groups, not just low and mid-dose animals. We also suggest that all harvested organ samples from the control and high-dose animals be examined histopathologically.

Until the safety and effectiveness of this drug product have been established, we reserve comment on the proposed labeling.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting should be requested 15 days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact Dr. Roy Blay, Project Manager, at (301) 827-2020.

Sincerely yours,

6/26/96

Jonathan K Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-404
HFD-540\Div. Files
HFA-100
HFD-105\Weintraub
HFC-130
HFD-5
HFD-540\DDIR\Wilkin
HFD-540\MO\Labib
HFD-540\CHEM\Rejali
HFD-2\Lumpkin
HFD-80
HFD-540\PROJ MGR\Blay

Concurrence:
HFD-540\DEP DIR\Katz\6.26.96
HFD-540\CHEM SUPV\DeCamp\6.26.96
HFD-540\PHARM SUPV\Jacobs\6.26.96
HFD-160\MICRO SUPV\Cooney
HFD-880\BIOPHARM SUPV\Bashaw
HFD-725\BIOSTAT SUPV\Harkins
HFD-540\PROJ MGT SUPV\Cook

drafted: RB/June 20, 1996/c:\royblay\letters\nda\approval\20400.001
r/d Initials: RAB
final:

NOT APPROVABLE (NA)

NDA 20-404

Penederm Inc.
Attn: Barry Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Mr. Calvarese:

Please refer to your September 29, 1993, new drug application (NDA) and to your resubmission dated March 28, 1994, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acticin (tretinoin cream) Cream, 0.025%,

We acknowledge receipt of your amendments dated March 30, June 2, 9 and 24, September 12 and 13, October 7 and 28, December 16, 1994; January 17, and March 9, 1995.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are as follows:

Clinical

1. The submitted information fails to provide substantial evidence consisting of adequate and well-controlled investigations that Acticin Cream 0.025%, will have the effects they are represented to have under the conditions of use prescribed, recommended, or suggested in their proposed labeling. Specifically, the submitted studies fail to demonstrate equivalence between Acticin Cream 0.025% and Retin-A Cream 0.025%, and fail to demonstrate equivalence between Acticin Cream 0.1% and Retin-A Cream 0.1%. Evidence was not submitted to support the safety and efficacy of Acticin Cream 0.05%.

   A demonstration of clinical superiority of Acticin Cream 0.025% and Acticin 0.1% when compared to their vehicles could be considered substantial evidence of efficacy provided that the demonstration was reproducible by independent investigators. Since only one study was submitted, the reproducibility has not been demonstrated.

If this application is resubmitted, it is recommended that an additional clinical trial with three treatment arms (Acticin Cream, Retin-A Cream and vehicle) be conducted and submitted for each concentration. Each trial should have sufficient statistical power to evaluate the potential equivalence between Acticin Cream and Retin-A Cream in the treatment of both inflammatory and non-inflammatory lesions. The new trials should also include a sufficient number of non-Caucasian patients in each treatment group to permit a statistically meaningful analysis of any differences between groups in adverse experiences associated with the skin, including changes in pigmentation.

In addition, the analysis of PDC 004-011 failed to demonstrate a statistical difference between Acticin Cream 0.025% and Acticin Cream 0.1%. A justification for the multiple concentrations is therefore needed for the development of each of these concentrations.

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

Microbiology, Chemistry, Manufacturing, and Controls

2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the finished product (or drug substance) are inadequate to preserve its identity, strength, quality, purity and stability. Specifically, the manufacturing operations at were not found to be in GMP compliance; the one month accelerated stability data at is not sufficient to support the proposed two year expiry date; the regulatory specification for the total degradant is not adequate; and a satisfactory impurity profile for the drug substance and drug product has not been developed. If the application is resubmitted, the following information should be included:

   a. Information on the globule size from microscopic studies from stability samples stored under normal and stress conditions.

   b. Regulatory specifications which include a more precise description of the tretinoin identity and appearance tests. The term "passes" is not sufficiently precise.

c. Regulatory specifications and methods which include a validated chromatographic method for quantification of the degradation products in the finished drug product. This should be both a release and a stability specification. The specifications should include limits for all known degradation products of tretinoin in this cream formulation.

d. Viscosity specifications for the finished drug product at release and during shelf life.

e. Limits for isotretinoin which conform to data obtained in the stability studies (%).

f. The fill weight method (PN92, PN93, & PN94).

g. Justification for the weight loss limit. The weight loss results of tretinoin cream presented in the stability studies (pp. 400-408, Table 1-9 of the December 16, 1994 amendment) do not match the proposed range on aging.

h. Stability data to support the proposed two year expiry date for lots manufactured at The data should include at least three months accelerated stability data and any updated room temperature data.

i. Revised reprocessing operations which reflect the correction of deficiencies observed during the inspection of

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

1. Lot 73511, 45 gram tube
2. Lot 73510, 20 gram tube
3. Lot 73509, 2 gram tube

In addition, although not the basis for the non-approval of this application, the following comments should be addressed in any resubmission of this application:

1. The carcinogenic potential of this product has not been fully addressed. The June 9, 1994, submission addresses your commitment to conduct a dermal carcinogenicity study utilizing the gel formulation. It is recommended that the protocol for this study be submitted for review prior to the study initiation and included in any resubmission of this application.

2. Information should be submitted on the degradation pathways of tretinoin.

3. The stability protocol should be revised as follows:

   a. to provide for additional test stations at initial, 3 and 9 months;

   b. to perform the homogeneity test at the top, middle, and bottom of the tube;

   c. to include the test procedures for testing the drug product; and

   d. to a provide sampling plan for testing the product.

4. A summary table with references to all the formulations investigated should be provided. All differences, such as route of synthesis, manufacturing sites, and purity profiles between the investigational and the marketed formulation(s) should be submitted.

5. If it is proposed that the product can be frozen during storage, then stability information under this condition of storage must be included in the application.

6. Stability data including microbial limits and preservative effectiveness testing on the first three lots at the proposed manufacturing facility should be submitted.

Please note that we cannot approve this application until we are informed that all sites involved in manufacture of the bulk drug and drug product have been found to be in compliance with good manufacturing procedures and are able to perform the production procedures specified in this NDA application.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Until the safety and effectiveness of this drug product has been established, we reserve comment on the proposed labeling.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Topical Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting should be requested at least 15 days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action, the Food and Drug Administration (FDA) may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have questions regarding this application, please contact Ms. Kennerly K. Chapman or Ms. Joanne A. Holmes of the Project Management Staff, at 301-594-4877.

Sincerely yours,

3/29/95

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-404
HFD-2/Lumpkin
HFR-PA200/LOS-DO
HFD-500
HFD-80
HFA-100
HFC-130
HFD-5
HFD-540
HFD-540/DDir/Wilkin
HFD-540/SMO/Chambers MK 3/27/95
HFD-540/MO/Labib
HFD-540/MO/Slifman
HFD-540/Chem/Rejali
HFD-540/Pharm/Sheevers/rd3/21/95
HFD-520/Micro/Utrup
HFD-426/Biopharm/Pelsor/rd/3/21/95
HFD-710/Biostat/Harkins
HFD-540/PMS/Chapman/n20404.na2 KKC 3/29/95

Revised: Chambers 3/24/95
Revised: Chapman 3/27/95

NOT APPROVABLE

Concurrence only:

HFD-540/SChem/DeCamp/rd3/21/95
HFD-540/ActSPharm/Jacobs/rd3/21/95
HFD-540/SPMS/Cook/rd3/20/95

Memo to File

NDA 20-400/20-404 (Labeling) December 26/1996

Subject: Review of the proposed draft labeling for Avita[R]

In the proposed draft labeling, both the Carcinogenicity and the Pregnancy sections need revisions. Clearly, the Sponsor has used the labeling for Retin-A as a model for this proposed labeling for Avita, the obvious reason being a common active ingredient in both the preparations, namely, the all-trans-retinoic acid (tretinoin). However, since the marketing of Retin-A about 25 years ago, much new information on reproductive toxicity of tretinoin has become available. Thus, the statement that "Long-term animal studies to determine the carcinogenic potential of tretinoin have not been performed" is not true anymore. Also, it is necessary to clearly differentiate the oral and topical teratogenic effects of tretinoin in various species. Most of this new information has been included in the labeling of Renova[R], another formulation containing tretinoin as the active ingredient. The labeling of the present formulation should follow that of Renova and not of Retin-A. It is to be noted that the Sponsor is committed to performing a mouse carcinogenicity study as a phase 4 study. The following changes in the labeling are proposed.

2 Pages deleted
(2-3)
Proposed Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

MEDICAL REVIEW(S)

Date of Review: December 18, 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-404 AMENDMENT

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

Drug: Avita (Acticin) 0.025%, , creams

Indication: Acne Vulgaris

Date of Submissions: July 12, 1996 and December 11, 1996

Background: The July 12, 1996 amendment was submitted to approve Avita cream, NDA 20-404 as a line extension to the gel formulation

This was reviewed by the present medical officer and its approval was recommended.

Recommendations: The 0.025% cream is approvable as a line extension pending the approval of the Avita gel.

Therefore, the 0.025% Avita cream should be approvable as a line extension of the gel.

Reviewing Medical Officer

Ramzy S. Labib

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

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

Date of Review: June 17, 1996
Final Review : June 24, 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-404 AMENDMENT

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

Drug: Avita (Acticin) 0.025%, creams

Indication: Acne Vulgaris

Date of Submission: Dec. 20, 1995

Background: This amendment is a response to the nonapprovable letter of March 29, 1995. NDA 20-404 is a line extension to the gel formulation Both NDA's were found to be nonapprovable in March 1995. In December 1995, the sponsor responded to the issues addressed in the nonapprovable letters for NDA 20-404. The sponsor has submitted a protocol for further clinical studies on the efficacy and safety of the gel formulation in comparison to its vehicle and to Retin-A gel (IND

Review:

The clinical section of this amendment consists of the following :

1- Supplemental statistical analysis of study PDC 004-011, submitted on October 28, 1994, in response to a request from the statistical reviewer.

Comment: This analysis was already reviewed by the statistical reviewer in her review dated 3/1/95, and by the medical officer in his review dated 12/19/94. It consists of the LOCF-ITT analysis, which did not differ appreciably from the evaluable subjects analysis.

2- Justification for the approval of 0.05% Avita (Acticin) cream formulations, submitted in November 14, 1995, in response to the nonapprovable letter.

This report consisted of three sections:

a- Statistical Report: a re-analysis of the clinical data from Penederm's study PDC 004-011 focusing on the differences between the Avita (Acticin) 0.025% and 0.1% creams.

> **Comments:** There is no new data in this section. The sponsor emphasized that numerically, the 0.1% cream was always better than the 0.025% cream. There were some statistically significant differences in effectiveness between the 0.025% and 0.1% strengths of the cream, although the trial was not sufficiently powered for this purpose. Most of these differences were in the early days of treatment, suggesting that the 1% cream may have a faster onset of action than the 0.025% cream. Both became almost equally effective on day 84 of the trial. Examples of these differences are shown in tables 2 and 3 (p.85 of Amendment, copies are attached).

b- Practice patterns in the use of topical tretinoin: a clinical section that demonstrates the medical need for several concentrations and formulations of topical tretinoin.

> **Comment:** The strongest argument in this section is the need for individualized treatment to meet each patient's therapeutic needs and tolerance.

c- Examples of other multiple strength therapies that have been previously approved in the absence of specific studies addressing differences between strengths.

> **Comment:** This discussion does not apply to the present drug formulation and the present standards of drug approval.

3- Safety update, consisting of final reports of three topical safety studies of Avita (Acticin) gel and Avita (Acticin) cream.

a- Human repeated insult patch test (PDC 004-018): One out of 202 subjects exhibited response to the 0.1% cream, and another one exhibited response to the vehicle, on challenge. None of them responded during rechallenge. No other concentration of the cream was tested.

> **Comment:** There is no evidence of delayed sensitization with the 0.1% cream.

b- Primary irritation potential (PDC 004-020M): The results of this study showed that both Avita (Acticin) and Retin-A creams (0.025, 0.05 and 0.1% concentrations) were slightly irritating (barely perceptible erythema). The raw scores ranged from to % for all the cream preparations tested. Numerically Avita (Acticin) cream was equal to, or less than Retin-A cream, but not higher.

Comment: The low degree of irritation is acceptable.

c- Primary irritation potential (PDC 004-021M): This study used occlusion in Hill Top Chamber for sample applications, whereas the previous study used occlusion of dried samples under Webril patch. All concentrations (0.025, 0.05 and 0.1%) of the creams tested (Avita [Acticin] or Retin-A) were slightly or mildly irritating. Least irritation was shown by 0.05% Avita (Acticin) cream (0.45 mean score) and the highest irritation (4.8 mean score) was obtained from 0.1% Retin-A applications.

Comment: The low degree of irritation is acceptable.

Conclusions and Recommendations:

The 0.025% Avita (Acticin) cream has shown equivalence to the corresponding Retin-A cream when 90% confidence interval was used ($p > 0.1$, see Statistical Review of Amendment) in addition to its statistically significant superiority to placebo ($p < 0.05$) in one study. This concentration is approvable as line extension (pending Avita gel approval) and as equivalent to innovator.

The 0.1% Avita (Acticin) cream is statistically significantly better than placebo ($p < 0.05$) in one clinical study, but is not equivalent to the corresponding Retin-A even at 90% confidence interval ($p < 0.1$, see Statistical Review of Amendment). The 0.1% Avita cream has occasionally shown some statistically significant differences in effectiveness at days 14, 28 and 56, but not at day 84, when compared with the 0.025% cream. However, these differences in the early days were not consistently significant. The presented data fail to show a significant advantage of the 0.1% cream over the 0.025% cream. For these reasons, the reviewing M.O. does not recommend approval of this concentration.

Reviewing Medical Officer,

Ramzy S. Labib

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

cc: Orig NDA
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
HFD-540
HFD-540/DivDir/Wilkin 6/26/96
HFD-540/SMO/Katz 6/26/96.
HFD-540/MO/Labib
HFD-540/MO/Slifman
HFD-540/Pharm/Jacobs
HFD-540/Chem/Mokhtari-Rejali
HFD-540/CSO/Blay
HFD-710/Biometrics/Harkins

Table 2. Percent decrease from baseline with Acticin Cream*

	Total Lesions		Noninflammatory Lesions		Inflammatory Lesions	
	0.025%	0.1%	0.025%	0.1%	0.25%	0.1%
Day 14	4.65	11.78^A	3.53	11.86^A	7.67	10.93
Day 28	17.31	22.42	16.57	22.32	15.33	20.59
Day 56	30.61	38.14	30.02	40.04^A	31.66	30.48
Day 84	38.84	44.06	38.51	44.84	39.09	41.54

* ITT-LOCF population

^ $P \leq 0.05$ relative to the 0.025% cream.

Table 3. Acticin Cream by strength and day*

	Categorical Improvement % Change Total Lesion Count				Global Assessment	
	"worse-no change" (%)		"50%–100% improvement" (%)		"good" or "excellent" (%)	
	0.025%	0.1%	0.025%	0.1%	0.025%	0.1%
Day 14	49.48	33.70^A	4.12	6.52^A	11.70	20.88^A
Day 28	31.96	17.39^A	13.40	13.04^A	28.87	32.61
Day 56	16.49	7.61^A	30.93	39.13^A	46.39	45.65
Day 84	16.40	11.96	45.36	46.74	51.55	58.70

* ITT-LOCF population

^ $P \leq 0.05$ relative to the 0.025% cream over all categories.

3/15/95

Date of first Review: November 17, 1994
Date of final review: December 19, 1994

MEDICAL OFFICER'S REVIEW OF NDA 20-404

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

Drug: Acticin[tm] (Tretinoin) 0.025%,
Cream

Indication: Topical treatment of acne vulgaris

Date of Submission: September 29, 1993: Refused to file;
Resubmitted March 28, 1994: Filable.

Related IND's: IND

Related NDA's: NDA

Composition: The composition of the 0.1% cream formulation is as follows:

Component	g
✓Tretinoin, USP	
✓Purified water	
✓Stearic acid, NF	
✓Polyolprepolymer-2	
✓Isopropyl myristate, NF	
✓Polyoxyl 40 stearate, NF	
✓Propylene glycol, USP	
✓Stearyl alcohol, NF	
✓Xanthan gum, NF, Food Grade	
✓Sorbic acid, NF	
✓Butylated hydroxytoluene, NF or FCC	

The 0.025% and the 0.05% creams differ from the 0.1% cream in their content of Tretinoin which is, respectively, , and Purified water which is, respectively,

Background: Because of the identity of the active principle (tretinoin) in Acticin cream (and gel) with the Innovator product, Retin-A cream (and gel), the Sponsor had initially submitted ANDAs for Acticin cream (and gel) in July of 1992. In August 1992, the FDA determined that these submissions were not acceptable for filing as ANDAs due to the inclusion, in the Acticin formulations, of two new excipients, which has not been previously approved for use in a new drug, and which is not present in the Retin-A formulations. Based on conversations with the Agency, the Sponsor submitted this NDA in September 29, 1993 as a line extension to the Acticin Gel NDA (submitted September 24, 1993) pursuant to section 505(b)(2) (literature based NDA) of the Food, Drug and Cosmetic act.

In a letter dated 11/23/93, the Agency informed the Sponsor that this NDA was incomplete and unacceptable for filing. A major deficiency was the lack of a human contact sensitization study using the formulation to be marketted. The Sponsor submitted the protocol for this study as an amendment to IND The results of this study as well as responses to the other deficiencies were submitted to the NDA in March 28, 1994 , and the NDA was subsequently determined to be filable

Chemistry, Manufacturing, and Controls Review:

Chemistry, manufacturing and controls are under review by Nahid Mokhtari-Rejali.

Pharmacology and Toxicology Review:

Pharmacology and toxicology are under review by Hilary Sheevers, Ph.D.

Microbiology Review:

Microbiology review of manufacturing and controls by Linda Utrup,. PH. D. was received October 21, 1994. The reviewer recommended approval after correction of 4 deficiencies.

Review of Clinical Studies

A. Clinical Pharmacology Studies:

In its first submission, the only clinical pharmacology study on the final cream formulation was PDC 004-009. This study was a one week standardized, three application, 24-hour primary irritation patch study on 19 patients (only 10 completed the study). Acticin and Retin-A 0.05% and 0.1% creams were tested in this study in addition to other products (e.g. prototype tretinoin creams). The results of this study showed that under occlusive conditions, Retin-A 0.05% and 0.1% creams were moderately irritating (mean scores: 3.30 for each), whereas the corresponding Acticin creams were slightly or mildly irritating (mean scores: 1.20 and 1.70, respectively, p. 4:032 of NDA).

The sponsor submitted the results of the FDA-requested contact sensitization study of the formulation to be marketted in the NDA resubmission. This was a vehicle controlled modified Draize patch test of 0.1 % Acticin cream on 225 subjects. Of the 202 subjects that completed the study, only two subjects (one Vehicle and one 0.1% Acticin) developed grade 1 reaction at challenge. On rechalenge, both subjects received scores of zero at the 48 and 96 hour assessments. These results indicated no evidence of induced cutaneous sensitization.

Other clinical pharmacology studies tested the topical safety of the excipient, Polyprepolymer-2. These included:

1- single application primary irritation patch test on 17 subjects,

2- two 14-day cumulative irritation patch tests on a total of 41 subjects,

3- single exaggerated application primary irritation patch test on 14 subjects, and

4- two phototoxicity/photoallergy patch tests on a total of 48 patients (only patients that completed the study are counted).

All these tests showed that the excipient, Polyprepolymer-2 is a non-irritating mild material with no identifiable phototoxic or photoallergic effects except in the exaggerated primary irritation test where all test materials, including the vehicle, demonstrated identifiable erythema with minimal edema and papules.

Comments: The topical safety studies failed to show any evidence of concerning side effects that may be different from the corresponding Retin-A cream.

B. Controlled Clinical Trials:

Six centers participated in a single bioequivalence protocol, PDC 004-011, which was a double-blind randomized vehicle-controlled parallel group clinical study to compare the efficacy and safety of Retin-A 0.025% and Acticin 0.025%, Retin-A 0.1% and Acticin 0.1%, tretinoin creams and Vehicle in the treatment of patients with FDA Grade II or III Acne Vulgaris. The investigators and centers involved in this study were:

1- Stanley I. Cullen, M.D., Gainsville, FL
2- Toni Funicella, M.D., Austin, TX
3- Michael T. Jarratt, M.D., Austin, TX
4- Terry M. Jones, M.D., Bryan, TX
5- Anne W. Lucky, M.D., Cincinnati, OH
6- Max E. Reddick, M.D.Houston, TX

Comments:

1- This NDA is submitted and reviewed as a "line extension" to the Acticin Gel application and, as such, a single clinical study is considered sufficient to support approval, provided NDA is approved.

2- The curricula vitae provided (Appendix C, p. 4:0504-0627) show that all the investigators mentioned above are qualified to conduct the study.

Patient population:

Healthy male or nonpregnant female patients, 13-40 years old with clinical diagnosis of mild to moderate Acne Vulgaris (grades II or III) were enrolled in the study. Acne vulgaris patients with the following specifications were included:
1- At least 30 non-inflammatory lesions.
2- At least 10 inflammatory lesions.
3- No significant nodulocystic acne (< 4 lesions).
4- Total lesion counts ≤ 200.

Patient exclusions:

Patients with the following conditions were excluded from the study:
1- Any obvious skin pathology or condition on the face other than mild to moderate acne vulgaris.
2- History of sensitivity to any of the study medications.
3- Use of topical acne treatments, medicated soaps or topical steroids on the face within last two weeks.
4- Use of steroids or systemic antibiotics (excluding penicillins) in the last 4 weeks.

5- Use of systemic retinoid therapy in the last 6 months.
6- Participation in any clinical research study in the last 6 months.
7- Use of other medication that could interfere with treatment or evaluation as determined by the investigator.
8- Pregnancy or nursing.
9- Female patients that do not use an acceptable birth control method (oral contraceptives, IUD, barrier method, tubal ligation, abstinence if not sexually active).

Treatment regimen:

Subjects were randomly assigned to one of the following treatment groups (arms) for twelve weeks of therapy:

1- Vehicle	PDT 004-054	Treatment Code 0
2- Acticin 0.025%	PDT 004-044	Treatment Code 1
3- Acticin 0.1%	PDT 004-046	Treatment Code 2
4- Retin-A 0.025%	PDT 004-024	Treatment Code 3
5- Retin-A 0.1%	PDT 004-031	Treatment Code 4

The test cream was applied to the face once at bed time, 20-30 minutes after washing the face with Purpose soap.

Effectiveness parameters:

In addition to a baseline visit on the first day, return visits were scheduled on days 14, 28, 56 and 84 of the treatment period. At each visit the following assessments were performed:

1- Lesion counts, both inflammatory and non-inflammatory;
2- Physician global evaluation of improvement;
3- Physician evaluation of erythema, peeling and dryness;
4- Patient evaluation of burning/stinging, itching and tightness.

Efficacy was to be determined by comparing the five treatment groups with respect to:

1. Lesion Counts: a) Mean count, b) mean change in count, c) mean percent change in count and d) categorical improvement in count for i- total lesions (non-inflammatory plus inflammatory), ii- total non-inflammatory lesions (open comedones and closed comedones) and iii- total inflammatory lesions (papules and pustules), on the forehead, cheeks and chin above the jaw line (nose excluded).

The protocol specified that the percent improvement categorization consists of four levels of response: 1- worse/no change, 2- 1-25% improvement, 3- 26-50% improvement and 4- 51-100% improvement. Any category that had too few observed patients could be combined with another appropriate category for analysis if necessary.

2. Global Assessment: The investigator made a global assessment of overall improvement in the condition from baseline. This included reduction in lesions, skin parameters and general clinical evaluation. The scale used was excellent, good, fair, no change, worse.

3. Skin parameters: These were evaluated by both physician and patient. The physician's evaluation included erythema, peeling, and dryness of the treatment area and each parameter was graded as 0 = none, 1 = mild, 2 = moderate and 3 = severe. The patient's evaluation included assessment of burning/stinging, itching, and tightness on a scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe.

The primary efficacy variable was the change, percent change and categorical change in total lesion count (non-inflammatory plus inflammatory lesions) from baseline to Day 84. The change in lesion counts was analyzed with an ANOVA model with treatment, investigator, and treatment by investigator terms. As secondary efficacy variables, the counts of non-inflammatory and inflammatory lesion types were similarly analyzed. As an additional measure of efficacy, the Investigator's global assessment was analyzed with a categorical mean score model. The null hypothesis was that the treatment means for these measures were equal.

Safety evaluations:

Patients were observed in the evaluation visits for any adverse reactions that may have occurred. Patients developing significant side effects were evaluated and could be withdrawn from the study at the discretion of the investigator. If the side effects were mild to moderate, the patient was encouraged to continue in the trial. If the patient developed severe irritation the dosing frequency could be reduced to every other night.

If excessive dryness, peeling or tightness occurred that was not amenable to reduced dosing freguency, a facial moisturizer could be provided by the investigator.

C. Results of the clinical trials:

The results of this clinical trial were presented by the sponsor in:-

1- The clinical summary (p. 1:092 to 1:104).
2- The integrated clinical and statistical report section (p. 4:353 to 4:410), report tables and figures (p. 4:411 to 4:469) and subject data listings (p. 4:1990 to 4:2525) of the NDA application. Case reports for patients withdrawn due to adverse events were provided in Appendix E (p. 4:644 to 4:699).
3- The statistical report: More detailed tables were provided in

this report and its appendices (p. 4:0700 to 4:1989).

The medical officer has reviewed this information, and has cross checked the clinical report tables against the available case reports, the data listings and/or statistical report tabulations.

Patient disposition:

1- A total of **471 patients** (99 Retin-A 0.025%, 99 Acticin 0.025%, 101 Retin-A 0.1%, 99 Acticin 0.1%, 73 Vehicle) were enrolled and received medication. Of these, **401 patients** were acceptable for efficacy analysis (86 Retin-A 0.025%, 82 Acticin 0.025%, 86 Retin-A 0.1%, 83 Acticin 0.1%, 64 Vehicle).

Sixty nine patients withdrew from the study prior to completion. One patient Retin-A 0.1%) completed the study, but was not evaluable for efficacy due to a violation of protocol entrance criteria (patient did not have at least 10 inflammatory lesions at baseline) which was not detected until study completion. Thus, a total of **402 patients** have completed the study and are safety evaluable for full period exposure per protocool (table 1.4, p. 4:780 of NDA).

The distribution of the enrolled and the efficacy-evaluable patients in the different arms and different invesigators is shown in the following table (modified from table on p. 4:372 of the NDA).

Investigator	Treatment	Number of Patients Entered, per arm	Cumulative	Evaluable, per arm	Cumulative
Cullen	Retin-A 0.025%	15		14	
	Acticin 0.025%	15		11	
	Retin-A 0.1%	16		13	
	Acticin 0.1%	14		13	
	Vehicle	10		9	
	SUBTOTAL	70		60	
Funicella	Retin-A 0.025%	16	31	12	26
	Acticin 0.025%	16	31	14	25
	Retin-A 0.1%	17	33	15	28
	Acticin 0.1%	17	31	14	27
	Vehicle	12	22	11	20
	SUBTOTAL	78		66	
Jarratt	Retin-A 0.025%	16	47	13	39
	Acticin 0.025%	16	47	13	38
	Retin-A 0.1%	16	49	13	41
	Acticin 0.1%	16	47	13	40
	Vehicle	12	34	10	30
	SUBTOTAL	76		62	
Jones	Retin-A 0.025%	16	63	15	54
	Acticin 0.025%	16	63	14	52
	Retin-A 0.1%	16	65	14	55
	Acticin 0.1%	16	63	14	54
	Vehicle	12	46	12	42
	SUBTOTAL	76		69	
Lucky	Retin-A 0.025%	20	83	18	72
	Acticin 0.025%	20	83	17	69
	Retin-A 0.1%	20	85	18	73
	Acticin 0.1%	20	83	19	73
	Vehicle	15	61	13	55
	SUBTOTAL	95		85	
Reddick	Retin-A 0.025%	16	99	14	86
	Acticin 0.025%	16	99	13	82
	Retin-A 0.1%	16	101	13	86
	Acticin 0.1%	16	99	10	83
	Vehicle	12	73	9	64
	SUBTOTAL	76		59	
	TOTAL	471		401	

Comments:- A smaller number of patients was assigned to the vehicle arm. However, this was decided in the protocol submitted to the IND because power calculations showed that 60 evaluable patients will be sufficient in the vehicle arm (p. 4:371, 474, 479 of NDA) whereas 80 evaluable patients are needed in each active group. The randomization was computer generated, assigning 100 patients for each active group and 80 patients to the vehicle group.

2- The number of patients excluded from efficacy evaluation (drop outs) from each arm of the study and the sponsor's classification of the reasons for their exclusion are shown in the following table (p. 4:373 of NDA).

Reason for Exclusion	Retin-A 0.025%	Acticin 0.025%	Retin-A 0.1%	Acticin 0.1%	Vehicle	Total
Lost to follow-up	7	7	2	8	2	26
Non-compliant	3	6	6**	3	3	21
Adverse experience	0	0	1+	0	0	1
Personal	1	2	1	3	2	9
Lack of efficacy	1	1	0	1	0	3
Protocol violation	0	0	3++	0	1	4
Concurrent illness	0	1*	2^	0	0	3
Other	1	0	0	1	1	3
TOTAL	13	17	15	16	9	70

* diagnosed with strep throat, treated with erythromycin.

** became pregnant during the study and was referred to an obstetrician for follow up.

\+ complained of skin irritation, increased erythema, peeling, burning and itching.

++ completed the study, but was excluded from efficacy analyses due to a violation of protocol entrance criteria undetected until completion.

^ hospitalized for severe depression; diagnosed with gastroenteritis, treated with tetracycline.

The sponsor provided tables on pp. 4:374, 375 & 376 for special cases of patients that have been considered evaluable at the investigator's or sponsor's discretion despite minor protocol violations or use of other medications or facial moisturizers.

Comments:

1- The higest drop out rate (22.4%, 17/76) was noticed with investigator Reddick, and the lowest (9.2%, 7/76) with investigator Jones. The drop out rate was also lower (10.5%, 10/95) with investigator Lucky. The drop out rate in the different arms of the study ranged from 12.3% (9/73, Vehicle arm) to 17.2% (17/99, Acticin 0.025% arm). It was also noticably high (16.2%, 16/99) in the Acticin 0.1% arm in comparison with the Retin-A arms (13.1% & 14.9%). The clinical significance of these differences by investigator or by arm of study is doubtful. The statistical reviewer was consulted to find if these differences were statistically significant. Statistical analysis showed they were not significant.

2- The cases that were considered not evaluable and the special cases considered evaluable by the sponsor, were reviewed and found to be apparently reasonable until further efficacy results are evaluated.

3- Case , in the table above, was considered noncompliant. This case would be more appropriately considered a protocol violation. The medical officer contacted the sponsor to discuss their reasons, especially if the case report (not provided in the NDA) showed that there was noncompliance in addition to the pregnancy event. In his response (9/13/94 Fax), the sponsor agreed that this subject would be more appropriately categorized as protocol violation.

Demographic characteristics:

Of the 471 patients entering the study, 243 (52%) were female. The mean ages for the five arms of the study ranged from 19-21 years old. The demographic characteristics of each arm are shown in the following table (modified from p. 4:377 of NDA).

	Retin-A 0.025%	Acticin 0.025%	Retin-A 0.1%	Acticin 0.1%	Vehicle	Total
Males	45	49	48	44	42	228
Females	54	50	53	55	31	243
Males %	45.5	49.5	47.5	44.4	57.5	48.4
Mean age (y.)	19.7	20.2	20.6	19.4	20.1	20.0

The sex distribution in each study center is shown in the following table (calculated from table 2.1, p. 4:411 and p. 4:783 of NDA).

	Cullen	Funicella	Jarratt	Jones	Lucky	Reddick
Males	18	45	44	37	43	41
Females	52	33	32	39	52	35
Males %	25.7	57.7	57.9	48.7	45.3	54.0

The sponsor did not find any statistically significant difference between the five arms in the distribution of either age or sex.

Comments: Although there were large differences in the percentage of males in the different centers (25.7%-57.9%) the differences were much lower (44.4%-57.5%) in the different arms of the study. The percentage of blacks in the population studied was not given by the sponsor. The reviewer could not find any information about race in line listings or case report forms. Because of its importance for the evaluation of safety (certain adverse events are more significant for blacks e.g. hypopigmentation) and efficacy, this information was requested from the sponsor on 8/17/94.

On 10/7/94, the sponsor submitted the updated summary tables of race information for PDC 004-011, listings of adverse events by treatment and race, and listings of adverse events by race and treatment. No summary tables showing incidence of adverse events by race and treatment were submitted and their manual compilation from the listings was not practical. In addition, the very low participation of blacks (3% to 7%, or 3 to 7 subjects per arm of study) percluded any statistically meaningful comparison of adverse events by race and treatment.

On 10/28/94, the sponsor submitted a summary of skin safety by race. These tables showed the incidence of the different safety parameters assessed at each visit in each race. No comparisons were made between the different races.

Effectiveness results:

The five treatment groups were compared with respect to the following endpoints:

1- Total Lesion Counts:

The change, percent change and categorical change in total lesion counts from baseline to Day 84 were chosen as the primary efficacy variables. The following two tables show the mean total counts (No.) of acne lesions (inflammatory and non-inflammatory) at each evaluation visit, and the decrease (or increase, +) in these means from their baseline values (day 00) expressed as absolute counts (Change) or as percent of baseline values (%Ch.) for all arms of the study.

TIME days	RETIN-A 0.025%				ACTICIN 0.025%				VEHICLE			
	N	No.	Change	%Ch.	N	No.	Change	%Ch.	N	No.	Change	%Ch.
00	98	91.4			99	92.6			72	93.7		
14	91	84.3	7.1	7.8	91	86.9	5.7	6.2	67	96.5	+2.8	+3.0
28	88	73.2	18.2	19.9	89	76.1	16.5	17.8	63	88.9	4.8	5.1
56	85	59.9*	31.5	34.5	81	63.0*	29.6	32.0	60	76.1	17.6	18.8
84	81	49.2*	42.2	46.2	75	51.3*	41.3	44.6	58	70.0	23.7	25.3

TIME days	RETIN-A 0.10%				ACTICIN 0.10%			
	N	No.	Change	%Ch.	N	No.	Change	%Ch.
00	98	96.6			98	96.2		
14	83	81.1	15.5	16.1	87	85.1	11.1	11.5
28	90	72.3	24.3	25.2	84	72.9	23.3	24.2
56	83	56.0*	40.6	42.0	77	55.2*	41.0	42.6
84	79	45.0*	51.6	53.4	75	50.0*	46.2	48.0

The data in these tables were calculated from tables 2 and 4 of the Integrated Clinical and Statistical report of the NDA (pp. 4:378 & 380). The asterisks denote significant differences from the vehicle as provided by the sponsor.

There was no statistically significant difference between the different arms in the baseline mean total counts. They

ranged from 91.4 (Retin-A 0.025%) to 96.6 lesions (Retin-A 0.1%).

The sponsor has provided tables showing the mean percent decrease in total lesion counts from baseline in the Integrated Clinical and Statistical report of the NDA (tables 3 and 5, pp. 4:379 & 381, copies of which are provided in the Addendum).

Also, tables showing the catgorized percent improvement and the mean absolute change in total lesion counts at all evaluation visits subsequent to the baseline were provided by the sponsor (a- table II, p. 4:412 and b- tables 3.2.1 & 3.2.2.1&2, pp. 4:788-790, respectively. Copies of these tables are provided in the Addendum).

These latter three sets of tables showed that improvement in total counts started to become statistically significantly better with all active treatments in comparison to the placebo, at day 14 except for Acticin 0.025% (significant at day 28 as judged by all three parameters).

There were no statistically significant differences betweeen Acticin 0.025% and Retin-A 0.025%, or betweeen Acticin 0.1% and Retin-A 0.1% at all evaluation points and with all of these evaluation parameters except for day 14, when the Retin-A 0.025% group showed significantly better categorized percent reduction than the Acticin 0.025% group (table II, p. 4:412 of NDA).

Comments:

1- Acticin 0.025% and 0.1% creams are effective and equivalent to the corresponding Retin-A creams as judged by all primary efficacy variables (84 days). However, the rate of onset of action of Acticin 0.025% cream is significantly slower than that of Retin-A 0.025% cream as judged by the categorical improvement on day 14. Also, at this time (day 14), Retin-A 0.025% cream was significantly better than placebo whereas Acticin 0.025% cream was not significantly better, as judged by mean absolute change, percent change or categorical improvement in total counts.

2- The percent change in the mean lesion counts shown in the above tables is different from the mean percent change presented by the sponsor (tables 3 and 5, pp. 4:379 & 381) in the NDA. This is understandable because each is calculated by a different (and non-equivalent) formula and each uses a different denominator (which is the mean of all patients at baseline for percent change in the mean in the above tables rather than the mean of the patients evaluable at the particular evaluation day) . However, the differences

are expected to be small under usual circumstances. In few cases where the differences were remarkable, detailed examination by the statistical reviewer showed no statistically significant differences that may have been indicative of bias.

3- The 95% confidence intervals (CI) of the differences between corresponding formulations of Acticin and Retin-A in the mean percent change in total lesion counts given in tables 3 and 5 (pp.4:379 & 380, copies of which are provided in the addendum) were calculated by the statistical reviewer because they were not provided by the sponsor. The sponsor provided standard errors only for these figures in table 3.3.1 (p. 4:791 of the NDA). The statistical reviewer has also provided the 20% range of the corresponding Retin-A values for comparison. The results of these calculations are provided in the following table:

DAY	95% C.I. of Acticin vs. Retin-A (0.025%)	20% of 0.025% Retin-A mean	95% C.I. of Acticin vs. Retin-A (0.1%)	20% of 0.1% Retin-A mean
Day 14	(-13.6 , 0.7)	± 2.3	(- 9.9 , 4.4)	± 2.9
Day 28	(-14.3 , 1.7)	± 4.9	(-10.4 , 5.5)	± 5.4
Day 56	(-12.1 , 6.8)	± 7.3	(-10.9 , 8.2)	± 8.6
Day 84	(-11.6 , 5.3)	± 9.7	(-17.1 , 2.5)	±10.7

According to this statistical analysis, the trial failed to establish equivalence of the 0.025% and 0.1% Acticin cream formulations to the corresponding Retin-A formulations within 20% of the latter.

2- Non-Inflammatory Lesion Counts:

The mean total non-inflammatory lesion counts at all evaluation visits were provided in tables 6 and 8 (pp. 4:381 & 383 of the NDA, copies are provided in the Addendum) for the 0.025% and the 0.01% formulations, respectively. There was no statistically significant difference between the different arms in the baseline mean non-inflammatory lesion counts. They ranged from 70.6 (Retin-A 0.025%) to 76.6 lesions (Acticin 0.1%). The counts in all the tretinoin formulations arms became significantly less than in the vehicle arm on days 56 and 84 of the study.

Tables showing the mean absolute change (tables 4.2) and the percent change (tables 4.3) from baseline as well as the categorical improvement (tables 4.4) in total non-inflamma-

tory lesion counts at all evaluation visits subsequent to baseline were provided by the sponsor on pages 4:801-4:810 of the NDA (copies are also provided in the Addendum to this review). These tables showed that the improvement in all the active treatment arms became significantly better than placebo from Day 14 and continued through out the study with one exception: categorical percent improvement on Day 28 in the Acticin 0.025% treatment was not significantly better than placebo. The improvement with Retin-A formulations was not significantly different from the corresponding Acticin formulations at all evaluation visits except at the end of the study (Day 84) when 0.1% Retin-a was better than 0.1% Acticin as determined by the categorical percent improvement.

3- Inflammatory Lesion Counts:

The mean total inflammatory lesion counts at all evaluation visits were provided in tables 10 and 12 (pp. 4:384 & 386 of the NDA) for the 0.025% and the 0.1% formulations, respectively. There was no statistically significant difference between the different arms in the baseline mean inflammatory lesion counts. They ranged from 19.6 (Acticin 0.1%) to 21.3 lesions (Retin-A 0.1%). The counts in all the tretinoin formulations arms did not become significantly less than in the vehicle at any time during the study.

Tables showing the mean absolute change (tables 5.2) and the percent change (tables 5.3) from baseline as well as the categorical improvement (tables 5.4) in total inflammatory lesion counts at all evaluation visits subsequent to baseline were provided by the sponsor on pages 4:811-4:823 of the NDA. These tables showed that the improvement in all the active treatment arms did not become significantly better than the placebo at any point during the study except for day 84 when the Retin-A 0.1% and 0.025% were better than placebo as judged by mean absolute change and percent change in counts, and Acticin 0.1% was better than placebo as judged only by the percent change in counts. The improvement with Retin-A formulations was not significantly different from the corresponding Acticin formulations at all evaluation visits.

Comments: As shown from the data on inflammatory (this section, #3) and non-inflammatory (previous section, #2) lesion counts and improvements, the initial therapeutic effects (first three months of therapy) of tretinoin are shown mostly on the **non-inflammatory lesions**. The improvement with Acticin cream formulations was quantitaively almost always (15/16 times in tables #7, 9, 11, 13, pp.4:382-386, copies of which are provided in the Addendum) lower than the improvement with the corresponding

Retin-A cream formulations, and this **reached statistical significance** at the end of the trial i.e. on day 84, for the 0.1% formulations as measured by the categorical improvement in **non-inflammatory lesions**. This finding indicates significant lack of equivalence between Acticin and Retin-A cream formulations.

4- Intent-to-Treat Analysis:

This is discussed in detail in the statistical report of the NDA, p. 4:743 and the tables are provided in Appendix F, p. 4:1558-1873.

Comments: On checking the statistical significance data in tables F.1.3.2.1, 2, pp. 4:843, 844, they were found wrong. When consulted, the statistical reviewer found 4 other wrong tables. The correct tables were requested from the sponsor who submitted them on 9/12/94, and were received by the medical and statistical reviewers on 10/26/94. The sponsor attributed these errors to manual transcription of data from the statistical output to WordPerfect.

Taking these corrections in consideration, no significant differences in the results were seen on comparison of the intent to treat analysis with the analysis of all effficacy evaluable patients.

5- Treatment-by-Investigator Interactions:

Significant interactions were found in many parameters at different evaluation points. These were discussed in the NDA, p. 4:387 and the tables were presented in Appendix B, p. 4:929-1124 of the NDA.

Comments: The treatment-by-investigator tables provided by the sponsor did not directly compare the different investigators. When the mean percent change in total lesions data at days 56 and 84 (tables B.1.2, pp. 4:935-940, copies of which are provided in the Addendum to this review) were compared by the reviewer, certain consistent patterns of variation were noticed. Investigator Jones consistently reported the highest improvement in all active treatment arms (54.84%-76.66%) whereas investigator Cullen consistently reported the highest improvement in the placebo arm (31.62%, 44.85%). The least improvement in the active treatment arms were reported by investigator Cullen in 3 of 4 points in Acticin cream (16.79%-28.09%), and by investigator Funicella in all points of Retin-A cream and the remaining point in Acticin cream (20.55%-35.81%). Also, these results showed an unexpectedly high degree of variation between the different investigators.

The results of investigator Cullen (55 and 56 subjects evaluable on days 56 and 84, respectively) show that Acticin 0.025% and 0.1% creams were less effective than placebo at day 56 (-17%, -18% and -32%, respectively) and Day 84 (-28%, -30% and -45%, respectively), whereas Retin-A 0.025% cream was similar to placebo and Retin-A 0.1% cream was better than placebo. These results show that Acticin cream was clearly less effective than placebo in one of the six centers of the clinical study.

6- Global Evaluations: Detailed results of by-investigator summaries of global evaluations were presented in Appendix B.8 (pp. 4:1113-1124). Statistical analysis of the global evaluation results were presented in Appendix D.5 (pp. 4:1461-1476). These evaluations did not lead to any conclusions that differ significantly from previously discussed evaluations.

7- Equivalence:

The sponsor assessed therapeutic equivalence by examining patterns of significant treatment effects and by testing for equivalence of mean absolute and mean percent change in total lesion counts on Days 56 and 84. The sponsor's analysis (NDA p. 4:389,390) showed equivalence of Acticin creams to the corresponding Retin-A creams within + 22-28% of the Retin-A data for Days 56 and 84. Exceptions to equivalence at Day 14 for 0.025% and Day 84 for 0.1% creams were also noted by the sponsor.

Comments: As discussed above (sections 1, 2, 3), the equivalence of Acticin and Retin-A creams is not supported by the data.

Safety results:

1- Extent of exposure: Of the 402 patients completing the study and evaluable for safety (see patient disposition) 64 were treated with placebo, 165 with Acticin (0.025%, 82 patients; 0.1%, 83 patients) and 173 with Retin-A (0.025%, 86 patients; 0.1%, 87 patients).

As specified in the protocol, 35 patients had the frequency of application reduced to every other night due to irritation. Of these 35 patients, 5 were in 0.025% Acticin arm, 9 in 0.025% Retin-A, 10 in 0.1% Acticin and 11 in 0.1% Retin-A.

2- Adverse Experience:

a- Skin parameters: Erythema, peeling, dryness, burning / stinging, itching and tightness were evaluated at each visit. The results at all visits are shown in tables 14-19 on pp. 4:394-400 of the NDA. The percent of patients reporting these events on day 84 of the study was:

Parameter	Retin-A 0.025%	Acticin 0.025%	Retin-A 0.1%	Acticin 0.1%	Vehicle
Erythema	21*	23*	30*	28*	5
Peeling	9	10	32*+	16	2
Dryness	17*	15*	28*	27*	3
Burng./Sting.	8	7	13*	14*	3
Itching	15	9	13	20	6
Tightness	24	18	22	34*	16

* Statistically significant from Vehicle
\+ Statistically significant from Acticin 0.1%

Of the 6 skin parameters tested, only peeling showed a significant difference in its incidence at day 84 of the study period. This difference showed that Acticin 0.1% produced only one half of the peeling side effect produced by Retin-A 0.1%.

b- Adverse events: Adverse events (AE) were reported by 36% vehicle patients and by 42-45% active treatment patients. There were no statistically significant differences between the different arms in the number of patients reporting at least one AE.

The body system accounting for most AE was "body as a whole" (Table XII, p.4:449 of NDA). The percent of patients reporting AE in this category ranged from 25% to 29% in the different arms of the study. The majority of the events were flu syndrome and headache (Table XII, p. 4:450-452 of NDA). In this body system, 15 events of pain were considered possibly or probably drug related. These were 1 event in Vehicle, 1 in Acticin 0.025%, 3 in Acticin 0.1%, 3 in Retin-A 0.025%, and 7 in Retin-A 0.1% (Table XIV, p. 4:453-459 of NDA). Nineteen (19) events of various description (Table XV, p. 4:460-466 of NDA) were classified as severe. These appeared to be distributed across treatment groups, and no

trends were evident.

"Skin and appendages" was the second most common body system involved. Of the Vehicle patients, 4% (3 patients) reported 4 events in this category, whereas 7% of Acticin 0.025%, 14% of Retin-A 0.025%, 15% of Acticin 0.1%, and 16% of Retin-A 0.1% patients reported 12, 18, 21 and 28 events, respectively. The most frequently reported events included rash (11 Acticin, 18 Retin-A), dry skin (13 Acticin, 15 Retin-A), exfoliative dermatitis (5 Acticin, 5 Retin-A) and were usually considered treatment related (Table XIV, p. 4:453-459 of NDA). Of the 32 patients reporting rash, 12 were considered severe and 6 of 11 patients reporting exfoliative dermatitisas well as 10 of 28 patients with dry skin were classified as severe (Table XV, p. 4:460-466 of NDA). Again, those patients reporting severe events were distributed evenly across treatment groups, and no trends were evident.

c- Deaths: No deaths were reported during this study.

d- Withdrawals due to adverse events or concomitant illness: As shown in the table under "patient Disposition" section, only 4 patients were withdrawn for these reasons. Three patients were in the Retin-A 0.1% arm and one patient was in the Acticin 0.025% arm. Summary of these cases is provided in the NDA pp. 4:402-403, and case report forms are provided in Appendix E (pp. 4:644-699 of NDA).

The single case in the Acticin 0.025% arm reported being treated with erythromycin for 10 days because of Streptococcal throat infection. The investigator dtermined that she should be discontinued on this account.

3- Safety in other studies:

Two other studies, PDC 004-012 and PDC 004-013, used Acticin 0.1% cream (0.2% cream was also used in PDC 004-012) for the treatment of plaque psoriasis and actinic or senile purpura in the forearms, respectively. Sixteen patients in the former study used Acticin cream for 8 weeks, and 15 patients in the latter study used it for 16 weeks. No serious or unexpected AE related to the use of Acticin were reported in these studies. The proportion of patients reporting AE is presented in the table below.

Study #	PDC 004-012			PDC 004-013	Total (both studies)
	0.1%/Veh	0.2%/Veh	All Pts		
N:	8	8	16	15	31
No. with AE	2	4	6	11	17
% with AE	25.0	50.0	37.5	73.3	54.8
Total No. AE	4	5	9	20	29

Comments: The data presented in the present NDA indicate that the safety of 0.025% and 0.1% Acticin creams is generally equivalent to the corresponding Retin-A creams. With regard to the peeling side effect, 0.1% Acticin appears to be safer than 0.1% Retin-A.

Summary and conclusions:

The following conclusions are based on the data presented in this NDA and discussed above:

1- Efficacy:

Acticin 0.025% and 0.1% creams are effective as judged by all primary efficacy variables (84 days) according to the sponsors analysis. However, the results of one of the six centers of the study (investigator Cullen, see section 5 of the efficacy results) showed that Acticin 0.025% and 0.1% creams were less effective than placebo at Days 56 (-17%, -18% and -32%, respectively) and 84 (-28%, -30% and -45%, respectively). This investigator's results cast doubt on the claimed efficacy.

2- Equivalence:

The 0.025% and 0.1% Acticin creams failed to show equivalence to the corresponding Retin-A creams in many of the results of the present clinical trial.

A- The rate of onset of action of Acticin 0.025% cream is significantly slower than that of Retin-A 0.025% cream as judged by the categorical improvement on day 14. Also, at this time (day 14), Retin-A 0.025% cream was significantly better than placebo whereas Acticin 0.025% cream was not significantly better, as judged by mean absolute change, percent change or categorical improvement in total counts.

B- The data on inflammatory and non-inflammatory lesion counts and improvements (sections #3 and #2, respectively, of effectiveness results), showed that the initial therapeutic effects of tretinoin are shown only in the non-inflammatory lesions. The improvement with Acticin cream formulations was almost always lower than the improvement with the corresponding Retin-A cream formulations, and this difference reached statistical significance at the end of the trial i.e. on day 84, for the 0.1% formulations as measured by the categorical improvement in non-inflammatory lesions.

C- The 95% confidence analysis of the percent improvement in total counts (which was discussed in comment 3 on section #1 of effectiveness results) showed that the clinical trial failed to show equivalence of both 0.025% and 0.1% Acticin creams to the corresponding Retin-A formulations.

D- As discussed in section #7 of the efficacy results, the sponsor's analysis (NDA p. 4:389,390) showed equivalence of Acticin creams to the corresponding Retin-A creams within + 22-28% of the Retin-A data for Days 56 and 84, whereas equivalence within 20% of the innovator product is expected. As noted by the sponsor, there were exceptions (in which Acticin was less effective) to equivalence even at the 22-28% range.

3- Safety:

The safety of 0.025% and 0.1% Acticin creams is generally equivalent to the corresponding Retin-A creams. With regard to the peeling side effect, 0.1% Acticin appears to be safer than 0.1% Retin-A.

Recommendations:

Because of lack of equivalence and because efficacy has not been established unequivocally, the Medical Officer recommends non-approval of this NDA.

Reviewing Medical Officer

Ramzy S. Labib

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

cc: Orig NDA
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
HFD-540
HFD-540/DivDir/Wilkin 2/3/1/95
HFD-540/SMO/Chambers 1/30/95
HFD-540/MO/Labib
HFD-540/MO/Slifman
HFD-540/Pharm/Sheevers
HFD-540/Chem/Mokhtari-Rejali
HFD-540/CSO/Chapman
HFD-710/Biometrics/Turney

ADDENDUM

The following tables are copied from the original NDA and are provided to make it easier to follow the review.

Table 3: Mean Percent Decrease from Baseline
Total Lesion Counts - 0.025% Formulations

Time	N	Retin-A 0.025%	N	Acticin 0.025%	N	Vehicle
Day 14	91	11.6*	91	5.2	67	1.5(+)
Day 28	88	24.4*	89	18.1*	63	7.0
Day 56	85	36.7*	81	34.0*	60	20.8
Day 84	81	48.6*	75	45.5*	58	27.6

* Statistically significant from Vehicle
(+) Increase in lesions from baseline

Table 5: Mean Percent Decrease from Baseline
Total Lesion Counts - 0.1% Formulations

Time	N	Retin-A 0.1%	N	Acticin 0.1%	N	Vehicle
Day 14	83	14.5*	87	11.7*	67	1.5(+)
Day 28	90	26.8*	84	24.4*	63	7.0
Day 56	83	42.8*	77	41.4*	60	20.8
Day 84	79	53.7*	75	46.4*	58	27.6

* Statistically significant from Vehicle
(+) Increase in lesions from baseline

Table 6: Mean Total Non-Inflammatory Lesion Counts
0.025% Formulations

Time	N	Retin-A 0.025%	N	Acticin 0.025%	N	Vehicle
Baseline	98	70.6	99	72.3	72	72.9
Day 14	91	66.4	91	68.2	67	78.9
Day 28	88	56.7	89	59.1	63	72.1
Day 56	85	47.0*	81	49.8*	60	62.3
Day 84	81	37.9*	75	40.1*	58	56.6

* Statistically significant from Vehicle

Table 8: Mean Total Non-Inflammatory Lesion Counts
0.1% Formulations

Time	N	Retin-A 0.1%	N	Acticin 0.1%	N	Vehicle
Baseline	98	75.3	98	76.6	72	72.9
Day 14	83	64.3	87	67.1	67	78.9
Day 28	90	56.9	84	57.1	63	72.1
Day 56	83	44.5*	77	41.9*	60	62.3
Day 84	79	35.7*	75	39.2*	58	56.6

* Statistically significant from Vehicle

Table 7: Mean Percent Decrease from Baseline
Non-Inflammatory Lesion Counts
0.025% Formulations

Time	N	Retin-A 0.025%	N	Acticin 0.025%	N	Vehicle
Day 14	91	9.8*	91	3.9*	67	7.1(+)
Day 28	88	24.8*	89	17.4*	63	4.8
Day 56	85	36.0*	81	32.9*	60	17.7
Day 84	81	48.7*	75	45.1*	58	27.1

* Statistically significant from Vehicle
(+) Increase in lesions from baseline

4 0382

Table 9: Mean Percent Decrease from Baseline
Non-Inflammatory Lesion Counts
0.1% Formulations

Time	N	Retin-A 0.1%	N	Acticin 0.1%	N	Vehicle
Day 14	83	14.2*	87	11.7*	67	7.1(+)
Day 28	90	28.0*	84	25.0*	63	4.8
Day 56	83	43.0*	77	43.9*	60	17.7
Day 84	79	53.7*	75	46.5*	58	27.1

* Statistically significant from Vehicle
(+) Increase in lesions from baseline

4 0383

Table 11: Mean Percent Decrease from Baseline
Total Inflammatory Lesion Counts
0.025% Formulations

Time	N	Retin-A 0.025%	N	Acticin 0.025%	N	Vehicle
Day 14	91	17.4	91	8.7	67	18.6
Day 28	88	22.0	89	15.2	63	11.3
Day 56	85	37.5	81	35.8	60	31.0
Day 84	81	48.6*	75	45.7	58	32.5

* Statistically significant from Vehicle

Table 13: Mean Percent Decrease from Baseline
Total Inflammatory Lesion Counts
0.1% Formulations

Time	N	Retin-A 0.1%	N	Acticin 0.1%	N	Vehicle
Day 14	83	16.1	87	11.0	67	18.6
Day 28	90	22.2	84	20.5	63	11.3
Day 56	83	40.3	77	32.5	60	31.0
Day 84	79	51.7*	75	46.2*	58	32.5

* Statistically significant from Vehicle

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 3.4.1: Patient improvement in total inflammatory plus non-inflammatory lesion counts,
from baseline to each evaluation time.
Includes only patients evaluable for efficacy.

		IMPROVEMENT CATEGORY								
		WORSE-NO CHANGE		1-25% IMPROVEMENT		26-50% IMPROVEMENT		51-100% IMPROVEMENT		ALL
		N	PCTN	N	PCTN	N	PCTN	N	PCTN	N
VISIT	TREATMENT GROUP									
DAY 14	PD 0.025%	43	47.25	33	36.26	11	12.00	4	4.40	91
	PD 0.10%	29	33.33	30	44.03	13	14.94	8	8.90	87
	RA 0.025%	20	30.77	40	43.06	16	17.58	7	7.69	91
	RA 0.10%	21	25.30	41	40.40	16	18.26	5	6.02	83
	VEHICLE	36	52.24	27	40.30	5	7.46	.	.	67
DAY 28	PD 0.025%	28	31.46	24	26.97	28	28.08	12	13.48	89
	PD 0.10%	13	16.46	33	38.28	26	30.05	12	14.28	84
	RA 0.025%	21	23.86	21	23.86	28	32.96	17	19.32	88
	RA 0.10%	18	20.00	21	23.33	34	37.78	17	18.89	90
	VEHICLE	27	42.86	18	28.57	16	25.81	3	4.76	63
DAY 56	PD 0.025%	8	8.08	23	28.48	23	28.48	27	33.33	81
	PD 0.10%	8	7.78	18	23.38	18	24.68	34	44.16	77
	RA 0.025%	13	15.28	18	18.82	28	38.58	38	35.28	85
	RA 0.10%	8	8.84	14	16.87	22	26.51	38	48.88	83
	VEHICLE	18	25.88	18	38.88	16	28.87	11	18.33	68
DAY 84	PD 0.025%	8	8.88	18	13.33	21	28.88	38	58.67	75
	PD 0.10%	9	12.88	8	8.88	21	28.88	38	52.88	78
	RA 0.025%	4	4.84	13	18.86	25	38.88	38	48.15	81

(CONTINUED)

Table II

4 of 12

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 3.4.1: Patient improvement in total inflammatory plus non-inflammatory lesion counts, *from* baseline to each evaluation time.
Includes only patients evaluable for efficacy.

		IMPROVEMENT CATEGORY								
		WORSE-NO CHANGE		1-25% IMPROVEMENT		26-50% IMPROVEMENT		51-100% IMPROVEMENT		ALL
		N	PCTN	N	PCTN	N	PCTN	N	PCTN	N
VISIT	TREATMENT GROUP									
DAY 84	RA 0.10%	7	8.00	4	5.00	17	21.52	51	64.56	79
	VEHICLE	11	18.97	18	31.03	14	24.14	15	25.86	58

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 3.2.1: Mean change from baseline in total inflammatory plus non-inflammatory lesion counts, from baseline to each evaluation time
Includes only patients evaluable for efficacy.

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	91	-5.85	23.49	87	-11.00	22.48	91	-9.45	24.54	83	-13.73	26.32	67	1.40	22.51
DAY 28	89	-16.43	26.16	84	-22.12	25.52	88	-20.72	24.80	90	-23.12	30.08	63	-4.98	33.33
DAY 56	81	-31.28	29.28	77	-39.31	33.98	85	-32.91	30.86	83	-40.53	33.04	60	-17.48	28.80
DAY 84	75	-43.21	31.26	76	-42.76	35.44	81	-45.02	30.26	79	-52.08	34.60	58	-24.02	32.49

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 3.2.2.1: Results of statistical analysis of mean change in total lesion counts, 0.025% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.025% vs VEHICLE	RETIN-A vs PD 0.025%
DAY 14	0.0008	0.0052	0.0578	0.3257
DAY 28	0.0001	0.0003	0.0071	0.2741
DAY 56	0.0001	0.0007	0.0031	0.6490
DAY 84	0.0001	0.0001	0.0002	0.6780

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 3.2.2.2: Results of statistical analysis of mean change in total lesion counts, 0.10% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.10% vs VEHICLE	RETIN-A vs PD 0.10%
DAY 14	0.0008	0.0001	0.0011	0.3758
DAY 28	0.0001	0.0001	0.0001	0.9527
DAY 56	0.0001	0.0001	0.0001	0.9243
DAY 84	0.0001	0.0001	0.0001	0.1147

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 4.2.1: Mean change from baseline in total non-inflammatory lesion counts, from baseline to each evaluation time
Includes only patients evaluable for efficacy.

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	91	-4.21	22.67	87	-8.97	19.17	91	-6.53	21.15	83	-10.41	23.81	67	4.69	22.74
DAY 28	89	-13.02	25.02	84	-18.21	21.88	88	-16.66	20.46	90	-18.07	27.54	63	-1.81	31.35
DAY 56	81	-23.74	26.50	77	-33.22	26.92	85	-25.29	26.56	83	-31.88	29.00	60	-11.55	28.34
DAY 84	75	-33.60	26.81	75	-34.69	31.69	81	-34.95	27.04	79	-40.85	31.38	58	-17.59	30.60

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.2.2.1: Results of statistical analysis of mean change in total noninflammatory lesion counts, 0.025% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.025% vs VEHICLE	RETIN-A vs PD 0.025%
DAY 14	0.0002	0.0018	0.0109	0.5236
DAY 28	0.0001	0.0002	0.0031	0.3627
DAY 56	0.0001	0.0005	0.0020	0.6743
DAY 84	0.0001	0.0001	0.0002	0.7177

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.2.2.2: Results of statistical analysis of mean change in total noninflammatory lesion counts, 0.10% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.10% vs VEHICLE	RETIN-A vs PD 0.10%
DAY 14	0.0002	0.0001	0.0001	0.5530
DAY 28	0.0001	0.0001	0.0001	0.8431
DAY 56	0.0001	0.0001	0.0001	0.6647
DAY 84	0.0001	0.0001	0.0001	0.2627

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 4.3.1: Mean percent change from baseline in total non-inflammatory lesion counts, from baseline to each evaluation time. Includes only patients evaluable for efficacy.

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	91	-3.93	28.32	87	-11.70	25.13	91	-9.83	27.04	83	-14.18	29.81	67	7.06	33.93
DAY 28	89	-17.41	31.33	84	-25.00	27.27	88	-24.79	28.19	90	-28.00	31.94	63	-4.76	37.65
DAY 56	81	-32.90	35.50	77	-43.86	29.66	85	-35.96	33.40	83	-43.04	35.81	60	-17.67	38.80
DAY 84	75	-45.05	29.58	75	-46.53	34.59	81	-46.70	28.33	79	-53.69	35.22	58	-27.08	36.46

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.3.2.1:. Results of statistical analysis of mean percent change in total noninflammatory lesion counts, 0.025% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.025% vs VEHICLE	RETIN-A vs PD 0.025%
DAY 14	0.0001	0.0006	0.0038 (2 corrected 9/12/94)	0.1904
DAY 28	0.0001	0.0001	0.0087	0.1038
DAY 56	0.0001	0.0007	0.0042	0.5689
DAY 84	0.0001	0.0001	0.0014	0.4811

4 0805

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.3.2.2: Results of statistical analysis of mean percent change in total noninflammatory lesion counts, 0.10% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.10% vs VEHICLE	RETIN-A vs PD 0.10%
DAY 14	0.0001	0.0001	0.0001	0.4492
DAY 28	0.0001	0.0001	0.0001	0.5963
DAY 56	0.0001	0.0001	0.0001	0.9921
DAY 84	0.0001	0.0001	0.0001	0.1768

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 4.4.1: Patient improvement in total non-inflammatory lesion counts, from baseline to each evaluation time. Includes only patients evaluable for efficacy.

		IMPROVEMENT CATEGORY								
		WORSE-NO CHANGE		1-25% IMPROVEMENT		26-50% IMPROVEMENT		51-100% IMPROVEMENT		ALL
VISIT	TREATMENT GROUP	N	PCTN	N	PCTN	N	PCTN	N	PCTN	N
DAY 14	PD 0.025%	41	45.05	32	35.16	12	13.19	6	6.59	91
	PD 0.10%	33	37 93	36	41.38	10	11.49	8	9.20	87
	RA 0.025%	34	37.36	34	37 36	14	15 38	9	9.89	91
	RA 0.10%	22	26 51	37	44.58	18	21.69	6	7.23	83
	VEHICLE	38	56.72	22	32.84	6	8.96	1	1.49	67
DAY 28	PD 0.025%	29	32.58	25	28.09	22	24.72	13	14.61	89
	PD 0.10%	16	19.05	27	32.14	29	34.52	12	14.29	84
	RA 0.025%	20	22.73	23	26.14	27	30.68	18	20.45	88
	RA 0.10%	19	21 11	23	25.56	24	28.87	24	28.87	90
	VEHICLE	27	42.86	16	25.40	16	25.40	4	6 35	63
DAY 56	PD 0.025%	10	12.35	17	20 99	24	29.63	30	37.04	81
	PD 0.10%	6	7.79	15	19.48	22	28.57	34	44.16	77
	RA 0.025%	13	15.29	17	20.00	23	27.06	32	37.65	85
	RA 0.10%	10	12 05	12	14.46	21	25.30	40	48.19	83
	VEHICLE	19	31.67	13	21.67	16	26.67	12	20 00	60
DAY 84	PD 0.025%	11	14.67	8	10 67	16	21.33	40	53.33	75
	PD 0 10%	12	16.00	5	6.67	20	26.67	38	50.67	75
	RA 0.025%	6	7.41	12	14.81	20	24 69	43	53.09	81

(CONTINUED)

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

TABLE 4.4.1: Patient improvement in total non-inflammatory lesion counts,
from baseline to each evaluation time
Includes only patients evaluable for efficacy.

		IMPROVEMENT CATEGORY								
		WORSE-NO CHANGE		1-25% IMPROVEMENT		26-50% IMPROVEMENT		51-100% IMPROVEMENT		ALL
		N	PCTN	N	PCTN	N	PCTN	N	PCTN	N
VISIT	TREATMENT GROUP									
DAY 84	RA 0.10%	6	7.59	7	8.86	11	13.92	55	69.62	79
	VEHICLE	14	24.14	12	20.69	13	22.41	19	32.76	58

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.4.2.1: Results of statistical analysis of categorical percent improvement in total noninflammatory lesion counts, 0.025% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.025% vs VEHICLE	RETIN-A vs PD 0.025%
DAY 14	0.0004	0.0014	0.0429	0.2324
DAY 28	0.0009	0.0012	0.1142	0.0827
DAY 56	0.0004	0.0053	0.0023	0.7934
DAY 84	0.0005	0.0014	0.0129	0.5414

PENEDERM, INCORPORATED Protocol PDC 004-011
Efficacy and Safety Study of Four Topical Retinoic Acid Formulations and a Vehicle Control in Patients with FDA Grade II or III Acne Vulgaris

TABLE 4.4.2.2: Results of statistical analysis of categorical percent improvement in total noninflammatory lesion counts, 0.10% formulations. Includes only patients evaluable for efficacy.

		PAIRWISE P		
	OVERALL P	RETIN-A VS. VEHICLE	PD 0.10% vs VEHICLE	RETIN-A vs PD 0.10%
DAY 14	0.0004	0.0001	0.0055	0.1997
DAY 28	0.0009	0.0001	0.0023	0.3398
DAY 56	0.0004	0.0001	0.0001	0.9726
DAY 84	0.0005	0.0001	0.0154	0.0416

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX 8.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts
from baseline to each evaluation time, by investigator.
Includes only patients evaluable for efficacy.

INVESTIGATOR=CULLEN

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	11	0.21	6.29	11	-5.00	13.44	14	-7.62	10.45	9	-12.92	18.82	8	-6.04	13.87
DAY 28	13	-1.41	13.92	13	-12.55	23.12	13	-18.62	19.38	14	-20.74	22.72	8	-16.10	18.20
DAY 56	10	-16.79	15.11	12	-17.97	34.26	12	-31.41	21.77	12	-41.32	18.94	9	-31.62	26.97
DAY 84	10	-26.09	20.86	13	-29.53	33.81	13	-43.98	23.65	12	-56.70	20.15	8	-44.65	27.32

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX 8.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts
from baseline to each evaluation time, by investigator.
Includes only patients evaluable for efficacy.

INVESTIGATOR=FUNICELLA

	TREATMENT GROUP															
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE			
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	
DAY 14	15	-6.73	24.00	14	-0.09	20.08	13	-2.93	20.49	16	1.28	29.66	10	-0.38	20.95	
DAY 28	15	-26.59	25.85	12	-21.01	22.35	13	-14.30	22.70	14	-2.83	27.19	10	-8.58	28.54	
DAY 56	15	-34.90	43.36	12	-32.38	22.38	13	-26.82	25.97	15	-20.55	38.02	10	-19.53	35.26	
DAY 84	14	-50.86	29.81	14	-27.39	31.55	12	-35.81	23.44	15	-30.03	40.96	9	-15.32	40.34	

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX B.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts
from baseline to each evaluation time, by investigator.
Includes only patients evaluable for efficacy.

INVESTIGATOR=JARRATT

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	15	1.18	9.23	16	-5.59	11.49	13	-2.45	18.09	16	-8.01	12.57	10	2.79	13.06
DAY 28	14	-15.20	20.45	15	-22.91	16.96	13	-19.93	27.40	15	-23.75	23.68	10	-8.83	21.16
DAY 56	13	-37.84	26.37	13	-50.40	24.96	13	-27.79	29.35	14	-38.42	30.75	9	-8.80	32.95
DAY 84	12	-42.09	29.23	11	-59.21	17.25	12	-36.85	32.43	13	-48.74	27.25	10	-8.32	38.06

PENEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX B.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts from baseline to each evaluation time, by investigator. Includes only patients evaluable for efficacy.

INVESTIGATOR=JONES

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	15	-19.18	23.21	15	-36.85	24.02	16	-35.00	20.29	15	-31.12	22.24	12	2.77	26.57
DAY 28	15	-43.92	20.42	14	-55.15	20.70	15	-50.17	20.00	15	-44.37	31.62	12	-17.81	36.03
DAY 56	14	-56.56	24.67	14	-68.73	20.43	15	-62 03	24.29	14	-70.32	21.59	12	-28.66	39.99
DAY 84	13	-54.64	23.21	13	-70.09	14.83	14	-63.18	28.56	14	-76.66	9.75	11	-43 80	24.35

PFNEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX B.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts
from baseline to each evaluation time, by investigator.
Includes only patients evaluable for efficacy.

INVESTIGATOR=LUCKY

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	19	-8.01	34.32	17	-10.57	22.70	19	-8.80	29.21	18	-19.41	19.38	15	-1.08	21.09
DAY 28	18	-14.92	30.86	17	-13.53	24.66	18	-23.00	26.86	18	-31.35	24.74	13	-12.82	20.95
DAY 56	16	-26.46	36.21	16	-29.90	23.60	17	-32.28	31.97	17	-40.78	27.68	12	-27.17	21.39
DAY 84	13	-39.31	28.63	14	-39.08	28.58	16	-49.19	23.70	16	-52.17	30.41	12	-27.21	35.58

PFNEDERM, INCORPORATED. Protocol PDC 004-011
Efficacy and safety study of four topical retinoic acid formulations
and a vehicle control in patients with FDA grade II or III acne vulgaris.

APPENDIX B.1.2: Mean percent change in total inflammatory plus non-inflammatory lesion counts
from baseline to each evaluation time, by investigator.
Includes only patients evaluable for efficacy.

INVESTIGATOR=REDDICK

	TREATMENT GROUP														
	PD 0.025%			PD 0.10%			RA 0.025%			RA 0.10%			VEHICLE		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
DAY 14	16	2.96	21.11	14	-9.92	17.41	16	-9.70	30.14	11	-18.03	35.42	12	9.17	39.26
DAY 28	14	-3.69	25.78	13	-22.08	16.92	16	-18.18	27.49	14	-35.40	22.38	10	21.95	53.42
DAY 56	13	-27.21	17.46	10	-48.81	26.91	15	-36.84	32.91	11	-48.13	28.65	8	-2.13	34.31
DAY 84	13	-52.99	21.93	10	-60.05	30.93	14	-58.78	19.20	9	-63.36	19.00	8	-26.76	33.36

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

STATISTICAL REVIEW(S)

has not gone to Doc. Room. Given to me on 6/21/96 RB

Statistical Review and Evaluation
(Amendment)

NDA#: 20-404

Applicant: Penederm Inc.

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

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

Indication: Acne Vulgaris

Type of Review: Clinical

Medical Input: Dr. Ramzy Labib, HFD-540

A. Background:

It was agreed that these cream formulations are to be treated as line extensions of the Gel formulation in NDA The approval of all three concentrations of this formulation is contingent on the approval of NDA By reference all agreements between FDA and the sponsor for NDA relative to OGD status are incorporated in this submission also. A further agreement is that the high concentration must be statistically superior to the low concentration, i.e., that the 0.05% concentration will be bracketed by the 0.025% and 0.1% concentrations. If the high concentration is superior to the low concentrations and the claims of therapeutic equivalency are supported and approved, then the middle concentration will also be approved.

The sponsor submitted study PDC 004-011 in support of this line extension. Prior evaluation found that the submission failed to demonstrate equivalency between Acticin Cream 0.025% and Renin-A Cream 0.025% and failed to demonstrate equivalency between Acticin Cream 0.1% and Renin-A Cream 0.1%. A claim of clinical superiority of Acticin Cream in each concentration compared to their vehicles could be considered substantial evidence of efficacy provided any efficacy demonstration was substantiated by an independent study.

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

sponsor.

A. Calculations and Evaluation

All confidence interval results for demonstrating therapeutic equivalency are presented as two-sided 90% confidence intervals in the format $_{nt,\ nc}(CI)_{[pt,std],\ [pc,std]}$, where n_t and n_c are respectively the sample size Avita and Retin-A or Vehicle and $[p_t,std]$ and $[p_c,std]$ are the mean improvement measures from baseline and standard deviation of the mean for the test agent and comparator respectively.

Table 1.2.1 presents % reduction from baseline in Total Lesion Counts. For Study PDC 004-011 the 90% CI and p value comparing Avita 0.025% to Retin-A 0.025% is $_{97,94}(-3.54,\ 11.6)_{[-38.8,32.7],\ [-42.89,30.7]}$, $p > .1$; the Avita 0.1% to Retin-A 0.1% comparison is $_{92,95}(.569,\ 15.7)_{[-44.1,31.7],\ [-52.17,30.6]}$, $p < .1$ in favor of Retin-A and the Avita 0.1% to Avita 0.025% comparison is $_{92,97}(-2.53,\ 13.0)_{[-44.1,31.7],\ [-38.8,\ 32.7]}$, $p > .1$, indicating the Avita 0.025% is therapeutically equivalent to the Avita 0.1% concentration. For the comparison of Avita 0.025% to Vehicle, the 90% CI is $_{97,\ 69}(-27.7,\ -6.4)_{[-38.8,\ 32.7],\ [-21.8,\ 36.4]}$,
$p < .05$.

For total lesion count reduction these data fail to support the sponsor's claim. Retin-A 0.1% is statistically superior to Avita 0.1%, and Avita 0.025% is therapeutically equivalent to Avita 0.1%. The criteria for success are that Avita is therapeutically equivalent to Retin-A at both the high and the low concentration, and the high concentration is statistically superior to the low concentration.

Table 2.2.1 presents % reduction from baseline in Noninflammatory lesion Counts. The 90% CI and p value comparing Avita 0.025% to Retin-A 0.025% is $_{97,94}(-3.59,\ 12.7)_{[-38.5,35.3],\ [-43.05,32.5]}$, $p > .1$; the Avita 0.1% to Retin-A 0.1% comparison is $_{92,95}(-.89,\ 15.7)_{[-44.8,34.3],\ [-52.27,34.5]}$, $p > .1$, and the Avita 0.1% to Avita 0.025% comparison is $_{92,97}(-2.05,\ 14.7)_{[-44.8,34.3],\ [-38.5,\ 35.3]}$, $p > .1$, indicating the Avita 0.025% is therapeutically equivalent to the Avita 0.1% concentration. For Avita 0.025% to Vehicle the 90% CI is $_{97,\ 69}(-27.0,\ -8.1)_{[-38.5,\ 35.3],\ [-20.9,\ 37.7]}$, $p < .05$.

Although Avita 0.025% is statistically superior to its Vehicle and is therapeutically equivalent to Retin-A, the Avita 0.025% is also therapeutically equivalent to the Avita 0.1% concentration. Thus, it fails to meet the acceptance criteria.

There is not a physician's Global Evaluation score. However, the sponsor provided improvement by category data for total lesion counts and noninflammatory lesion counts. These data are thought by some to be closely associated with a global evaluation.

Table 4.3.1 given the sponsor's statistical evaluation of total lesion count improvement. Since this is a nonparametric, categorical tabulation of data, no confidence intervals are given.

These analyses show Avita 0.025% is statistically superior to its vehicle; Avita 0.025% to be statistically equivalent to Avita 0.1%, Avita 0.025% to be statistically equivalent to Retin-A 0.025% and Avita 0.1% to be statistically inferior to Retin-A 0.1%.

Table 4.2.1 gives the sponsor's statistical evaluation of noninflammatory Lesion count improvement. Since this is a nonparametric, categorical tabulation of data, no confidence intervals are given. These analyses show Avita 0.025% is statistically superior to its vehicle; Avita 0.025% to be statistically equivalent to Avita 0.1%, Avita 0.025% to be statistically equivalent to Retin-A 0.025% and Avita 0.1% to be statistically inferior to Retin-A 0.1%.

These data fail to support the sponsor's claim of therapeutic equivalency of Avita 0.1% to Retin-A 0.1% and also fail to demonstrate that the Avita 0.1% concentration is statistically superior to the Avita 0.025% concentration.

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

Based on the analyses of these data, the sponsor has failed to support the claim for a need of the middle and high dose of Avita and has failed to demonstrate therapeutic equivalency to the Retin-A product.

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

cc:
Archival: NDA-20-400
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Katz
HFD-540/Dr. Slifman
HFD-540/Mr. Blay
HFD-725/Dr. Harkins
Chron.
This review contains 3 pages.

STATISTICAL REVIEW AND EVALUATION

NDA:	20-404	MAR 6 1995
Applicant:	Penederm Incorporated	
Name of Drug:	tretinoin (ACTICIN) 0.025% cream	
Documents Reviewed:	Volumes 1.1, 1.17, 1.18, and 1.19 dated September 29, 1993	
	Data on diskette provided by the applicant on 5/16/94 and 1/24/95	
Indication:	acne vulgaris	
Date Assigned:	4/27/94	
Date Completed:	3/1/95	
Medical Officer:	Ramzy Labib, M.D., HFD-540	

I. INTRODUCTION

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

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

In support of their claims, the applicant has submitted data from one primary study, protocol PDC 004-011. This study compares the safety and efficacy of two strengths of Acticin tretinoin cream, 0.025% and 0.10% to two strengths of Retin-A tretinoin cream, 0.025% and 0.10%, and Acticin vehicle in the treatment of patients with mild to moderate acne vulgaris.

Throughout the review, the term "study 011" refers to protocol PDC 004-011. The treatment name abbreviations VEH, ACT025, ACT10, RET025, and RET10 refer to Acticin vehicle, Acticin 0.025%, Acticin 0.10%, Retin-A 0.025%, and Retin-A 0.10%, respectively.

The design and analytical methods of study 011 are very similar to the Acticin tretinoin gel studies described in the statistical review of NDA The design and analytical methods of study 011 are briefly summarized in section II below.

II. METHODS

Study 011 is a randomized, double blind, multicenter, controlled, parallel group trial that was conducted at 6 US centers. The randomization schedule was designed to allocate patients across the treatment groups in a 3:4:4:4:4 VEH: ACT025: ACT10: RET025: RET10 ratio.

The study was to include only those patients with mild to moderate facial acne (FDA grades II and III). As specified in the protocols, a patient met this criterion at study entry if he/she had at least 30 open and closed comedones (non-inflammatory lesions), at least 10 papules and pustules (inflammatory lesions), no significant nodulocystic acne (<4 lesions), and no more than 200 lesions by total lesion count (non-inflammatory plus inflammatory lesions). Please refer to the Medical Officer's Review for the other inclusion/exclusion criteria.

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

At each follow up assessment, patients were evaluated via lesion counts, skin safety parameters and a global assessment. Clinical adverse events were also recorded.

Two patient populations, evaluable (EVAL) and intent-to-treat (ITT), were defined by the reviewer. Observed case (OC) analyses were performed in the EVAL population and last observation carried forward

analyses (LOCF) analyses were performed in the ITT population. The EVAL-OC results are of primary interest for efficacy. The ITT-LOCF analyses are of primary interest for safety.

This reviewer considers three efficacy parameters as primary: 1) the percent change from baseline to day 84 in non-inflammatory lesion count 2) the percent change from baseline to day 84 in total lesion count, and 3) the global assessment at day 84. The percent change from baseline to day 84 in inflammatory lesion count is considered a secondary efficacy parameter.

The treatment main effect will be deemed significant at the 0.05 level of significance. Interactions will be deemed significant at the 0.15 level of significance. The p-values from pairwise treatment comparisons will be presented only if the overall treatment p-value is significant. With 5 treatment arms, there are 10 possible pairwise comparisons. However only 5 of the 10 possible pairwise comparisons are of primary interest: VEH versus ACT025, VEH versus ACT10, ACT025 versus ACT10, ACT025 versus RET025, and ACT10 versus RET10. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons will be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of $0.05/5 = 0.010$. A Bonferroni adjustment for ten pairwise comparisons would use a significance level of $0.05/10 = 0.005$. Although all possible pairwise comparisons are presented, this reviewer will apply the multiple comparisons adjustment for 5 comparisons.

Center weighted 95% confidence intervals will be used to assess the therapeutic equivalence of ACT025 to RET025 and ACT10 to RET10 with respect to the percent change from baseline to day 84 in lesion counts.

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

Safety was assessed by this reviewer using the categorized change from baseline to day 84 in the skin safety parameter scores, and the rate of clinical adverse events for all events, by body system, and by individual event.

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

III. RESULTS

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

ITT-LOCF efficacy analyses were performed, but for the sake of brevity, are not presented. Unless otherwise stated, the ITT-LOCF efficacy results are similar to the EVAL-OC efficacy results.

EVAL-OC safety analyses were performed, but for the sake of brevity, are not presented. Unless otherwise stated, the EVAL-OC safety results are similar to the ITT-LOCF safety results.

Study 011 was initiated on September 23, 1991, and completed on February 13, 1992. A total of 471 patients were enrolled, where 73, 99, 99, 99, and 101 patients were randomized to receive VEH, ACT025, ACT10, RET025 and RET10, respectively.

Six US investigators (Jarratt, Funicella, Lucky, Cullen, Reddick, and Jones) participated in the trial. Enrollment by center was fairly similar across the centers, ranging from 70 patients in center Cullen to 95 patients in center Lucky. Jarratt and Funicella were two investigators located at the same study site; however, they have been treated as separate investigators in all analyses.

Table 1 displays the number of patients included in the EVAL and ITT populations by treatment, with reasons for patient exclusion. A total of 368 patients were included in the EVAL population, where 58, 75, 75, 81 and 79 patients received VEH, ACT025, ACT10, RET025 and RET10, respectively. A total of 447 patients were included in the EVAL population, where 69, 97, 92, 94 and 95 patients received VEH, ACT025, ACT10, RET025 and RET10, respectively. There were no significant treatment differences in the proportion of patients included in the EVAL or ITT patient populations.

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

Mean baseline non-inflammatory lesion counts by treatment and center in the EVAL population are displayed in Table 3A. There were no significant treatment differences in the mean baseline non-inflammatory lesion count for all centers combined or by center. Mean baseline inflammatory and total lesion counts by treatment in the EVAL population are displayed in Table 3B. There were no significant treatment differences in the mean baseline inflammatory or total lesion count.

Table 4 displays the results from analyses of variance by center for the percent change from baseline to day 84 in non-inflammatory lesion count in the EVAL-OC population. Investigators Jarratt, Reddick, and Jones showed a clearly significant overall treatment effect, investigators Cullen and Funicella showed a marginally significant overall treatment effect, and Lucky showed a clearly non-significant overall treatment effect. In the three centers which had a significant overall treatment effect, ACT10 had a significantly larger percent decrease in non-inflammatory lesion than VEH. However, ACT025 did not have had a significantly larger percent decrease in non-inflammatory lesion than VEH.

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

The most interesting differences among the centers with respect to the percent change from baseline to day 84 in non-inflammatory lesions involve the behavior of the VEH arm in Cullen's patients and the ACT025 arm in Funicella's patients. Both of these patient groups performed exceptionally well compared to the other treatment arms within the center, and compared to the same treatment arms in the other centers. These two patient groups appear to be the causing the statistically significant treatment by center interaction observed for this parameter as well as for the percent change from baseline to day 84 in total lesion count.

Figures 1A, 1B, and 1C display the mean percent change from baseline to each visit in non-inflammatory lesion counts by treatment and center in the EVAL-OC population. When focusing only on the VEH, ACT025 and ACT10 treatment arms, ACT025 and ACT10 were better than VEH and ACT10 was better than ACT025 at all visits for investigators Jarratt, Reddick, and Jones. For investigator Funicella, ACT025 and ACT10 were better than VEH, but ACT025 was better than ACT10 at all visits. For investigator Cullen, VEH was better than ACT025 at all visits, VEH was better than ACT10 at days 28, 56 and 84,

Study 011 was initiated on September 23, 1991, and completed on February 13, 1992. A total of 471 patients were enrolled, where 73, 99, 99, 99, and 101 patients were randomized to receive VEH, ACT025, ACT10, RET025 and RET10, respectively.

Six US investigators (Jarratt, Funicella, Lucky, Cullen, Reddick, and Jones) participated in the trial. Enrollment by center was fairly similar across the centers, ranging from 70 patients in center Cullen to 95 patients in center Lucky. Jarratt and Funicella were two investigators located at the same study site; however, they have been treated as separate investigators in all analyses.

Table 1 displays the number of patients included in the EVAL and ITT populations by treatment, with reasons for patient exclusion. A total of 368 patients were included in the EVAL population, where 58, 75, 75, 81 and 79 patients received VEH, ACT025, ACT10, RET025 and RET10, respectively. A total of 447 patients were included in the EVAL population, where 69, 97, 92, 94 and 95 patients received VEH, ACT025, ACT10, RET025 and RET10, respectively. There were no significant treatment differences in the proportion of patients included in the EVAL or ITT patient populations.

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

Mean baseline non-inflammatory lesion counts by treatment and center in the EVAL population are displayed in Table 3A. There were no significant treatment differences in the mean baseline non-inflammatory lesion count for all centers combined or by center. Mean baseline inflammatory and total lesion counts by treatment in the EVAL population are displayed in Table 3B. There were no significant treatment differences in the mean baseline inflammatory or total lesion count.

Table 4 displays the results from analyses of variance by center for the percent change from baseline to day 84 in non-inflammatory lesion count in the EVAL-OC population. Investigators Jarratt, Reddick, and Jones showed a clearly significant overall treatment effect, investigators Cullen and Funicella showed a marginally significant overall treatment effect, and Lucky showed a clearly non-significant overall treatment effect. In the three centers which had a significant overall treatment effect, ACT10 had a significantly larger percent decrease in non-inflammatory lesion than VEH. However, ACT025 did not have had a significantly larger percent decrease in non-inflammatory lesion than VEH.

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

The most interesting differences among the centers with respect to the percent change from baseline to day 84 in non-inflammatory lesions involve the behavior of the VEH arm in Cullen's patients and the ACT025 arm in Funicella's patients. Both of these patient groups performed exceptionally well compared to the other treatment arms within the center, and compared to the same treatment arms in the other centers. These two patient groups appear to be the causing the statistically significant treatment by center interaction observed for this parameter as well as for the percent change from baseline to day 84 in total lesion count.

Figures 1A, 1B, and 1C display the mean percent change from baseline to each visit in non-inflammatory lesion counts by treatment and center in the EVAL-OC population. When focusing only on the VEH, ACT025 and ACT10 treatment arms, ACT025 and ACT10 were better than VEH and ACT10 was better than ACT025 at all visits for investigators Jarratt, Reddick, and Jones. For investigator Funicella, ACT025 and ACT10 were better than VEH, but ACT025 was better than ACT10 at all visits. For investigator Cullen, VEH was better than ACT025 at all visits, VEH was better than ACT10 at days 28, 56 and 84,

and ACT10 was better than ACT025 at all visits. For investigator Jones, the three treatments behaved similarly over time.

Tables 5A, and 5B display results from analyses of variance for the percent change from baseline to day 84 in non-inflammatory lesion count and total lesion count, respectively, in the EVAL-OC population. With all centers combined, there is a significant overall treatment effect for both lesion types, where ACT025 and ACT10 have significantly larger mean decreases than VEH. ACT10 has a numerically larger mean decrease than ACT025, but the difference is not statistically significant. RET025 and RET10 have numerically larger mean decreases than ACT025 and ACT10, respectively, but the differences are not statistically significant.

As discussed previously, there is a significant treatment by center interaction for the percent change from baseline to day 84 in non-inflammatory and total lesion counts. The significant interaction is due to the response of Cullen's VEH patients and Funicella's ACT025 patients. When either or both of these centers is excluded from the analysis, the treatment by center interaction is no longer significant.

REVIEWER COMMENTS: *Investigator Cullen was also a highly influential investigator in the Acticin gel study 003 of NDA In the gel study 003, Cullen's vehicle patients also exhibited an exceptionally high mean percent decrease from baseline to day 84 in lesion count. In study 003 and in this study, the reason for the exceptional performance of Cullen's vehicle patients is unclear. This reviewer recommends investigator Cullen for inspection by DSI.*

With respect to the significant treatment by center interaction, the behavior of Cullen's VEH patients is of greater concern than the behavior of Funicella's ACT025 patients. Due to the influential nature of Cullen's VEH patients, this reviewer excluded all of Cullen's patients from the primary efficacy analyses.

Excluding Cullen, there is a significant overall treatment effect with respect to the mean percent change from baseline to day 84 in non-inflammatory and total lesions. ACT025 and ACT10 have significantly larger mean decreases than VEH. ACT10 has a numerically larger mean decrease than ACT025, but the difference is not statistically significant. RET025 and RET10 have numerically larger mean decreases than ACT025 and ACT10, respectively, but the differences are not statistically significant.

Table 5C displays results from an analysis of variance for the percent change from baseline to day 84 in inflammatory lesion count. Excluding Cullen, there is a significant overall treatment effect. ACT025 and ACT10 have significantly larger mean decreases than VEH. ACT10 has a numerically larger mean decrease than ACT025, but the difference is not statistically significant. ACT025 has a numerically larger mean decrease than RET025, but the difference is not statistically significant. RET10 has a numerically larger mean decrease than ACT10, but the difference is not statistically significant.

Figures 2A and 2B present the mean percent change from baseline to each visit in non-inflammatory and inflammatory lesion counts by treatment in the EVAL-OC population with Cullen included and excluded. The treatment response profiles were similar whether Cullen was included or excluded. For non-inflammatory lesions all the active treatments decreased over time, and were better than VEH at all visits. ACT10, RET025, and RET10 had similar response profiles, and were better than ACT025 at all visits. For inflammatory lesions, the active treatments had similar response profiles. The active treatments were better than VEH only at days 56 and 84.

Figures 3, 4 and 5 present the mean percent change from baseline to each visit in non-inflammatory lesion counts by treatment and sex, treatment and race, and treatment and age, respectively, in the EVAL-OC population. Cullen was included in these graphs. For simplicity, these figures only include the VEH, ACT025, and ACT10 treatment arms. The most noteworthy pattern of treatment effect among the subgroups is that among the ACT10 patients, females and patients ≥ 30 had larger decreases than males and patients < 30 at all visits.

Table 6 displays results from analyses of variance for the percent change from baseline to day 14, 28, and 56 in non-inflammatory lesion count in the EVAL-OC population. These analyses exclude investigator Cullen. At each visit, there is a significant overall treatment effect. ACT10 is significantly better than VEH at all visits. ACT025 is significant better than VEH only at day 56. A significant treatment by center interaction was observed at days 28 and 56, but is not a cause for concern since it appears to be due to the behavior of Funicella's ACT025 patients.

Therapeutic equivalence of ACT025 to RET025 and ACT10 to RET10 with respect to the percent decrease in lesion count from baseline to day 84 was assessed using the confidence interval approach. The results of this analysis are shown in Table 7. With Cullen included or excluded, the results from the EVAL-OC population fail to demonstrate therapeutic equivalence for non-inflammatory, inflammatory, or total lesions.

Results from analyses of the investigator's global assessment at day 84 for the EVAL-OC population are presented in Table 8. With Cullen included or excluded, there is a significant overall treatment difference in the distribution of global assessment outcome. ACT025 and ACT10 have significantly more patients with favorable outcomes than VEH. The distribution of outcomes between ACT025 and ACT10, ACT025 and RET025, and ACT10 and RET10 are not significantly different.

Change from baseline to day 84 results for the skin safety parameters in the ITT-LOCF population are presented in Table 9. There are significant overall treatment differences in the distribution of dryness, erythema, and peeling outcomes. With respect to dryness, ACT10 has significantly more patients with outcome "worse" than VEH. With respect to erythema, ACT025 and ACT10 have significantly more patients with outcome "worse" than VEH. With respect to peeling, ACT10 has significantly more patients with outcome "worse" than VEH, and RET10 has significantly more patients with outcome "worse" than ACT10.

Figures 6A, 6B, and 6C display the percentage of patients by treatment at each visit in the ITT-LOCF population who had a "worse" skin safety parameter outcome compared to baseline. The most notable treatment differences with respect to the response profiles is that at all visits, ACT10 had fewer patients with "worse" dryness, erythema and peeling than RET10.

Table 10 displays the rate of selected adverse events. The treatments are not significantly different with respect to the percentage of patients with at least one adverse event. However, there is a significant overall treatment difference with respect to the percentage of patients with at least one event in the skin and appendage body system. None of the pairwise treatment comparisons with respect to the percentage of patients with at least one event in the skin and appendage body system are significant at the 0.010 level.

REVIEWER CONCLUSIONS: ***Based on results from the EVAL-OC population excluding investigator Cullen, study 011 demonstrates that after 84 days of treatment, Acticin 0.025% cream and Acticin 0.10% cream have significantly larger mean percent decreases from baseline in non-inflammatory lesion count and total lesion count than the Acticin cream vehicle. The results also show that Acticin 0.10% cream does not have not significantly larger mean percent decreases from baseline in non-inflammatory lesion count and total lesion count than Acticin 0.025% cream.***

Investigator Cullen's vehicle patients performed exceptionally well in this study. The response of these patients was the primary cause of the treatment by center interactions observed for non-inflammatory and total lesion counts. Investigator Cullen had similar results in the Acticin gel study 003 of NDA
This reviewer recommends investigator Cullen for inspection by DSI.

Study 011 fails to show that after 84 days of treatment, Acticin 0.025% cream is therapeutically equivalent to Retin-A 0.025% cream or that Acticin 0.10% cream is therapeutically equivalent to Retin-A

0.10% cream with respect to the mean percent decrease from baseline in non-inflammatory lesion count and total lesion count.

With respect to the investigator's global assessment at day 84, study 011 demonstrates that there are significant treatment differences in the distribution of outcomes, where Acticin 0.025% cream and Acticin 0.10% cream have more patients with favorable outcomes than the Acticin vehicle cream.

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

In comparison to Acticin vehicle cream, statistical evaluation of the efficacy of Acticin 0.025% and Acticin 0.10% cream is based upon the mean percent change from baseline to day 84 in non-inflammatory lesion count and total lesion count, and the distribution of the investigator's global assessment at day 84. In comparison to the active controls, Retin-A 0.025% cream and Retin-A 0.10% cream, statistical evaluation of the efficacy of Acticin 0.025% cream and Acticin 0.10% cream is based upon the mean percent change from baseline to day 84 in non-inflammatory lesion count and total lesion count. The set of evaluable patients with observed case visits is the primary efficacy analysis population. The original, untransformed data are used in the lesion count analyses.

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

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

Investigator Cullen's vehicle patients performed exceptionally well, and were the primary cause of the significant treatment by center interactions observed for non-inflammatory and total lesion counts. Due to the influential nature of Cullen's patients, they were excluded from all efficacy analyses. The reason for the influential nature of Cullen's vehicle patients is not clear.

Excluding Cullen's patients, 50, 65, 62, 68, and 67, Acticin vehicle, Acticin 0.025%, Acticin 0.10%, Retin-A 0.025% and Retin-A 0.10% patients, respectively, were included in the efficacy analyses. Cullen's patients were included in the safety analyses. Sixty-nine, 97, 92, 94, and 95 Acticin vehicle , Acticin 0.025% , Acticin 0.10% , Retin-A 0.025% and Retin-A 0.10% , respectively, were included in the safety analyses.

1. Non-inflammatory Lesions: The mean decrease (standard error) is 24.4 (5.2), 47.6 (3.7), and 49.3 (4.4) for Acticin vehicle , Acticin 0.025% , and Acticin 0.10% , respectively. Acticin 0.025% and Acticin 0.10% have significantly larger mean decreases than the vehicle ($p<0.001$ for both tests). Acticin 0.10% does not have significantly larger mean decrease than Acticin 0.025% ($p=0.567$).

The mean decrease (standard error) is 49.8 (3.5), and 52.9 (4.6) for Retin-A 0.025% and Retin-A 0.10%, respectively. These means are numerically larger, but not significantly larger than the means for Acticin 0.025% and Acticin 0.10% ($p=0.801$ and $p=0.566$, respectively).

The center weighted treatment difference in the mean decrease between Acticin 0.025% and Retin-A 0.025% is -1.8, with standard error 5.0 and 95% confidence interval (-11.7, 8.1). The center weighted mean decrease for Retin-A 0.025% is 47.8. Twenty percent of the mean decrease for Retin-A is 9.6.

The center weighted treatment difference in the mean decrease between Acticin 0.10% and Retin-A 0.10% is -3.9, with standard error 5.8 and 95% confidence interval (-15.3, 7.6). The center weighted mean decrease for Retin-A 0.10% is 55.1. Twenty percent of the mean decrease for Retin-A is 11.0.

2. Total Lesions: The mean decrease (standard error) is 24.9 (5.0), 48.2 (3.3), and 49.9 (3.8) for Acticin vehicle , Acticin 0.025% , and Acticin 0.10% , respectively. Acticin 0.025% and Acticin 0.10% have significantly larger mean decreases than the vehicle ($p<0.001$ for both tests). Acticin 0.10% does not have significantly larger mean decrease than Acticin 0.025% ($p=0.531$).

The mean decrease (standard error) is 49.5 (3.3), and 53.2 (3.9) for Retin-A 0.025% and Retin-A 0.10%, respectively. These means are numerically larger, but not significantly larger than the means for Acticin 0.025% and Acticin 0.10% ($p=0.880$ and $p=0.546$, respectively).

The center weighted treatment difference in the mean decrease between Acticin 0.025% and Retin-A 0.025% is -1.1, with standard error 4.6 and 95% confidence interval (-10.1, 7.9). The center weighted mean decrease for Retin-A 0.025% is 48.0. Twenty percent of the mean decrease for Retin-A is 9.6.

The center weighted treatment difference in the mean decrease between Acticin 0.10% and Retin-A 0.10% is -3.7, with standard error 4.8 and 95% confidence interval (-13.1, 5.9). The center weighted mean decrease for Retin-A 0.10% is 55.4. Twenty percent of the mean decrease for Retin-A is 11.1.

3. Global Assessment: The distributions of global assessment outcomes are presented in Table 8 The distributions of global assessment outcome for Acticin 0.025% and Acticin 0.10% are significantly different from Acticin vehicle ($p\leq0.001$ for both tests), where Acticin 0.025% and Acticin 0.10% have more patients with favorable outcomes than its vehicle. The distribution of global assessment outcomes for Acticin 0.10% is not significantly different from Acticin 0.025% ($p=0.262$).

4. Safety: The distribution of skin safety parameter outcomes are presented in Table 9. The distribution of dryness outcomes for Acticin 0.10% is significantly different from Acticin vehicle ($p<0.001$), where Acticin 0.10% has more patients with "worse" dryness than Acticin vehicle . The distribution of erythema outcomes for Acticin 0.025% and Acticin 0.10% are significantly different from Acticin vehicle ($p=0.009$ and $p=0.010$, respectively), where Acticin 0.025% and Acticin 0.10% have more patients with "worse" erythema than Acticin vehicle. The distribution of peeling outcomes for Acticin 0.10% is significantly different from Acticin vehicle and Retin-A 0.10% ($p=0.004$ for both tests), where Acticin 0.10% has more patients with "worse" peeling than Acticin vehicle, and significantly fewer patients with "worse" peeling than Retin-A 0.10%.

The rate of at least one adverse event is 38%, 45%, 48%, 45% and 47% for Acticin vehicle, Acticin 0.025%, Acticin 0.10%, Retin-A 0.025% and Retin-A 0.10%, respectively. The differences in adverse event rate among the treatments are not statistically significant.

REVIEWER CONCLUSIONS: Study 011 provides evidence for the applicant's claim that Acticin 0.025% cream and Acticin 0.10% cream are superior in efficacy to Acticin vehicle cream in the treatment of mild to moderate acne vulgaris. However, study 011 does not provide evidence for the applicant's claim that Acticin 0.10% cream is superior in efficacy to Acticin 0.025% cream in the treatment of mild to moderate acne vulgaris.

Study 011 fails to provide evidence for the applicant's claims that Acticin 0.025% cream is therapeutically equivalent in efficacy to Retin-A 0.025% cream, or that Acticin 0.10% cream is therapeutically equivalent in efficacy to Retin-A 0.10% cream in the treatment of mild to moderate acne vulgaris.

Study 011 supports the applicant's claim that Acticin 0.025% cream and Acticin 0.10% cream have tolerable safety profiles. Any safety problems can be adequately addressed in the label.

REVIEWER COMMENTS: Since Acticin 0.10% cream is not superior in efficacy to Acticin 0.025% cream, 0.025% should be the marketed strength.

If Acticin 0.025% cream or Acticin 0.10% is considered as a line extension of Retin-A 0.025% cream or Retin-A 0.10% cream , one adequate and well controlled study which shows Acticin's superiority over vehicle and therapeutic equivalence to Retin-A would be required. Study 011 is generally adequate and well controlled in design, shows superiority over vehicle, but fails to meet the equivalence criterion for approvability.

If Acticin 0.025% cream or Acticin 0.10% cream is considered as a new drug product, two adequate and well controlled studies which show Acticin's superiority over vehicle would be required. Study 011 meets this efficacy criterion for approvability, but its results have not been replicated. An argument could be made for the use of the Acticin gel studies from NDA as evidence to support the claims for the cream. However, all the investigators who participated in the gel studies 003 and 015 also participated in the cream study 011. The gel studies 003 and 015 cannot be considered independent of the cream study 011, therefore, they cannot be considered of adequate and well controlled in design.

The exceptional performance of investigator Cullen's vehicle patients is puzzling. Similar results were observed in Cullen's vehicle patients from the Acticin gel study 003.

RECOMMENDED REGULATORY ACTION: From a statistical standpoint, Acticin 0.025% cream and Acticin 0.10% are not approvable for the treatment of mild to moderate acne vulgaris. Investigator Cullen should be recommended for inspection by DSI.

Elizabeth A. Turney 3/1/95

Elizabeth A. Turney, M.S.
Mathematical Statistician, Group 7

Ralph Harkins, Ph.D. 3/2/95

Concur: Ralph Harkins, Ph.D.
Supervisory Mathematical Statistician, Group 7

Satya D. Dubey, Ph.D. 3-6-95
Branch Chief, SERB

cc:
Orig. NDA 20-404
HFD-540
HFD-540/Chapman
HFD-540/Wilkin
HFD-540/Labib
HFD-540/Slifman
HFD-540/Chambers
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFD-713/Turney
HFD-344/Lisook
Chron.

This review contains 10 pages with two appendices containing 10 tables and 6 figures.
WordPerfect 6.0/NDA20404.wpd/3-1-95

V. APPENDIX OF TABLES

TABLE 1: Study 011 Patient Evaluablilty Status at Day 84

patient status	EVAL					ITT				
	VEH	ACT025	ACT10	RET025	RET10	VEH	ACT025	ACT10	RET025	RET10
enrolled	73	99	99	99	101	73	99	99	99	101
evaluable at day 84	58 (79%)	75 (76%)	75 (76%)	81 (82%)	79 (78%)	69 (95%)	97 (98%)	92 (93%)	94 (95%)	95 (94%)
excluded total	15	24	24	18	22	4	2	7	5	6
excluded from all visits	4	2	7	5	6	4	2	7	5	6
excluded from day 84	11	22	17	13	16	0	0	0	0	0
reason for exclusion:										
adverse experience	0	1	0	0	2	0	0	0	0	1
lack of efficacy	0	1	1	1	0	0	0	0	0	0
lost to follow up	2	7	8	7	2	0	1	4	3	0
protocol violation	1	0	0	0	4	1	0	0	0	1
non-compliant	3	6	3	3	5	2	1	2	1	4
personal	2	2	3	1	1	1	0	0	0	0
other	1	0	1	1	1	0	0	1	1	0
visit late (day 84)	6	6	8	5	7	0	0	0	0	0
nterfering therapy (day 84)	0	1	0	0	0	0	0	0	0	0

TABLE 2: Study 011 Demographic Distribution for EVAL Population

trt	sex n (%)		race n (%)		age n (%)	
	M	F	B/O	W	<30	≥30
VEH (n=58)	35 (60)	23 (40)	11 (19)	47 (81)	53 (91)	5 (9)
ACT025 (n=75)	42 (56)	33 (44)	10 (13)	65 (87)	68 (91)	7 (9)
ACT10 (n=75)	37 (49)	38 (51)	9 (12)	66 (88)	71 (95)	4 (5)
RET025 (n=81)	36 (44)	45 (56)	17 (21)	64 (79)	74 (91)	7 (9)
RET10 (n=79)	42 (53)	37 (47)	12 (15)	67 (85)	72 (91)	7 (9)
p-value*	0.384		0.536		0.896	

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

TABLE 3A: Study 011: Baseline Non-Inflammatory Lesion Counts for EVAL Population

lesion	center	trt	n	mean	se	min	max	p**
non-inf	ALL	VEH	58	74.2	5.4	30	177	0.985
		ACT025	75	73.7	4.2	30	185	
		ACT10	75	73.9	3.9	30	180	
		RET025	81	72.8	3.8	30	177	
		RET10	79	76.5	4.5	30	190	
	Jarratt	VEH	10	49.1	7.1	30	99	0.273
		ACT025	12	83.8	14.5	31	185	
		ACT10	11	63.8	11.5	30	135	
		RET025	12	46.4	7.9	30	129	
		RET10	13	57.7	10.4	31	159	
	Funicella	VEH	9	111.1	16.8	40	177	0.079
		ACT025	14	69.6	8.3	38	140	
		ACT10	14	69.1	7.5	36	140	
		RET025	12	85.2	11.3	41	138	
		RET10	15	110.0	13.8	37	190	
	Lucky	VEH	13	55.7	7.6	31	115	0.211
		ACT025	13	57.2	10.1	30	140	
		ACT10	14	74.1	9.0	35	128	
		RET025	16	74.6	9.0	32	165	
		RET10	16	63.0	6.9	30	125	
	Cullen	VEH	8	57.5	6.1	38	95	0.458
		ACT025	10	70.5	5.7	36	98	
		ACT10	13	59.0	6.9	36	119	
		RET025	13	60.4	5.9	33	107	
		RET10	12	58.4	5.8	34	95	
	Reddick	VEH	8	104.5	17.9	32	171	0.802
		ACT025	13	90.2	11.2	38	155	
		ACT10	10	104.3	15.0	47	180	
		RET025	14	85.4	11.6	35	177	
		RET10	9	91.7	11.5	55	151	
	Jones	VEH	11	77.0	9.4	32	128	0.745
		ACT025	13	71.2	8.2	36	116	
		ACT10	13	78.9	4.9	51	110	
		RET025	14	81.9	5.2	32	115	
		RET10	14	79.5	8.6	47	139	

** P-value from the Kruskal-Wallis test.

TABLE 3B: Study 011: Baseline Inflammatory and Total Lesion Counts for EVAL Population

lesion	center	trt	n	mean	se	min	max	p**
inf	ALL	VEH	58	19.8	1.2	10	45	0.318
		ACT025	75	20.8	1.3	10	61	
		ACT10	75	18.8	1.2	10	74	
		RET025	81	21.4	1.1	10	53	
		RET10	79	20.6	1.1	10	60	
total	ALL	VEH	58	94.0	5.5	42	196	0.980
		ACT025	75	94.5	4.3	44	199	
		ACT10	75	92.7	4.3	40	200	
		RET025	81	94.2	4.2	41	200	
		RET10	79	97.1	4.7	41	200	

**-value from the Kruskal-Wallis test.

TABLE 4: Study 011: Percent Change From Baseline to Day 84 in Non-Inflammatory Lesion Counts by Center

center	trt	EVAL-OC Analysis					
		n	mean	se	adj. se*	overall p	pairwise p
Jarratt	VEH	10	-14.9	12.1	10.0	0.018	V v A025: 0.074
	ACT025	12	-39.5	9.6	9.1		V v A10: 0.001
	ACT10	11	-61.3	5.6	9.5		V v R025: 0.122
	RET025	12	-36.1	9.7	9.1		V v R10: 0.009
	RET10	13	-50.8	8.5	8.7		A025 v A10: 0.103
							A025 v R025: 0.793
							A025 v R10: 0.373
							A10: v R025 0.061
							A10 v R10: 0.420
							R025 v R10: 0.248
Funicella	VEH	9	-7.8	14.9	12.9	0.117	
	ACT025	14	-50.6	8.3	10.4		
	ACT10	14	-21.9	9.7	10.4		
	RET025	12	-32.0	7.3	11.2		
	RET10	15	-24.7	13.1	10.0		
Lucky	VEH	12	-32.1	9.6	9.8	0.378	
	ACT025	13	-44.5	9.7	9.5		
	ACT10	14	-40.5	10.0	9.1		
	RET025	16	-53.5	6.9	8.5		
	RET10	16	-55.0	9.1	8.5		
Cullen	VEH	8	-43.7	10.6	8.9	0.073	
	ACT025	10	-28.5	7.1	8.0		
	ACT10	13	-33.5	8.5	7.0		
	RET025	13	-42.8	6.8	7.0		
	RET10	12	-57.9	4.8	7.3		
Reddick	VEH	8	-19.8	14.0	9.8	0.014	V v A025: 0.015
	ACT025	13	-51.3	6.8	7.7		V v A10: 0.004
	ACT10	10	-59.8	11.5	8.8		V v R025: 0.002
	RET025	14	-60.1	5.1	7.4		V v R10: 0.003
	RET10	9	-62.5	6.7	9.3		A025 v A10: 0.471
							A025 v R025: 0.414
							A025 v R10: 0.356
							A10: v R025 0.978
							A10 v R10: 0.832
							R025 v R10: 0.840
Jones	VEH	11	-41.6	7.9	7.1	0.003	V v A025: 0.319
	ACT025	13	-51.2	7.6	6.5		V v A10: 0.005
	ACT10	13	-69.9	5.1	6.5		V v R025: 0.031
	RET025	14	-62.4	7.8	6.3		V v R10: 0.001
	RET10	14	-76.5	3.4	6.3		A025 v A10: 0.047
							A025 v R025: 0.221
							A025 v R10: 0.007
							A10: v R025 0.410
							A10 v R10: 0.465
							R025 v R10: 0.116

* In the analyses by center, adjusted standard error and p-values are from an analysis of variance of treatment using SAS PROC GLM type III sums of squares on the original data. The adjusted standard error is the standard error that would be expected if the treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 5A: Study 011: Percent Change From Baseline to Day 84 in Non-Inflammatory Lesion Count

lesion	center	trt	EVAL-OC Analysis							
			n	mean	se	adj. mean	adj. se*	overall p trt (trt*cen)	pairwise p	
non-inf	ALL	VEH	58	-27.1	4.8	-26.6	4.1	<0.001	V v A025:	0.001
		ACT025	75	-45.0	3.4	-44.3	3.6		V v A10:	<0.001
		ACT10	75	-46.5	4.0	-47.8	3.6	(0.077)	V v R025:	<0.001
		RET025	81	-48.7	3.1	-47.8	3.4		V v R10:	<0.001
		RET10	79	-53.7	4.0	-54.6	3.5		A025 v A10:	0.485
									A025 v R025:	0.476
									A025 v R10:	0.041
									A10: v R025	>0.999
									A10 v R10:	0.179
									R025 v R10:	0.170
	excl. Funicella	VEH	49	-30.6	4.9	-30.4	4.2	<0.001	V v A025:	0.025
		ACT025	61	-43.8	3.8	-43.0	3.7		V v A10:	<0.001
		ACT10	61	-52.2	4.1	-53.0	3.7	(0.280)	V v R025:	<0.001
		RET025	69	-51.6	3.4	-51.0	3.5		V v R10:	<0.001
		RET10	64	-60.5	3.3	-60.6	3.7		A025 v A10:	0.058
									A025 v R025:	0.119
									A025 v R10:	0.001
									A10: v R025	0.693
									A10 v R10:	0.150
									R025 v R10:	0.060
	excl. Cullen	VEH	50	-24.4	5.2	-23.2	4.5	<0.001	V v A025:	<0.001
		ACT025	65	-47.6	3.7	-47.4	3.9		V v A10:	<0.001
		ACT10	62	-49.3	4.4	-50.7	4.1	(0.219)	V v R025:	<0.001
		RET025	68	-49.8	3.5	-48.8	3.9		V v R10:	<0.001
		RET10	67	-52.9	4.6	-53.9	4.0		A025 v A10:	0.567
									A025 v R025:	0.801
									A025 v R10:	0.245
									A10: v R025	0.741
									A10 v R10:	0.566
									R025 v R10:	0.356
	excl. Funicella and Cullen	VEH	41	-28.0	5.4	-27.1	4.7	<0.001	V v A025:	0.002
		ACT025	51	-46.8	4.2	-46.6	4.2		V v A10:	<0.001
		ACT10	48	-57.3	4.4	-57.9	4.3	(0.636)	V v R025:	<0.001
		RET025	56	-53.7	3.8	-53.0	4.0		V v R10:	<0.001
		RET10	52	-61.1	4.0	-61.2	4.2		A025 v A10:	0.061
									A025 v R025:	0.267
									A025 v R10:	0.014
									A10: v R025	0.410
									A10 v R10:	0.578
									R025 v R10:	0.158

*The adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 5B: Study 011: Percent Change From Baseline to Day 84 in Total Lesion Count

lesion	center	trt	EVAL-OC Analysis							
			n	mean	se	adj. mean	adj. se*	overall p trt (trt*cen)	pairwise p	
total	ALL	VEH	58	-27.6	4.6	-27.7	3.7	<0.001	V v A025:	0.001
		ACT025	75	-45.5	3.1	-44.7	3.2		V v A10:	<0.001
		ACT10	75	-46.4	3.6	-47.6	3.2	(0.050)	V v R025:	<0.001
		RET025	81	-48.6	3.0	-48.0	3.1		V v R10:	<0.001
		RET10	79	-53.7	3.4	-54.6	3.2		A025 v A10:	0.531
									A025 v R025:	0.466
									A025 v R10:	0.029
									A10: v R025	0.928
									A10 v R10:	0.120
									R025 v R10:	0.135
	excl. Funicella	VEH	49	-29.9	4.8	-30.1	3.8	<.0001	V v A025:	0.010
		ACT025	61	-44.2	3.3	-43.5	3.4		V v A10:	<0.001
		ACT10	61	-50.7	3.8	-51.6	3.4	(0.132)	V v R025:	<0.001
		RET025	69	-50.8	3.2	-50.4	3.2		V v R10:	<0.001
		RET10	64	-59.3	3.1	-59.5	3.4		A025 v A10:	0.091
									A025 v R025:	0.137
									A025 v R10:	0.001
									A10: v R025	0.797
									A10 v R10:	0.097
									R025 v R10:	0.049
	excl. Cullen	VEH	50	-24.9	5.0	-24.3	4.0	<0.001	V v A025:	<0.001
		ACT025	65	-48.2	3.3	-48.0	3.5		V v A10:	<0.001
		ACT10	62	-49.9	3.8	-51.2	3.6	(0.267)	V v R025:	<0.001
		RET025	68	-49.5	3.3	-48.8	3.4		V v R10:	<0.001
		RET10	67	-53.2	3.9	-54.2	3.5		A025 v A10:	0.531
									A025 v R025:	0.880
									A025 v R10:	0.212
									A10: v R025	0.629
									A10 v R10:	0.546
									R025 v R10:	0.268
	excl. Funicella and Cullen	VEH	41	-27.0	5.4	-26.5	4.2	<0.001	V v A025:	<0.001
		ACT025	51	-47.4	3.6	-47.3	3.7		V v A10:	<0.001
		ACT10	48	-56.5	3.7	-57.1	3.8	(0.659)	V v R025:	<0.001
		RET025	56	-52.4	3.6	-52.0	3.6		V v R10:	<0.001
		RET10	52	-59.8	3.6	-60.2	3.7		A025 v A10:	0.068
									A025 v R025:	0.361
									A025 v R10:	0.015
									A10: v R025	0.330
									A10 v R10:	0.561
									R025 v R10:	0.112

*The adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 5C: Study 011: Percent Change From Baseline to Day 84 in Inflammatory Lesion Count

lesion	center	trt	EVAL-OC Analysis							
			n	mean	se	adj. mean	adj. se*	overall p trt (trt*cen)	pairwise p	
inf	ALL	VEH	58	-32.5	6.3	-34.0	4.6	0.033	V v A025:	0.083
		ACT025	75	-45.7	3.7	-44.7	4.0		V v A10:	0.032
		ACT10	75	-46.2	4.3	-47.3	4.0	(0.211)	V v R025:	0.014
		RET025	81	-48.6	3.7	-48.9	3.9		V v R10:	0.002
		RET10	79	-51.7	4.2	-53.1	4.0		A025 v A10:	0.653
									A025 v R025:	0.455
									A025 v R10:	0.140
									A10: v R025	0.772
									A10 v R10:	0.305
									R025 v R10:	0.450
	excl. Cullen	VEH	50	-30.1	7.2	-31.4	4.9	0.007	V v A025:	0.008
		ACT025	65	-48.7	3.9	-48.5	4.2		V v A10:	0.001
		ACT10	62	-51.9	3.7	-52.9	4.4	(0.591)	V v R025:	0.004
		RET025	68	-49.4	4.1	-49.7	4.2		V v R10:	0.001
		RET10	67	-51.4	4.7	-53.0	4.2		A025 v A10:	0.464
									A025 v R025:	0.836
									A025 v R10:	0.452
									A10: v R025	0.592
									A10 v R10:	0.993
									R025 v R10:	0.581

*The adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 6: Study 011: Percent Change From Baseline to Days 14, 28 and 56 in Non-inflammatory Lesion Count Excluding Cullen

lesion	day	trt	EVAL-OC Analysis							
			n	mean	se	adj. mean	adj. se*	overall p trt (trt*cen)	pairwise p	
non-inf	14	VEH	49	5.6	4.7	6.7	4.3	0.004	V v A025:	0.059
		ACT025	65	-4.1	4.2	-4.0	3.7		V v A10:	0.001
		ACT10	61	-14.5	3.4	-13.7	3.8	(0.588)	V v R025:	0.003
		RET025	67	-11.3	3.6	-10.2	3.6		V v R10:	0.002
		RET10	67	-12.2	4.0	-10.9	3.7		A025 v A10:	0.069
									A025 v R025:	0.236
									A025 v R10:	0.192
									A10: v R025	0.505
									A10 v R10:	0.591
									R025 v R10:	0.898
	28	VEH	50	-9.1	4.9	-7.6	4.3	0.007	V v A025:	0.023
		ACT025	65	-21.8	4.0	-20.6	3.7		V v A10:	0.003
		ACT10	62	-24.6	3.7	-24.6	3.8	(0.044)	V v R025:	0.001
		RET025	68	-27.0	3.6	-26.1	3.7		V v R10:	0.001
		RET10	67	-25.2	4.4	-25.9	3.7		A025 v A10:	0.450
									A025 v R025:	0.288
									A025 v R10:	0.308
									A10: v R025	0.776
									A10 v R10:	0.803
									R025 v R10:	0.974
	56	VEH	50	-18.7	5.2	-16.8	4.5	<0.001	V v A025:	0.001
		ACT025	65	-37.2	4.2	-37.0	3.9		V v A10:	<0.001
		ACT10	62	-46.8	3.5	-47.4	4.0	(0.123)	V v R025:	<0.001
		RET025	68	-40.9	3.7	-40.2	3.8		V v R10:	<0.001
		RET10	67	-42.7	4.7	-43.4	3.9		A025 v A10:	0.063
									A025 v R025:	0.559
									A025 v R10:	0.247
									A10: v R025	0.193
									A10 v R10:	0.473
									R025 v R10:	0.558

*The adjusted mean, adjusted standard error, and p-values, are from an analysis of variance of treatment, center, and the treatment by center interaction using SAS PROC GLM type III sums of squares on the original data. The adjusted mean and adjusted standard error are those that would be expected if the centers and treatment arms had equal sample sizes. The p-values from pairwise treatment comparisons are displayed only if the overall treatment p-value is significant at the 0.05 level. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 7: Study 011 95% Confidence Intervals of the Center Weighted Acticin minus Retin-A Difference in Mean Percent Decrease* From Baseline in Lesion Count at Day 84

lesion	center	analysis	EVAL-OC Analysis				
			wgt diff	wgt se	95% CI	wgt RET mean	20% of RET mean
non-inf	ALL	ACT025 minus RET025	-3.6	4.5	(-12.5, 5.3)	46.9	9.4
		ACT10 minus RET10	-7.2	5.1	(-17.3, 2.9)	55.6	11.1
	excl. Cullen	ACT025 minus RET025	-1.8	5.0	(-11.7, 8.1)	47.8	9.6
		ACT10 minus RET10	-3.9	5.8	(-15.3, 7.6)	55.1	11.0
inf	ALL	ACT025 minus RET025	-3.8	5.0	(-13.6, 6.0)	49.1	9.8
		ACT10 minus RET10	-6.0	5.5	(-17.0, 5.0)	55.0	11.0
	excl. Cullen	ACT025 minus RET025	-1.2	5.4	(-11.9, 9.5)	49.9	10.0
		ACT10 minus RET10	-0.6	5.5	(-11.5, 10.4)	55.3	11.1
total	ALL	ACT025 minus RET025	-3.3	4.1	(-11.4, 4.9)	47.3	9.5
		ACT10 minus RET10	-7.4	4.4	(-16.1, 1.3)	55.6	11.1
	excl. Cullen	ACT025 minus RET025	-1.1	4.6	(-10.1, 7.9)	48.0	9.6
		ACT10 minus RET10	-3.7	4.8	(-13.1, 5.9)	55.4	11.1

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

TABLE 8: Study 011 Investigator Global Assessment at Day 84 for EVAL-OC Analysis

center	trt	total n	outcome n (%)*					CMH p-values*		
			excell.	good	fair	no change	worse	overall	pairwise	
ALL	VEH	58	8 (14)	15 (26)	9 (16)	19 (33)	7 (12)	<0.001	V v A025:	0.007
	ACT025	75	22 (29)	22 (29)	17 (23)	14 (19)	0 (0)		V v A10:	0.001
	ACT10	75	23 (31)	24 (32)	16 (21)	12 (16)	0 (0)		V v R025:	0.001
	RET025	81	20 (25)	33 (41)	16 (20)	12 (15)	0 (0)		V v R10:	<0.001
	RET10	79	20 (25)	40 (51)	11 (14)	6 (8)	2 (3)		A025 v A10:	0.197
									A025 v R025:	0.515
									A025 v R10:	0.074
									A10: v R025	0.728
									A10 v R10:	0.476
									R025 v R10:	0.192
excl. Cullen	VEH	50	7 (14)	10 (20)	8 (16)	18 (36)	7 (14)	<0.001	V v A025:	0.001
	ACT025	65	21 (32)	19 (29)	13 (20)	12 (18)	0 (0)		V v A10:	<0.001
	ACT10	62	21 (34)	18 (29)	14 (23)	9 (15)	0 (0)		V v R025:	<0.001
	RET025	68	18 (26)	25 (37)	14 (21)	11 (16)	0 (0)		V v R10:	<0.001
	RET10	67	17 (25)	32 (48)	10 (15)	6 (9)	2 (3)		A025 v A10:	0.262
									A025 v R025:	0.938
									A025 v R10:	0.320
									A10: v R025	0.481
									A10 v R10:	0.923
									R025 v R10:	0.318

*Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

TABLE 9: Study 011 Change From Baseline In Assessment of Skin Safety Parameters at Day 84

rameter	trt	ITT-LOCF Analysis					
		n	outcome n (%)*			CMH p-values*	
			worse	no change	improve	overall	pairwise
burning/ stinging	VEH	69	2 (3)	66 (96)	1 (1)	0.060	
	ACT025	97	8 (8)	88 (91)	1 (1)		
	ACT10	92	13 (14)	79 (86)	0 (0)		
	RET025	94	8 (9)	84 (89)	2 (2)		
	RET10	95	15 (16)	78 (82)	2 (2)		
dryness	VEH	69	1 (1)	63 (91)	5 (7)	<0.001	V v A025: 0.070
	ACT025	97	10 (10)	82 (85)	5 (5)		V v A10: <0.001
	ACT10	92	22 (24)	68 (74)	2 (2)		V v R025: 0.007
	RET025	94	16 (17)	73 (78)	5 (5)		V v R10: <0.001
	RET10	95	27 (28)	64 (67)	4 (4)		A025 v A10: 0.012
							A025 v R025: 0.261
							A025 v R10: 0.003
							A10: v R025 0.172
							A10 v R10: 0.514
							R025 v R10: 0.056
erythema	VEH	69	3 (4)	61(88)	5 (7)	<0.001	V v A025: 0.009
	ACT025	97	14 (14)	81 (84)	2 (2)		V v A10: 0.010
	ACT10	92	20 (22)	66 (72)	6 (7)		V v R025: 0.009
	RET025	94	15 (16)	76 (81)	3 (3)		V v R10: <0.001
	RET10	95	29 (31)	64 (67)	2 (2)		A025 v A10: 0.615
							A025 v R025: 0.928
							A025 v R10: 0.008
							A10: v R025 0.704
							A10 v R10: 0.079
							R025 v R10: 0.017
tching	VEH	69	6 (9)	62 (90)	1 (1)	0.060	
	ACT025	97	7 (7)	88 (91)	2 (2)		
	ACT10	92	20 (22)	71 (77)	1 (1)		
	RET025	94	14 (15)	77 (82)	3 (3)		
	RET10	95	14 (15)	79 (83)	2 (2)		
peeling	VEH	69	3 (4)	66 (96)	0 (0)	<0.001	V v A025: 0.136
	ACT025	97	10 (10)	87 (90)	0 (0)		V v A10: 0.004
	ACT10	92	17 (18)	75 (82)	0 (0)		V v R025: 0.092
	RET025	94	11 (12)	83 (88)	0 (0)		V v R10: <0.001
	RET10	95	33 (35)	62 (65)	0 (0)		A025 v A10: 0.087
							A025 v R025: 0.784
							A025 v R10: <0.001
							A10: v R025 0.173
							A10 v R10: 0.004
							R025 v R10: <0.001
tightness	VEH	69	11 (16)	54 (78)	4 (6)	0.064	
	ACT025	97	17 (18)	73 (75)	7 (7)		
	ACT10	92	30 (33)	59 (64)	3 (3)		
	RET025	94	21 (22)	67 (71)	6 (6)		
	RET10	95	25 (26)	64 (67)	6 (6)		

*Due to rounding, percentages may not add to 100%. P-values are from the Cochran-Mantel-Haenszel test adjusting for center using modified ridit scores. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

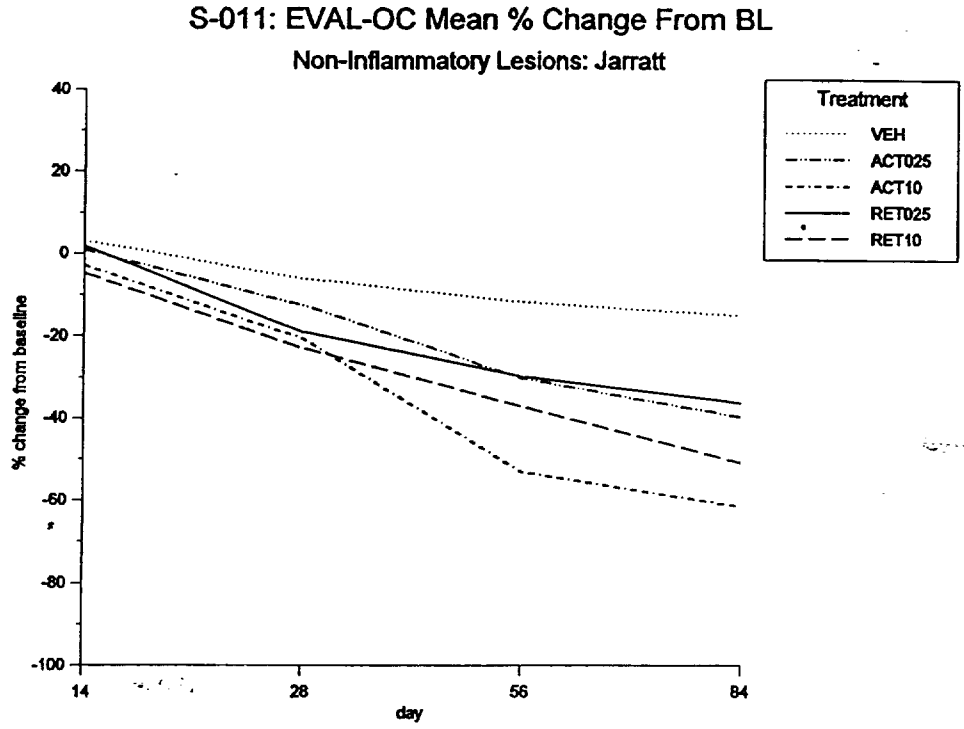
TABLE 10: Study 003 Clinical Adverse Events*

event	trt	total n	event n (%)	p-values* overall	pairwise	
any AE	VEH	69	26 (38)	0.734		
	ACT025	97	44 (45)			
	ACT10	92	44 (48)			
	RET025	94	42 (45)			
	RET10	95	45 (47)			
skin and appendage body system	VEH	69	3 (4)	0.028	V v A025:	0.525
	ACT025	97	7 (7)		V v A10:	0.022
	ACT10	92	15 (16)		V v R025:	0.037
	RET025	94	14 (15)		V v R10:	0.014
	RET10	95	16 (17)		A025 v A10:	0.069
					A025 v R025:	0.108
					A025 v R10:	0.047
					A10: v R025	0.842
					A10 v R10:	>0.999
					R025 v R10:	0.843

*Results are displayed only for those body systems and the individual events within the body system which have a significant overall p-value. Only those patients with at least one post baseline visit were included in the analysis. P-values are from the two-sided Fisher's exact test. To maintain an overall significance level of 0.05, an adjustment for multiple comparisons should be applied to the pairwise comparisons. A Bonferroni adjustment for five pairwise comparisons would use a significance level of 0.05/5 = 0.010.

VI. APPENDIX OF FIGURES

FIGURE 1A: Study 011 Non-Inflammatory Lesions by Treatment and Center



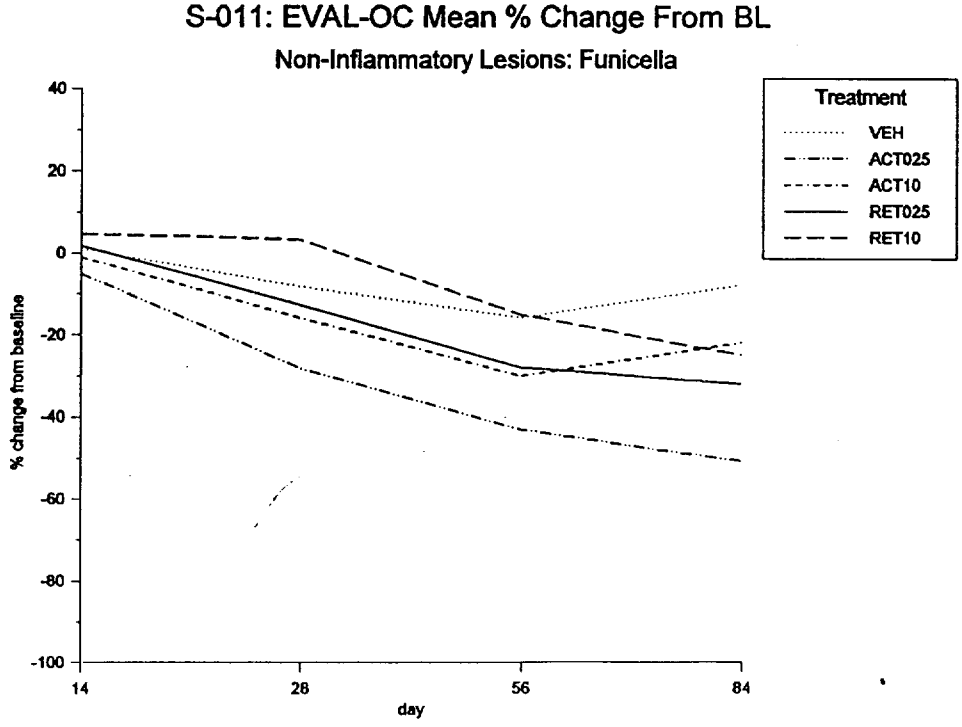
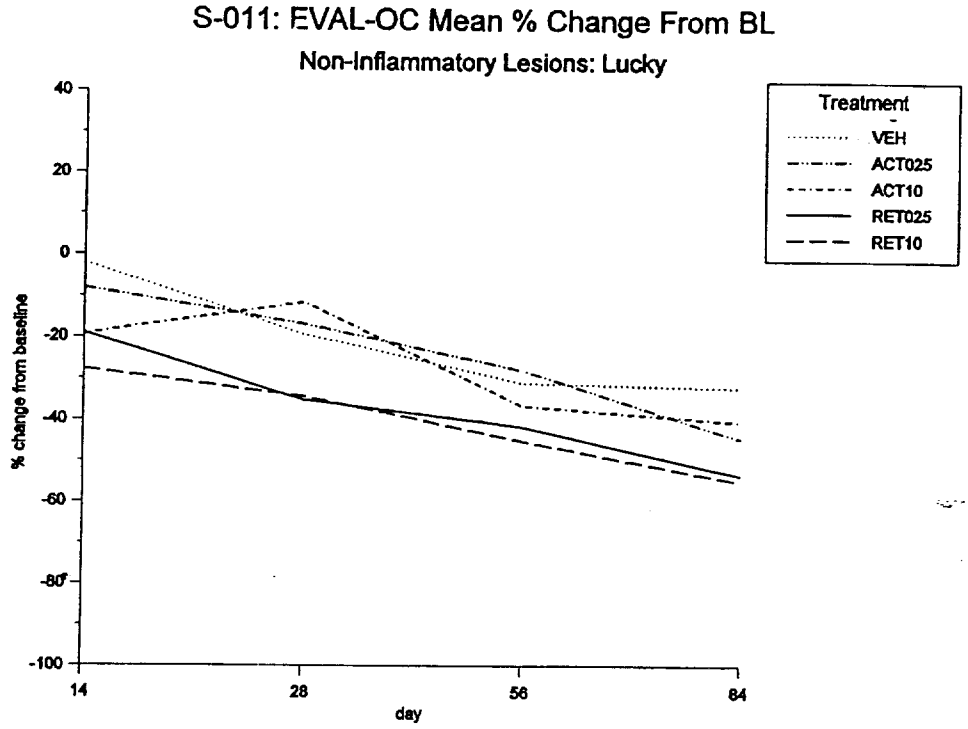


FIGURE 1B: Study 011Non-Inflammatory Lesions by Treatment and Center



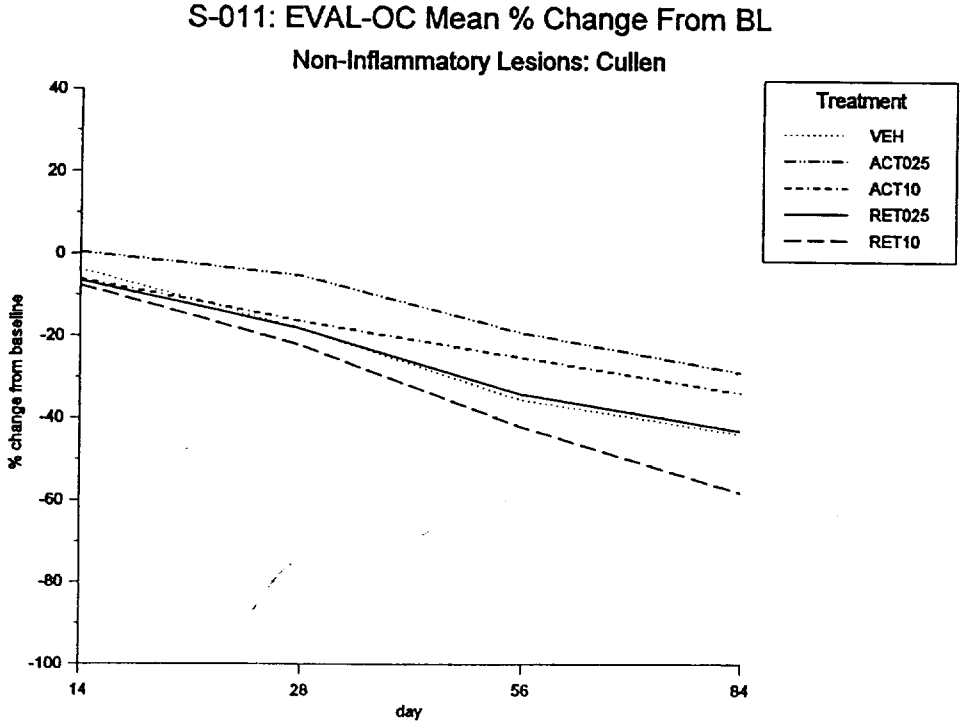
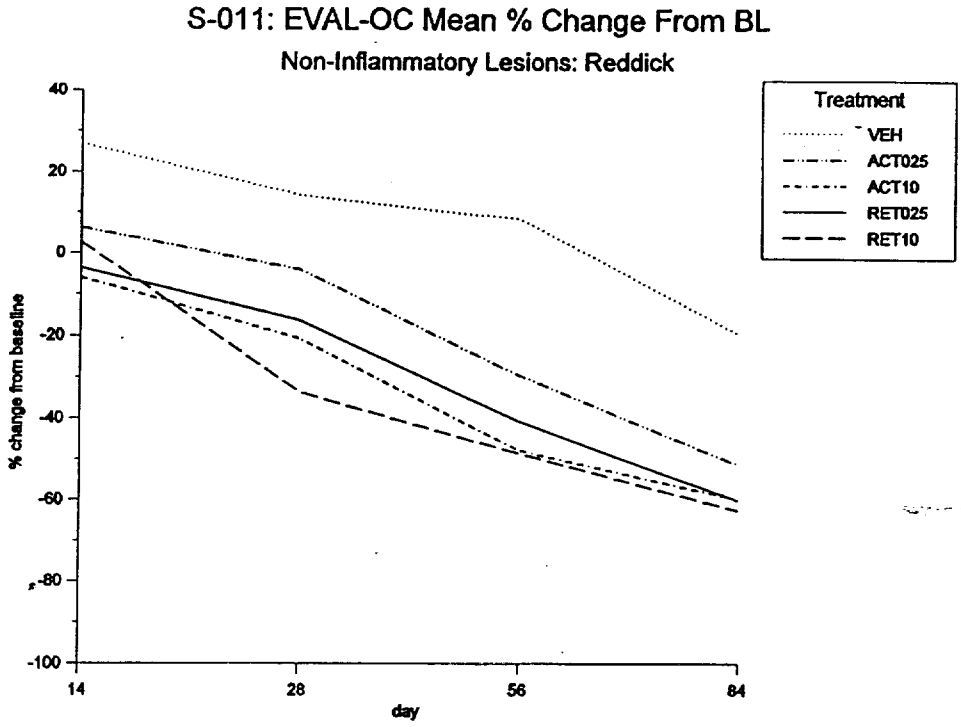


FIGURE 1C: Study 011Non-Inflammatory Lesions by Treatment and Center



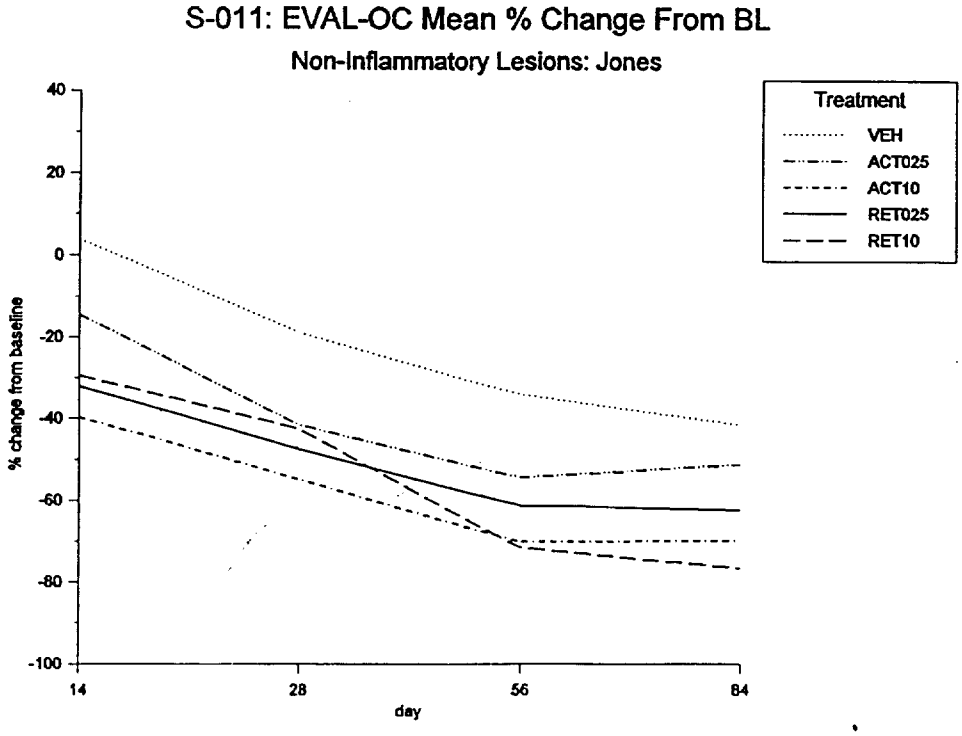
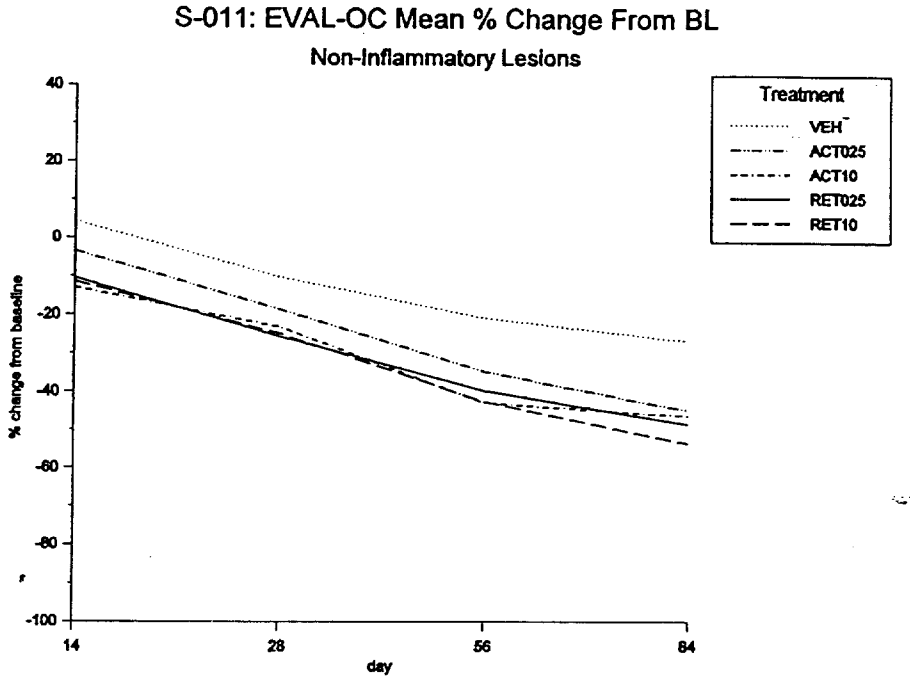
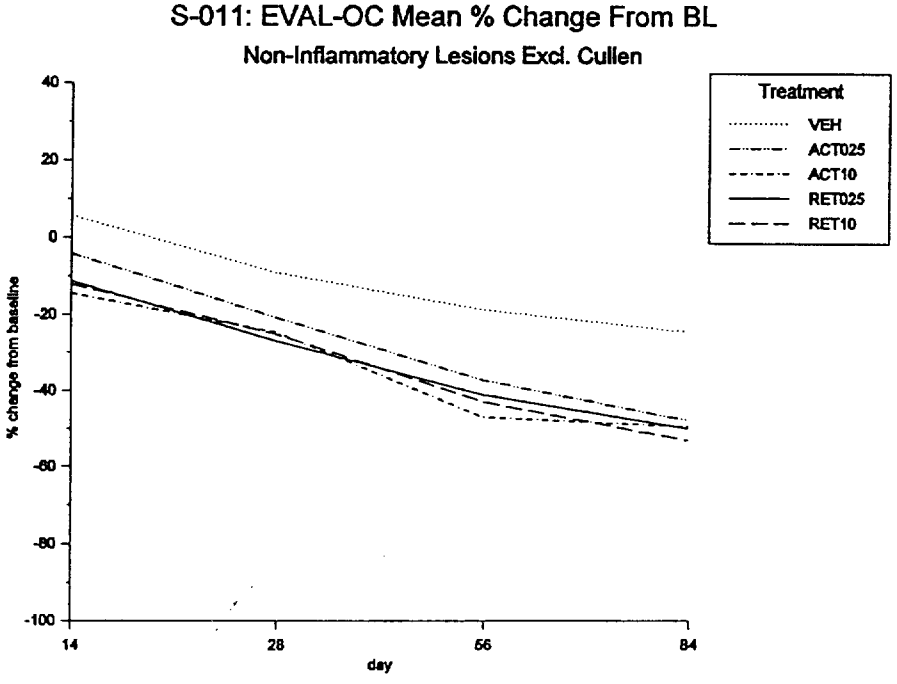


FIGURE 2A: Study 011 Non-Inflammatory Lesions by Treatment





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APPENDIX I

in vitro percutaneous absorption studies

Performing Laboratory:
Penederm Incorporated
320 Lakeside Drive
Forter City, CA 94404

BIOPHARMACEUTICS REVIEW

NDA 20,404

A.1. REVIEW OF THE PERCUTANEOUS ABSORPTION STUDIES

***in vitro* Percutaneous Absorption from Cream**

Acticin Cream: 0.025% (PDT 004-044), 0.05% (PDT 004-045), 0.1% (PDT 004-046)
Study No. #PD94:71

Methods: The *in vitro* percutaneous absorption of tritiated tretinoin was evaluated from Acticin (test) and Retin-A (control) Cream formulations at tretinoin concentrations of 0.025%, 0.05% and 0.1%. Dermatomed human skin was mounted into Bronaugh flow-through diffusion cells. Each formulation was applied to the epidermal surface of the skin at a dose of 10 mg over the 0.64 cm^2 test area. The dermal surface of the skin was perfused with phosphate-buffered saline and the cells were maintained at 37 °C. The receptor phase was collected at 6-hour intervals, for 48 hours, and assayed for radioactivity to assess tretinoin percutaneous penetration from the test and control formulations. At 48 hours post-dose application, the test and control materials were removed from the skin surface by washing with 95% ethanol. The washes were pooled and assayed for radioactivity. Finally, each skin sample was solubilized and assayed for radioactivity to assess retention of tritiated tretinoin in the skin.

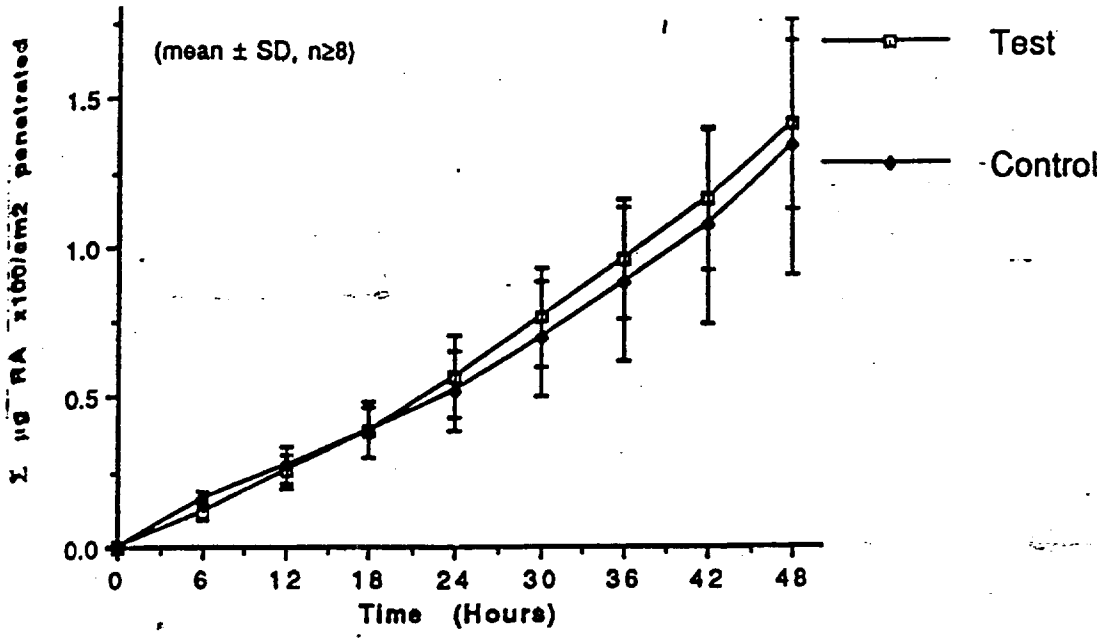
Results: The percutaneous absorption of tritiated tretinoin from Acticin Cream and Retin-A Cream formulations, after a 48-hour exposure period is given at Table 1. Drug penetration -time profile are given at page 19 and 20.

Table 1.
Percutaneous Absorption of Tretinoin from Cream Formulations
(% of Applied Dose; Mean±SD)

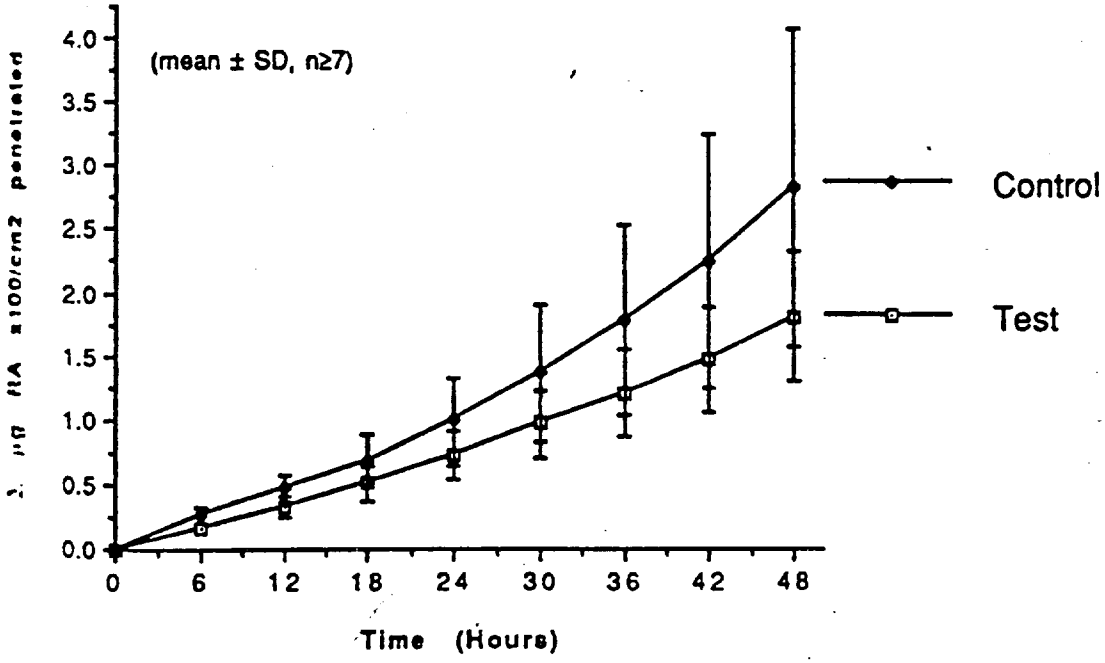
Test and Control	skin Content (%)	Receptor phase (%)	Total Recovery (%)
Acticin 0.025% (PDT 004-044) n=11	4.7 ± 2.2	0.28 ± 0.06	104 ± 4
Retin-A 0.025% (PDT 004-024) n=8	2.8 ± 0.9	0.27 ± 0.08	105 ± 3
Acticin 0.05% (PDT 004-045) n=9	6.5 ± 3.0	0.17 ± 0.04 *	10.4 ± 5
Retin-A 0.05% (PDT 004-030) n=7	3.5 ± 0.4	0.33 ± 0.15	106 ± 2
Acticin 0.1% (PDT 004-046) n=9	5.5 ± 1.7	0.21 ± 0.07	106 ± 2
Retin-A 0.1% (PDT 004-031) n=12	4.6 ± 2.3	0.32 ± 0.10	106 ± 4

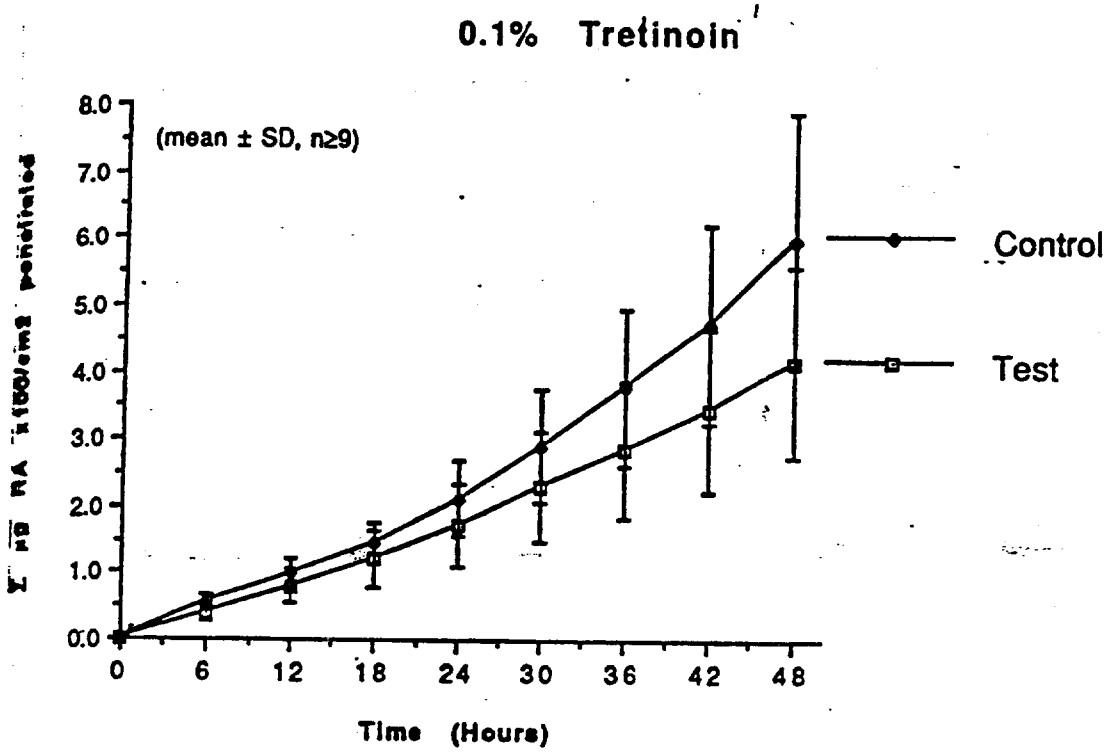
* statistically significant different.

0.025% Tretinoin



0.05% Tretinoin




0.1% Tretinoin
(mean ± SD, n≥9)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
6
12
18
24
30
36
42
48
Time (Hours)
Control
Test

The penetration of radiolabel from the Acticin formulations never exceeded 0.3%. Furthermore, receptor phase data indicate that the Acticin Creams, at concentrations of 0.025% and 0.1%, deliver statistically equivalent amounts of tretinoin compared to the corresponding Retin-A Creams. The Acticin 0.05% Cream formulation, however, delivered statistically less tretinoin to the receptor phase compared to the Retin-A 0.05% Cream.

Tretinoin skin levels, although generally greater from the Acticin Cream formulations than from the Retin-A formulations, were not statistically different at any of the corresponding tretinoin concentrations.

Summary and Conclusion: Based upon the results of this study, the Acticin Creams offer similar low tretinoin penetration as do the commercial Retin-A products.

***in vitro* Percutaneous Absorption of Tretinoin from Gel.**

Acticin Gel (PDT 004-002)
Study No. #PD168-60

Method: the *in vitro* percutaneous absorption of tretinoin was evaluated from Acticin (test) and Ortho Retin-A (control) 0.025% tretinoin Gels. Both formulations were spiked with tritiated tretinoin. Dermatomed human skin was mounted into Bronaugh flow-through diffusion cells. Each formulation was applied to the epidermal surface of the skin at a dose of approximately 10 mg over the 0.64 cm^2 test area. The dermal surface of the skin was perfused with phosphate-buffered saline and the cells were maintained at 37 °C. The receptor phase was collected at 6-hour intervals, for 48 hours, and assayed for radioactivity to assess tretinoin percutaneous penetration from the test and control formulations. At 48 hours post-dose application, test and control materials were removed from the skin surface by detergent and water washing. The washes were assayed for radioactivity. Finally, each skin sample was separated into epidermis and dermis. Then, each skin section was solubilized and assayed for radioactivity to assess retention of tritiated tretinoin in the skin.

Results: The percutaneous absorption of tritiated tretinoin from Acticin Gel and Retin-A Gel formulations, after a 48-hour exposure period, is given at below:

Table 2.
Percutaneous Absorption of Tretinoin from Gel Formulations
(% of Applied Dose; Mean±SD) n=7-9

Test/Control Formulations	Receptor (%)	Epidermis* (%)	Dermis (%)	Total Recovery (%)
Acticin Gel (PDT 004-002)	0.22(0.04)	0.58(0.19)	0.26(0.10)	93.5(3.7)
Retin-A Gel (PDT 004-003)	0.28 (0.06)	1.76(0.82)	0.28(0.16)	101.9(5.6)

* Statistical difference ($p<0.05$) between test and control formulations

Discussion: There are some inconsistencies between these results and the results of pilot studies

given below, using different techniques for removal of test materials. The absolute receptor levels of radiolabeled tretinoin from Acticin Gel and Retin-A Gel are similar and consistent with the preliminary studies described below, although receptor levels are statistically less from Acticin Gel. The epidermal content of radiolabeled tretinoin following detergent and water washing is statistically greater from Retin-A Gel than from Acticin Gel. Therefore, the washing procedure employed is more efficacious in the removal of Acticin Gel from the skin compared to Retin-A Gel. Dermal radiolabel deposition, however, is virtually identical between the two Gel formulations.

Acticin Gel (PDT 004-002)
Study Nos. #PD34-21, 24-77, 37-21, 37-25 (Supportive Studies)

In addition to the study summarized above, four supportive, developmental studies were conducted to investigate the *in vitro* percutaneous absorption of tritiated tretinoin from Acticin Gel and Retin-A Gel formulations. These studies were previously referenced in the Sponsor's IND Topical All-Trans-Retinoic Acid, serial #003. The study conditions used to measure *in vitro* percutaneous penetration of tritiated tretinoin from Acticin Gel and Retin-A Gel formulations in these four supportive studies were similar to those employed in the above study, #PD168-60.

Method: A major difference in the study design of these supportive studies was that methods were employed to assess the effect of rubbing, instead of detergent washing, on epidermal levels of tretinoin. These procedures were conducted after the collection of receptor fluid samples and, therefore, would have no effect on observed tretinoin penetration.

Results: Penetration of radiolabeled tretinoin from Acticin Gel and Retin-A Gel formulations from all five studies is summarized in Table 3 below:

Table 3
Percutaneous Penetration of Tretinoin from Gel Formulations
(% of Applied Dose in Receptor Fluid; Mean±SD)

Test/Control	Study Identification				
Formulations	#PD168-60*	#PD34-21*	#PD24-77*	#PD37-21*	#PD37-25
Acticin Gel (PDT 004-002)	0.22±0.04	0.33±0.06	0.35±0.10	0.14±0.01	0.12±0.02
Retin-A Gel (PDT 004-003)	0.28±0.06	0.43±0.05	0.43±0.07	0.28±0.07	0.20±0.08

* statistical difference ($p<0.05$) between test and control formulations

The small differences in the penetration of radiolabel among these studies can be attributed to the variation in the skin employed in each study and to differences in study conditions. Nevertheless, the levels of radiolabeled tretinoin in the receptor fluid from all five studies indicate that the penetration of radiolabel is in the same range for Acticin Gel and for Retin-A Gel. The penetration of radiolabel from Acticin Gel is consistently less than that from Retin-A Gel. Furthermore, the

penetration of radiolabel from both formulations never exceeded 0.5% of the applied radiolabel in any of the studies. The ability of Acticin Gel to resist the removal of tretinoin from the epiderm- relative to Retin-A Gel was evaluated by dry wiping the skin followed by five repetitive tape stripping of the surface of the skin. Because of the presence of formulation, the hydrated state of the skin following removal from the diffusion cells, and the vigor in which the investigator engages the wiping and tape stripping procedures, the techniques employed may be insufficient to remove all of the superficial residual test material from the epidermis. However, these techniques were designed to simulate material that would remain on the site of application if the patient did not wash and loss was due solely to rubbing and exfoliation Epidermal levels of tretinoin observed in the three most recent studies are summarized in the following table:

Table 4
Epidermal Levels of Tretinoin from Gel Formulations
(% of Dose; mean ± SD)

Test and Control Formulations	Study Identification		
	#PD168:60 detergent washing	#PD37:25 dry wipe/ tape strip	#PD37:21 dry wipe/ tape strip
Acticin Gel (PDT 004-002)	0.58 ± 0.19	6.58 ± 1.80	6.50 ± 2.62
Retin-A Gel (PDT 004-003)	1.76 ± 0.82	1.18 ± 0.94	2.81 ± 1.50

Discussion: The absolute epidermal levels of radiolabeled tretinoin varied in magnitude among these studies, especially for Acticin Gel, whereas Retin-A Gel was relatively constant across studies. When the wipe and tape strip procedure was used, higher epidermal levels of the radiolabel were observed following topical application of Acticin Gel compared to Retin-A Gel. This suggests a greater resistance to the rub off of tretinoin following topical application of Acticin Gel than Retin-A Gel. In contrast, when a detergent washing procedure was employed, lower epidermal levels of tretinoin are observed following topical application of Acticin Gel compared to Retin-A (study #PD168:60 in table above). This suggests that washing with detergent is more efficacious in the removal of tretinoin from the skin following topical application of Acticin Gel when compared to Retin-A Gel.

Summary and Conclusion: Epidermal and dermal levels of tretinoin were low following topical application of either Acticin Gel or Retin-A Gel. The presence of PPP-2 in the Acticin Gel formulation may afford greater resistance to the rub-off of tretinoin and greater ease in tretinoin removal by detergent washing when compared to Retin-A Gel.

Percutaneous Absorption of Polyolprepolymer-2 (PPP-2)

***in vitro* Percutaneous Absorption**

Introduction: PPP-2 is a liquid mixture of two polyol components with a combined average molecular weight of approximately 4000 daltons. The chemical composition of PPP-2 was reviewed in section 3.4.1 of the submission. Both polyol components comprising PPP-2, the higher molecular weight oligomers and lower molecular weight PPG-725, were radiolabeled and incorporated individually into several vehicles. Two *in vitro* studies were conducted to evaluate the extent of PPP-2 (PDT 002-002) percutaneous absorption into and through human skin. In addition, three pilot studies were conducted to characterize the percutaneous absorption of PPP-2 *in vivo*. This section summarizes the results of these studies.

Methods: The test materials were applied (3-6 mg/cm^2) to the epidermal surface of dermatomed human skin mounted on Franz static diffusion cells and then spread evenly with a glass rod. The dermal surface of the skin was perfused with phosphate buffered saline containing .% sodium azide and % Oleth 20 equilibrated at 37 °C. Receptor phase samples were collected at 5, 24, 29 and 48 hours post-dose application and analyzed for radioactivity. At 48 hours, the skin surface was washed with one soap:water (50:50, v/v) cotton swab, 3 consecutive ethanol swabs and one dry swab. Along with each individual wash sample, skin samples were solubilized and assayed for radioactivity.

Results: The results of two pivotal investigations (#PD168-33, #PD91-79) characterizing PPP-2 *in vitro* percutaneous absorption are summarized in Table 5 and discussed separately in detail.

Table 5
Percutaneous Penetration of PPP-2 and its Components
(% of applied dose; mean ± SD)

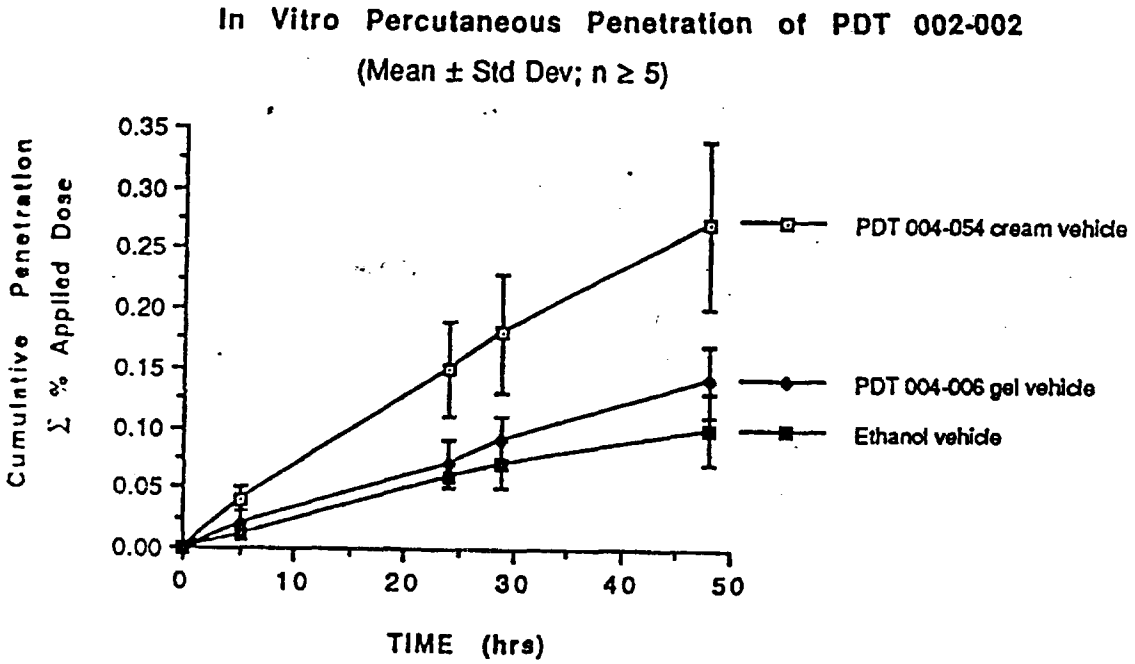
Test Materials	^{3}H-PDT 002-002 (% penetrated)	^{3}H-Oligomers (% penetrated) n=6	^{3}H-PPG-725 (% penetrated) n=6
#PD168-33			
neat (PDT 002-002)		<0.0012[b]	0.05+0.02
Gel (PDT 004-006)[a]		<0.0015[c]	0.32+0.11
#PD91-79			
Cream (PDT 004-054)[a]	0.27+0.07		
Gel (PDT 004-006)[a]	0.14+0.03		
ethanol solution	0.10+0.03		

a: vehicle contains 10% PDT 002-002
b: 0.0012% is the limit of detection
c: 0.0015% is the limit of detection
Note: PDT 004-054 is the Acticin Cream vehicle

a. Detail of Study No. #PD168-33
PPP-2 (PDT 002-002), research Gel vehicle (PDT 004-006)

Method: The individual polyol Components of PPP-2, tritiated higher molecular weight oligomers and tritiated PPG-725, were incorporated separately into neat PPP-2 and into Acticin Gel (PDT 004-006) to characterize the percutaneous absorption of each component into and through human skin.

The results indicate that the higher molecular weight oligomers of PPP-2 do not penetrate the skin. The lower molecular weight PPG-725 penetrates the skin from both vehicles, but levels are very low (< 0.35% of the applied dose). Skin levels of each component, from both vehicles, are very low (< 0.30%), with the majority of the polyols localized in the epidermis. In addition, the soap/water and ethanol wash employed readily removes both components of PPP-2 from the skin.



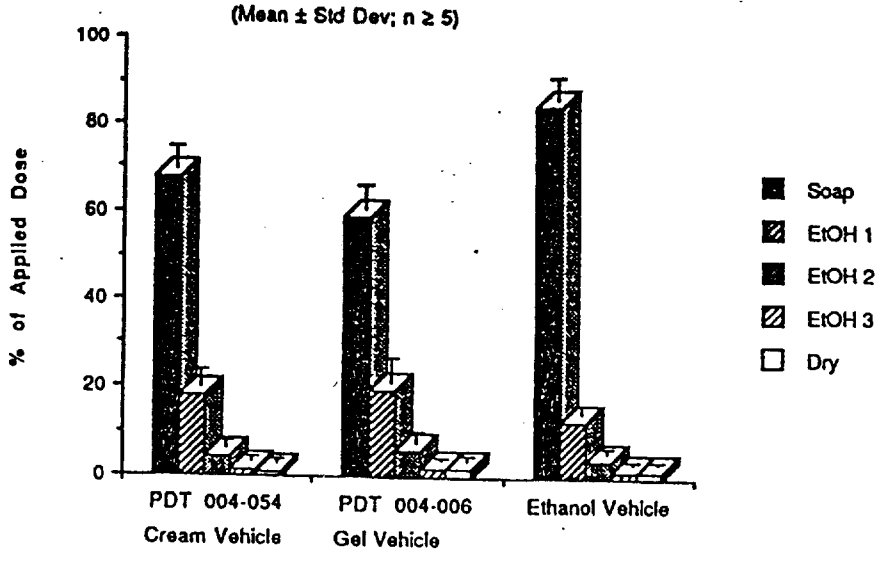
Mass Absorption of Polyolprepolymer-2 into and Through Skin
(µg / cm^2; Mean ± Std Dev)

Test Material	Receptor (µg / cm^2/48 hrs)	Skin Content (µg / cm^2/48 hrs)
PDT 004-054 Cream vehicle	1.37 ± 0.35	1.86 ± 0.62
PDT 004-006 Gel vehicle	0.75 ± 0.16	1.81 ± 1.28
PD89:54.00 Ethanol vehicle	0.40 ± 0.10	0.79 ± 0.21

Percent Absorption of Polyolprepolymer-2 into and Through Skin
(% of Applied Dose; Mean ± Std Dev)

Test Material	Receptor	Skin Content	Total Recovery (including washes)
PDT 004-054 Cream Vehicle	0.27 ± 0.07	0.36 ± 0.12	94.75 ± 4.50
PDT 004-006 Gel Vehicle	0.14 ± 0.03	0.33 ± 0.24	89.12 ± 4.12
PD89:54.00 ethanol Vehicle	0.10 ± 0.03	0.20 ± 0.05	106.7 ± 6.77

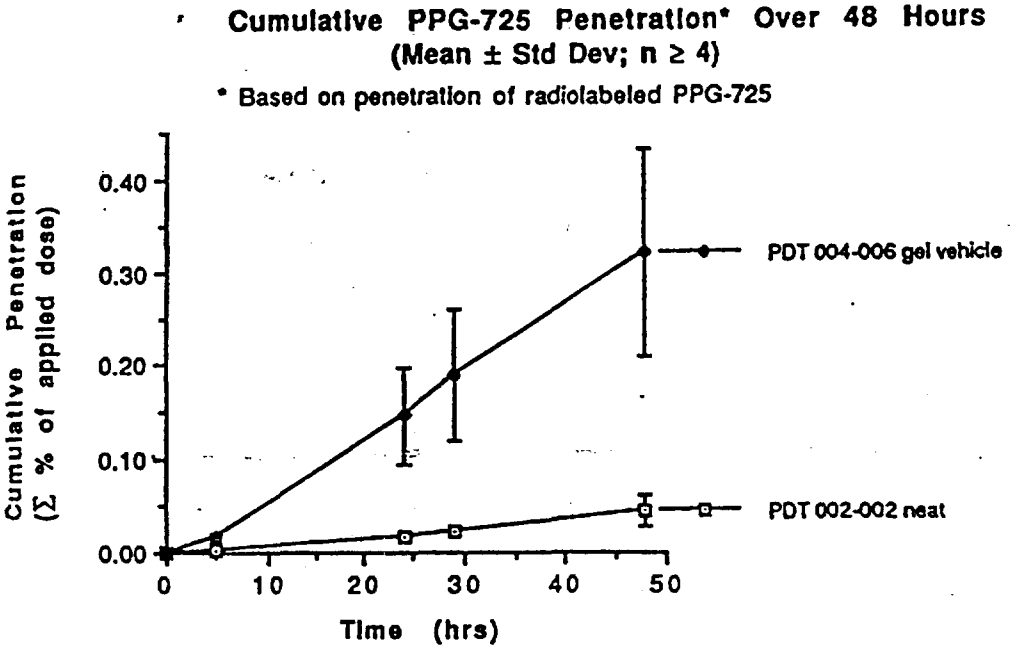
Skin Surface Wash Profile
(Mean ± Std Dev; n ≥ 5)



b. Detail of Study No. #PD91-79
Acticin Cream vehicle (PDT 004-054), research Gel vehicle (PDT 004-006), ethanol vehicle (#PD89-54.00)

Acticin Cream vehicle (PDT 004-054), containing % PPP-2, was tested for its effect on the *in vitro* percutaneous absorption of tritiated PPP-2. A research Gel vehicle and an ethanol vehicle, each containing % PPP-2, were also tested. Both polyol components of PPP-2, oligomers and PPG-725, were radiolabeled in each vehicle, i.e., the penetration of the polyol components was measured in combination, not independently.

The majority of the radiolabeled PPP-2 in the test materials was readily removed from the skin surface by washing with soap/water and ethanol (96% +/- 9%). Receptor fluid data indicated that only a very small amount, less than 0.30% of the applied dose of PPP-2, penetrated through the skin from all three vehicles. In addition, PPP-2 skin levels were very low from all three vehicles (<0.40%).



Mass Absorption of Polyols Comprising PDT 002-002 Into and Through Skin
(µg / cm²; Mean ± Std Dev)

Test Material	Epidermis (µg/cm²)	Dermis (µg/cm²)	Receptor (µg / cm²/48 hrs)
³H-PPG-725 In:			
PDT 002-002, neat	0.86 ± 0.72	0.10 ± 0.11	0.36 ± 0.14
PDT 004-006 (gel vehicle)	0.21 ± 0.08	0.01 ± 0.01	0.24 ± 0.10
³H-HMW oligomers In:			
PDT 002-002, neat	5.76 ± 6.71	0.11 ± 0.09	0.00 ± 0.00[a]
PDT 004-006 (gel vehicle)	0.71 ± 0.18	0.03 ± 0.04	0.00 ± 0.00[b]

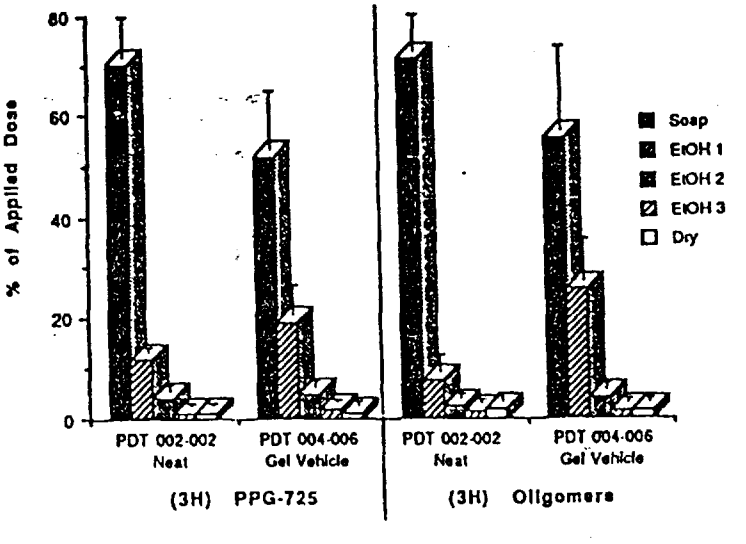
[a] Below limit of detection: <0.050 µg/cm²
[b] Below limit of detection: <0.006 µg/cm²
Note: Mass of PDT 002-002 applied is 10-fold less from the gel vehicle than from neat PDT 002-002

Percent Absorption of Polyols Comprising Polyolprepolymer-2 Into and Through Skin
(% of Applied Dose; Mean ± Std Dev)

Test Material	Epidermis	Dermis	Receptor	Total Recovery (including washes)
³H-PPG-725 In:				
PDT 002-002, neat	0.11 ± 0.10	0.01 ± 0.01	0.05 ± 0.02	89.50 ± 8.83
PDT 004-006 (gel vehicle)	0.29 ± 0.10	0.01 ± 0.01	0.32 ± 0.11	80.39 ± 7.89
³H-HMW oligomers In:				
PDT 002-002, neat	0.14 ± 0.16	0.003 ± 0.002	0.00 ± 0.00[a]	87.34 ± 7.60
PDT 004-006 (gel vehicle)	0.20 ± 0.04	0.01 ± 0.01	0.00 ± 0.00[b]	89.03 ± 12.58

[a] Below limit of detection: <0.0012% of applied dose
[b] Below limit of detection: <0.0015% of applied dose
Note: Mass of PDT 002-002 applied is 10-fold less from the gel vehicle than from neat PDT 002-002

Skin Surface Wash Profile (Mean ± Std Dev; n ≥ 4)



Other Supportive Studies (*in vivo*)

Several *in vivo* studies were conducted to develop methods to evaluate the localization of PPP-2 and its higher molecular weight polyol component in human skin.

***PPP*-2 (PDT 002-002)**
Study No. #PD168-21, #PD168-27

In order to characterize the localization of PPP-2 in skin *in vivo*, the higher molecular weight polyol component of PPP-2 was radiolabeled and then incorporated into neat PPP-2. The radiolabeled polymer was applied to the dorsal forearm of **two** subjects (3-5 mg/cm2) under either occluded or semi-occluded, protected conditions. At 24 hours post-dosing, the chamber was removed and the skin surface was washed. The upper layers of the stratum corneum were removed with 10 tape-strips and each tape-strip was analyzed for radioactivity.

Approximately 95% of the applied radiolabeled dose was readily removed from the skin surface by washing with soap and water. In addition, all of the radiolabeled oligomers were removed from the skin surface after the sixth tape-strip, suggesting that minimal amounts of the higher molecular weight oligomers of PPP-2 were localized in the upper layers of the stratum corneum (< 0.2% of the applied dose).

***in vivo* Skin Localization of PPP-2 (PDT 002-002)**
Study No. #PD112-18

The *in vivo* localization of PPP-2 in human skin was characterized by FTIR-ATR spectrophotometric methodology. Cotton pads were saturated with a test solution of % PPP-2 in ethanol:water (60:40 v/v) and applied to the dorsal forearm of **two** subjects under occluded conditions. At 3 hours post-dosing, the pads were removed and the test area was lightly wiped with two cotton swabs. The skin was tape-stripped eight times and after each tape-strip, analyzed by FTIR-ATR for the presence of PPP-2.

The results reveal that PPP-2 is localized in the upper layers of the stratum corneum under the conditions employed. In addition, all detectable PPP-2 is completely removed from the skin surface by five repetitive tape-strips, *in vivo*.

***in vivo* Research Cream vehicle (PDT 004-054)**
Study No. #TOX 002-020

An *in vivo* study with monkeys, employing topical application of tritiated PPP-2 incorporated in a research Cream vehicle containing % PPP-2, was attempted. The data from this study are not interpretable because of problems encountered during preparation of samples and operation of instrumentation. In addition, concerns were noted in the animal handling techniques employed. The potential for tritium exchange raises concerns as to whether this label accurately reflects PPP-2 absorption. A report for the study is not currently available.

APPENDIX II

In vivo Pharmacokinetic Study

#PDC 004-017

in vivo Plasma concentration measurement (#PDC004-017)

Title: A SINGLE CENTER, DOUBLE-BLIND, PARALLEL STUDY TO DETERMINE THE EFFECT OF MULTIPLE APPLICATIONS OF TRETINOIN-CONTAINING FORMULATIONS ON PLASMA LEVELS OF TRETINOIN IN NORMAL VOLUNTEERS (#PDC 004-017)

Principle Investigators:

INTRODUCTION

This study was designed to determine the effect of multiple applications of tretinoin containing formulations, Retin-A 0.025% Gel (PDT 004-003) and Acticin 0.025% Gel (PDT 004-002), on the endogenous plasma levels of tretinoin (all-trans-5-retinoic acid) and isotretinoin (1,3-cis-retinoic acid) in normal volunteers over a 28-day daily topical application regimen to their face.

Previous studies in humans with radioactive tretinoin in both Gel and Cream formulations indicate minimal systemic absorption of the drug following topical administration. With the recent advent of highly sensitive analytical techniques which allow the accurate measurement of tretinoin in plasma, non-radioactive percutaneous absorption studies are now possible.

METHODS

Human Subjects

Eighteen subjects (9 males and 9 females) were enrolled into this study. They ranged in ages from 21 to 41 years (29 +/- 6, Mean± SD yrs), were within 20% of their ideal body weight using the Metropolitan Life Insurance Company standards, were in good health as assessed by medical history, physical examination and clinical laboratory results, were free of any skin disease, and had not used any topical medications or retinoid therapies within the 60 days prior to enrollment. All subjects who were enrolled completed the study. However, Subjects were unable to have Study Day 14 visit activities performed due to a scheduling conflict. No adverse events occurred during this study. The subjects were carefully advised to avoid Vitamin A supplements that would exceed its recommended daily allowance or foods with high Vitamin A content (e.g. liver) throughout the study and specifically within 48 hours prior to each blood sampling day.

Initials	Sex*/ID	Age (yrs)	Weight (lb)
		25	165
		37	196
		25	181
		33	187
		24	195
		26	127
		25	190

41	190
34	156
27	135
26	139
24	155
21	141
21	130
24	128
39	132
37	150
32	131

a: M male, F Female

Subjects were provided with a single 20 gm tube of either Retin-A 0.025% Gel or Acticin 0.025% Gel. Both subjects and investigators were blinded to product identification throughout the study. Each subject was carefully instructed and received a demonstration on the proper application of the Gel. Application was to the forehead and both cheeks (~125-175 cm^2), excluding the nose, around the eyes and chin., At each study visit day, the tubes were collected and tube weights recorded. Additional instructions were provided to those subjects demonstrating an over or under average daily use of product. Target application was to be 2 mg/cm^2 Gel to 150 cm^2. Tube weights demonstrated that mean daily usage over 28 days was 0.307±0.066 gms ($x \pm SD$) for Retin-A Gel and 0.312±0.057 gms for Acticin Gel. Applications commenced on study day 1 and there after on each evening 30-40 minutes prior to bed. On the morning of study days 7, 14, and 28, the subjects washed their face with soap and water (Purpose Soap, Johnson and Johnson, Skillman, NJ). Thirty minutes after the face wash a weighed application was performed by the investigator to each subject. Subjects remained in a darkened room lit only by low wattage yellow tungsten lamps for four hours after Gel application. Blood samples were collected at 15 minutes prior to and at 2, 4, 8, 10, 12, and 24 hours after Gel application. Ten hours post-dosing the subjects washed their face to remove any unabsorbed drug. After the 24 hour blood sample the tubes of medication were returned to the subject for subsequent evening applications until the next study day.

Clinical Observations

On each selected study day (Day 0, 7, 14, and 28), prior to the face wash, subject's forehead and both cheeks were first evaluated for signs of cutaneous irritation defined as erythema, peeling, and dryness. Each factor was graded on a 3 point scale (0= none, 1=light, 2 = moderate, 3 = severe) and 0.5 unit increments. In addition, trans-epidermal-water-loss (TEWL) was measured from the center of the forehead and both cheeks simultaneously using a multi-probe Courage+Khazaka Tewameter (Germany).

Blood Sample Collection

Blood samples were collected in 10 ml, sodium heparin (Becton Dickson, Franklin Lakes, NJ) under dim yellow light. Tubes were immediately covered with aluminum foil and placed in ice. Within 30 minutes of collection, the blood tubes were centrifuged, plasma isolated into 0.5 ml (for direct analysis) and 2.0 ml (for storage reserve) aliquot in amber microcentrifuge tubes and stored at -70°C protected from light. The protocol stated that duplicate 1.0 ml aliquots were to be prepared,

however, by reducing the analysis aliquot to 0.5 ml the sample was ready for direct use in the assay procedure by removing an initial pipetting step.

Retinoic Acid Assay

Tretinoin and isotretinoin were assayed by a sensitive high pressure liquid chromatography/particle beam/mass spectrometry method (detailed methodology was submitted). The mass spectrometer was operated in the negative chemical ionization mode with selected ion monitoring at 325.2 for the internal standard and 299.2 for the retinoic acids. Methane was used as the reagent gas at a source pressure of 1-2 x 10^4 torr. With each set of twenty-four samples a control spiked plasma sample and duplicate 3-point standard curve samples (1, 2 and 5 ng/ml) were analyzed. Tretinoin and isotretinoin were quantified using the internal standard normalization method to the mean standard curve generated from that batch run of samples.

Statistics

Data were collected by subject, sample hour and day, and by formulation. The data were tested across all days for statistical differences between days and between treatments. For continuous data (AUC, Css, Cmax, TEWL), a repeated measures analysis was used. For scaled data (erythema, dryness and peeling), nonparametric analyses were used (Kruskal-Wallis test and Wilcoxon Signed Rank test). Correlation analyses were performed by calculating Pearson correlation coefficients.

RESULTS

Plasma Levels of Tretinoin and isotretinoin

Plasma levels were determined at seven time points over twenty-four hours on Study Days 0, 7, 14 and 28. Study Day 0 represents baseline endogenous levels of tretinoin and isotretinoin. Days 7, 14 and 28 plasma concentrations were monitored for any change in endogenous retinoic acid levels during the topical exposure of the tretinoin containing products. The data are summarized in Tables 6 and 7.

Baseline mean retinoic acid plasma level across the entire 24 hour sampling period was found to be 1.49 $\pm$ 0.69 ng/ml (mean $\pm$ SD) for tretinoin and 1.03 $\pm$ 0.60 ng/ml for isotretinoin. These levels of endogenous retinoic acids are consistent with reported values by others. Plasma tretinoin levels on study day 7 tended to increase slightly within the 8 and 10 hour samples. Study Day 14 and 28 tretinoin plasma levels were lower, on average, when compared to Study Days 0 and 7. Isotretinoin concentrations were consistently lower throughout all study day visits.

Table 6
Summary of measured plasma tretinoin values at each sampling time on each study day.
Values are the mean $\pm$ SD as ng/ml of all-trans retinoic acid.

Day	Time (hr)	Acticin Gel	Retin-A Gel
0	0	1.42 $\pm$ 0.95	1.68 $\pm$ 0.85
	2	1.88 $\pm$ 1.01	1.53 $\pm$ 0.66
	4	1.60 $\pm$ 0.72	1.63 $\pm$ 0.75
	8	1.40 $\pm$ 0.59	1.04 $\pm$ 0.87
	10	1.18 $\pm$ 0.19	1.39 $\pm$ 0.66

	12	1.46 ± 0.36	1.52 ± 0.83
	24	1.45 ± 0.51	1.50 ± 0.50
7	0	1.72 ± 0.52	1.67 ± 0,73
	2	1.51 ± 1.01	1.14 ± 0.64
	4	1.68 ± 0.96	1.74 ± 0.61
	8	2.13 ± 1.60	1.82 ± 0.45
	10	2.36 ± 0.54	2.26 ± 0.34
	12	1.54 ± 0.39	1,39 ± 0.61
	24	2.06 ± 1.01	1.44 ± 0.59
14	0	1.49 ± 0.77	1.58 ± 0.65
	2	1.27 ± 0.15	1.36 ± 0.51
	4	1.36 ± 0.28	1.53 ± 0.40
	8	1.06 ± 0.41	1.07 ± 0.39
	10	1.24 ± 0.44	1.06 ± 0.56
	12	1.20 ± 0.23	1.38 ± 0.59
	24	1.25 ± 0.35	1.27 ± 0.75
28	0	1.40 ± 0.35	1.07 ± 0.60
	2	1.33 ± 0.32	1.59 ± 0.72
	4	1.40 ± 0.12	1.57 ± 0.69
	8	1.61 ± 0.85	0.98 ± 0.23
	10	1.29 ± 0.73	1.13 ± 0.29
	12	1.23 ± 0.27	1.11 ± 0.55
	24	1.53 ± 0.45	1.06 ± 0.22

Table 7.
Summary of measured plasma isotretinoin values at each sampling time on each study day.
Values are the mean ± SD as ng/ml 13-cis retinoic acid.

Day	Time (hr)	Acticin Gel	Retin-A Gel
0	0	1.10 ± 0.72	0.89 ± 0.66
	2	1.28 ± 0.96	1.07 ± 0.79
	4	1.23 ± 1.02	0.96 ± 0.43
	8	1.03 ± 0.13	0.82 ± 0.47
	10	1.02 ± 1.13	0.87 ± 0.47
	12	1.13 ± 0.42	1.13 ± 0.80
	24	0.90 ± 0.25	0.89 ± 0.38
7	0	1.16 ± 0.48	1.49 ± 0.79
	2	0.76 ± 0.56	0.69 ± 0.48
	4	0.64 ± 0.44	0.75 ± 0.59
	8	0.66 ± 0.34	0.64 ± 0.37
	10	0.75 ± 0.25	0.75 ± 0.25
	12	0.86 ± 0.25	0.83 ± 0.19
	24	0.77 ± 0.29	0.46 ± 0.26
14	0	0.87 ± 0.43	0.83 ± 0.26
	2	0.97 ± 0.67	0.91 ± 0.39
	4	0.97 ± 0.51	0.94 ± 0.26
	8	0.89 ± 0.40	0.77 ± 0.26
	10	0.93 ± 0.31	0.83 ± 0.34
	12	0.88 ± 0.47	0.73 ± 0.22
	24	1.02 ± 0.86	0.72 ± 0.25
28	0	0.80 ± 0.50	0.55 ± 0.31
	2	0.83 ± 0.50	0.73 ± 0.35
	4	0.80 ± 0.54	0.83 ± 0.42
	8	0.72 ± 0.40	0.82 ± 0.56
	10	0.79 ± 0.37	0.59 ± 0.40
	12	0.81 ± 0.51	0.69 ± 0.29
	24	0.91 ± 0.50	0.70 ± 0.33

The area-under-the-curve (AUC_{24}), Cmax (maximum concentration observed within each 24 hour period) and C_{ss} (mean concentration across the 24 hour period assuming steady-state levels) for both tretinoin and isotretinoin were calculated. The data are presented in Tables 9-10 and Figure in page 36.

Study Day 7 tretinoin values were slightly higher than the other study days, and Study Days 14 and 28 tended to be lower than Study Day 0. As can be seen in Table 9, Study Days 14 and 28 were found to be statistically different from Study Day 7 for AUC, Cmax and Css regardless of formulation. For Css, Study Day 7 was statistically greater than Study Day 0; both AUC and Cmax were not statistically different from Study Day 0 (baseline). There were no statistical differences observed in these parameters for the isotretinoin data (Table 10). In addition, there was no statistically relevant correlation between these three parameters and the clinical observation data.

Table 9:
Summary of plasma level data for tretinoin.

Product	Day	AUC	Cmax (ng/ml)	Css (ng/ml)
Acticin Gel	0	35.42 ± 8.70	2.37 ± 0.98	1.48 ± 0.42[c]
	7	42.47 ± 8.98	3.39 ± 1.01	1.83 ± 0.31
	14	29.70 ± 3.90[a]	1.83 ± 0.59[b]	1.27 ± 0.14[c]
	28	33.74 ± 9.45[a]	1.96 ± 0.75[b]	1.37 ± 0.27[c]
Retin-A Gel	0	34.63 ± 10.89	2.42 ± 0.72	1.50 ± 0.40[c]
	7	37.57 ± 4.91	2.53 ± 0.42	1.64 ± 0.18
	14	31.51 ± 9.84[a]	1.93 ± 0.60b	1.32 ± 0.37[c]
	28	27.83 ± 7.95[a]	1.67 ± 0.64b	1.19 ± 0.36[c]

a. AUC values found to be statistically different from study day 7; p = 0.0162
b. Cmax values found to be statistically different from study day 7; p = 0.0073
c. Css values found to be statistically different from study day 7; p = 0.0033
AUC = area under the plasma concentration-time curve, ng/ml-hr.
Cmax = maximum concentration observed with the 24 hour study day period, ng/ml.
Css = mean concentration over the 24 hr study day sampling period.

Table 10
Summary of plasma level data for isotretinoin.

Product	Day	AUC	Cmax(ng/ml)	Css(ng/ml)
Acticin Gel	0	25.72 ± 8.20	1.91 ± 0.98	1.09 ± 0.43
	7	18.08 ± 4.30	1.34 ± 0.36	0.89 ± 0.24
	14	22.49 ± 11.81	1.41 ± 0.84	0.93 ± 0.45
	28	20.49 ± 12.83	1.15 ± 0.51	0.91 ± 0.38
Retin-A Gel	0	23.04 ± 9.85	1.57 ± 0.82	0.97 ± 0.43
	7	17.12 ± 2.85	1.69 ± 0.65	0.80 ± 0.14
	14	18.85 ± 5.77	1.08 ± 0.33	0.82 ± 0.26
	28	17.61 ± 7.25	1.00 ± 0.44	0.72 ± 0.31

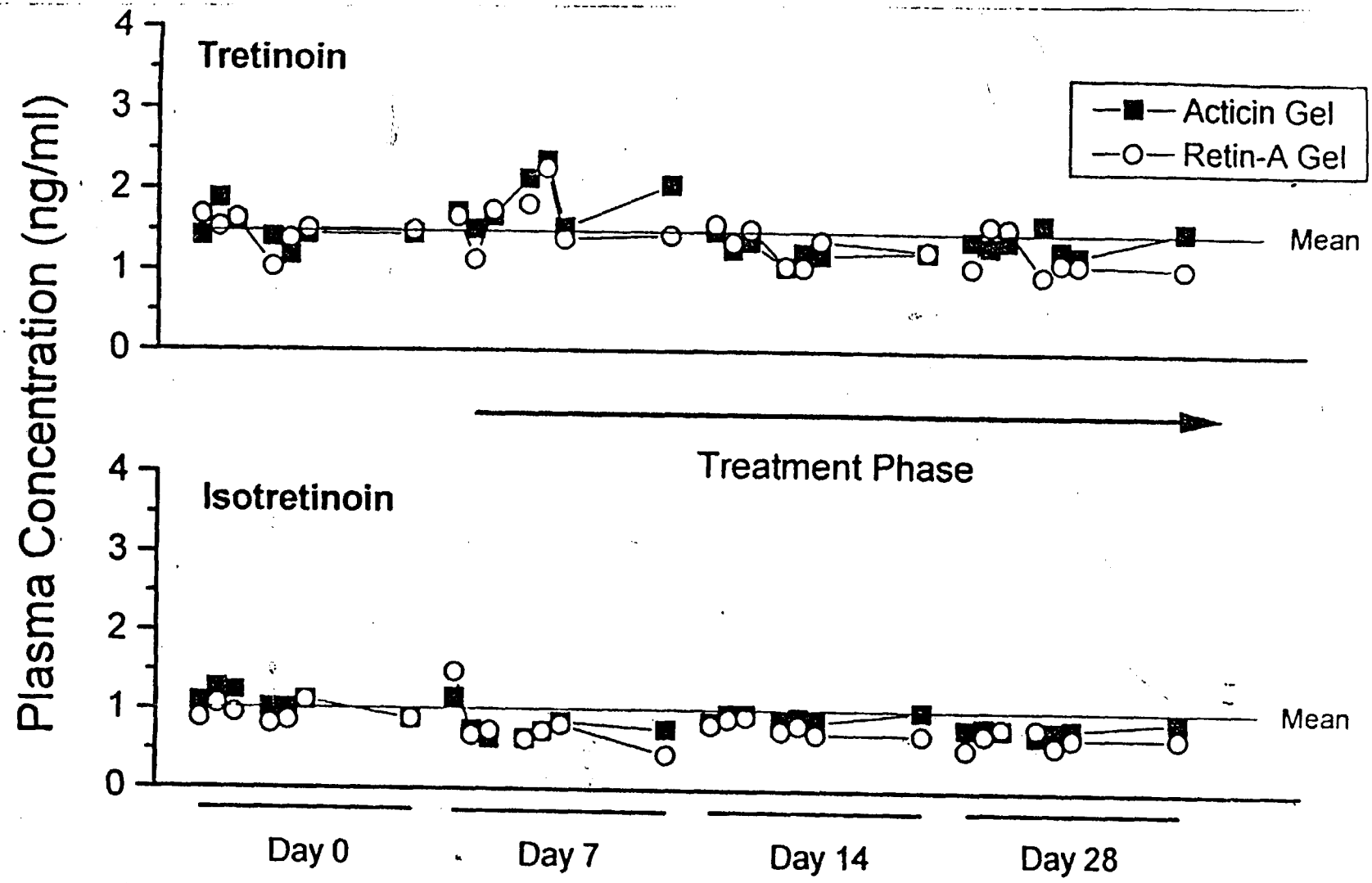


Figure 3: Mean plasma levels of tretinoin and isotretinoin grouped by formulation. Mean line derived from the baseline values across all subjects and time points on Study Day 0. Data are ng/ml from Tables 5 and 6.

Conclusion:

1. There were no statistical differences in tretinoin and isotretinoin plasma pharmacokinetic parameters between Retin-A 0.025% Gel and Acticin 0.025% Gel.

2. Decrease in AUC, Cmax and Css plasma tretinoin values from Study Day 7 to Study Days 14 and 28. Further, there was a slight but statistically significant increase in Css tretinoin from Study Day 0 to Study Day 7.

3. There were no statistical differences in the plasma pharmacokinetic parameters for isotretinoin cross study days.

APPENDIX III

Clinical observation associated with the PK study

Clinical observation associated with the PK study

In the clinical PK study, two types of clinical observation were recorded. All subjects began this study with no observable erythema, peeling or dryness. After 6 days of topical application, virtually every subject demonstrated at least two of the three observable irritation responses. These results are presented in Table 11 and 12.

Table 11

Summary of clinical observations. Number of subjects recorded per grading score for erythema, peeling and dryness for **Acticin Gel** on each Study Day visit.

Observation	Days	# of Subjects per Score				
	Score	0	0.5	1	1.5	2
	0	9	0	0	0	0
Erythema	7	4	2	3	0	0
	14	0	2	6	0	0
	28	1	3	3	2	0
	0	9	0	0	0	0
Peeling	7	3	2	4	0	0
	14	0	4	2	2	0
	28	2	4	1	2	0
	0	8	1	0	0	0
Dryness	7	1	1	7	0	0
	14	0	2	4	2	0
	28	0	4	2	0	3

Table 12

Summary of clinical observations. Number of subjects recorded per grading score for erythema, peeling and dryness for **Retin-A** on each Study Day visit.

Observation	Days	# of Subjects per Score				
	Score	0	0.5	1	1.5	2
	0	9	0	0	0	0
Erythema	7	8	0	0	0	1
	14	1	6	1	0	0
	28	0	7	1	0	1
	0	9	0	0	0	0
Peeling	7	4	2	1	1	1
	14	0	5	1	1	1
	28	0	6	2	0	1
	0	9	0	0	0	0
Dryness	7	4	1	3	1	0
	14	0	4	3	1	0
	28	1	4	0	3	1

Erythema was observable in 6 of the 18 subjects on Study Day 7, This was more evident for the Acticin Gel formulation (5 of 9 subjects > 0 score) than for the Retin-A Gel formulation (1 of 9 subjects > 0). Peeling was observable in 11 of 18 subjects (61%) and skin dryness was noted in 13 of 18 subjects (72%) on Study Day 7. Peeling and dryness were essentially equally distributed between the two formulations.

On Study Days 14 and 28, all the subjects demonstrated two or more of the three criteria for retinoic acid irritation. Consistent with the results seen on Study Day 7, the Retin-A Gel formulation gave lower scores for erythema than the Acticin Gel formulation on Study Day 14 and 28, Peeling and dryness scores were similarly distributed for both formulations on Study Days 14 and 28. Regardless of formulation, overall irritation scores lessened (indicating accommodation to the retinoic acid exposure) with daily application of the products.

No subject demonstrated an excessive irritation response, nor were any withdrawn from the study and no subject required an alteration in the dosing schedule due to the irritation. The observations were consistent with the typical irritation response seen in acne patients who have been prescribed Retin-A Gel products.

Trans-Epidermal-Water-Loss (TEWL)

All subjects demonstrated a change in normal trans-epidermal-water-loss after 6 days of topical retinoic acid exposure. The data are summarized in Table 11. To simplify the observations, the values from both cheeks and forehead were averaged for each subject on each study day to provide a mean "face" value for TEWL. On Study Day 7, mean TEWL on all three sites had significantly increased by 50% or greater over baseline values ($p = 0.0001$). Further, this increased TEWL is maintained throughout the 28 days of topical tretinoin exposure. There was no statistical difference between the two formulations for a given site on a given study day.

Table 13.
Summary of recorded (TEWL) from each site on each study day. Mean Face value is the average across the three sites per subject on each study day. Values are the mean ± SD as $gm/m^2/hr$ water.

Product	Day	Forehead	Left Cheek	Right Cheek	Mean
Acticin Gel	0	21 ± 15.6	15.9 ± 4.9	13.9 ± 3.7	17.0 ± 4.0
	7	32.6 ± 11.1	43.2 ± 14.8	43.2 ± 11.1	35.5 ± 9.7
	14	34.7 ± 7.7	32.9 ± 7.8	32.7 ± 8.6	33.4 ± 7.4
	28	37.1 ± 10.8	36.4 ± 15.9	37.5 ± 14.8	37.0 ± 12.5
Retin-A Gel	0	21.4 ± 4.3	20.0 ± 8.3	20.0 ± 7.8	20.5 ± 6.6
	7	31.6 ± 10.5	33.6 ± 11.1	33.0 ± 13.6	32.7 ± 7.5
	14	33.8 ± 8.0	41.5 ± 9.7	41.9 ± 13.9	39.1 ± 7.6
	28	34.5 ± 10.1	32.6 ± 13.9	36.6 ± 12.9	35.5 ± 12.

Conclusion:

1. Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal irritation response as assessed by erythema, peeling and dryness.

2. Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal physiological alteration of the stratum corneum as assessed by TEWL

APR 18 1994

NDA:	20,404
SUBMISSION DATE:	OCT. 28, 1993
PRODUCT:	Acticin Cream and Gel.
SPONSOR:	Penederm 320 Lakeside Drive, Suite A Foster City, CA 94404
TYPE OF SUBMISSION:	NDA amendment
REVIEWER:	HE SUN, Ph.D.

BIOPHARMACEUTICS REVIEW

NDA 20,404

1. BACKGROUND

Tretinoin is a metabolite formed from all-trans-retinol, vitamin A, via conversion to all-trans-retinaldehyde. The sponsor developed two topical formulations, cream and gel, for acne treatment. The original NDAs 20,404) were submitted to the Agency on Oct. 24, 1993. This amendment includes two Research Protocols of two ongoing studies (as of Oct. 28, 1994) for tretinoin gel formulation. As learned from the sponsor, both studies were completed and study reports are awaiting to be submitted to the Agency.

The original NDAs 20,404) were refused to be filed by the Agency (RTF) after initial review. The RTF letters were sent to the sponsor on Nov. 23, 1993.

2. RECOMMENDATION

One of these two studies, entitled "A 91-day dermal toxicity study in mice with PDT 004-006 and PDT 004-002" was designed as a in-life phase of a 91 day dermal toxicity study in mice exposed to daily doses of Acticin Gel 0.025% and vehicle. The study has been completed before December 15, 1993.

The other study entitled "A single center, double-blind, parallel study to determine the effect of multiple applications of tretinoin-containing formulations on plasma levels of tretinoin in normal volunteers" was scheduled to be completed on October 31, 1993.

In the light of this information, no review of these protocols is necessary. Please convey the Recommendation, as appropriate, and the following comments #1-4 to the sponsor.

3. **COMMENTS:**

1. The sponsor mentions that up to 18 subjects would be enrolled in the volunteer study. It is requested that all data be submitted for all subjects who participated in the study irrespective of whether (or not) they completed the study.

2. Detailed HPLC/PB/MS assay method and assay validation features (sensitivity, specificity, linearity, accuracy and precision within and between runs) for the parent compound (as well as the active metabolite if possible) should be submitted in the final study report. In addition, stability data during the collection and processing of plasma samples, during storage and assay procedures should be provided for tretinoin.

3. The firm should submit all individual (as well as mean±SD) plasma concentration/time data for tretinoin.

4. The sponsor is encouraged to submit the results of the study as an electronic submission (i.e., text and raw data via the ASCII file) to help facilitate review of the submission.

4/14/94

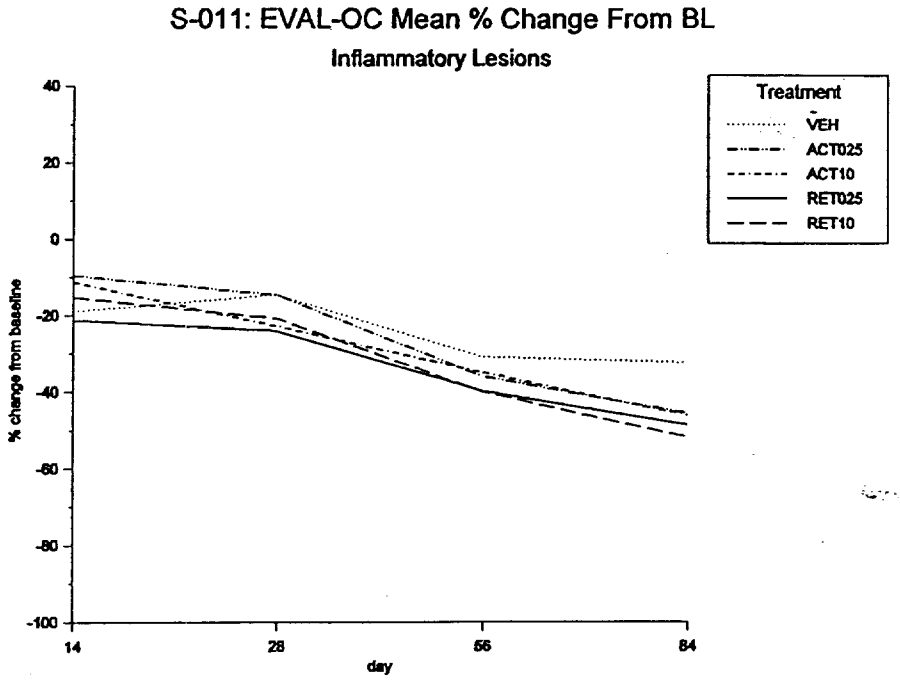
He Sun, Ph.D.

Pharmacokinetics Evaluation Branch II

RD/FT Initialed by Frank Pelsor, Pharm. D. F. Pelsor 4/14/94

cc: NDA 20,404, HFD-520 (Clinical, Fogarty), HFD-426(Fleischer, Pelsor), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340(Viswanathan).

FIGURE 2B: Study 011 Inflammatory Lesions by Treatment



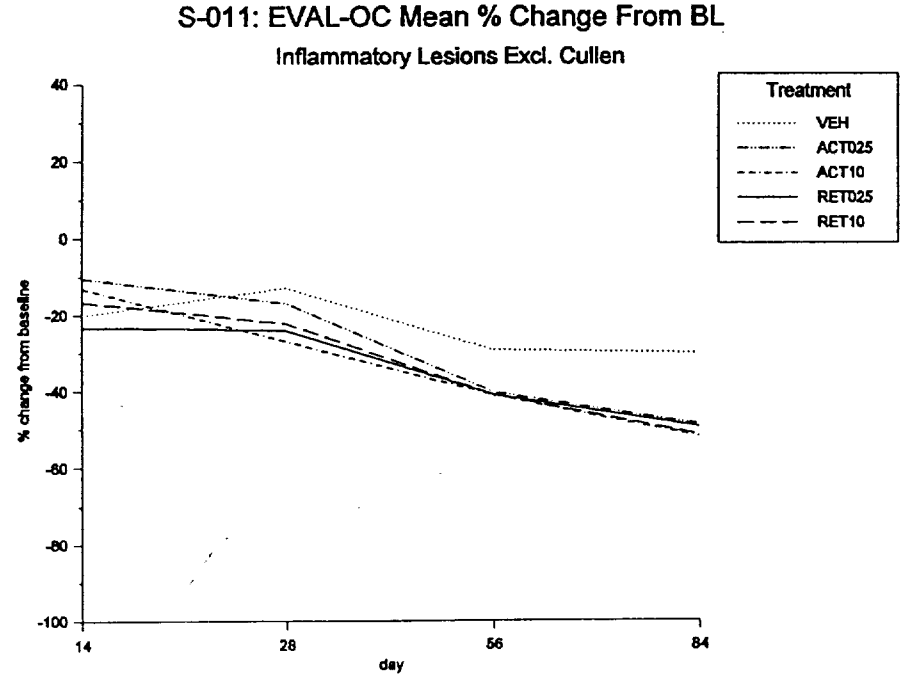


FIGURE 3: Study 011Non-Inflammatory Lesions by Sex

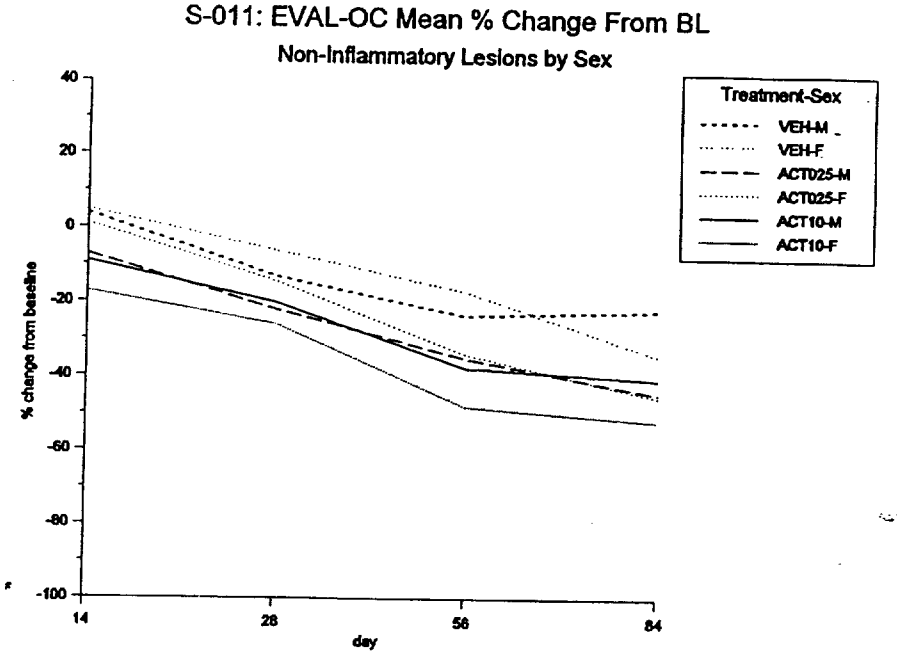


FIGURE 4: Study 011Non-Inflammatory Lesions by Race

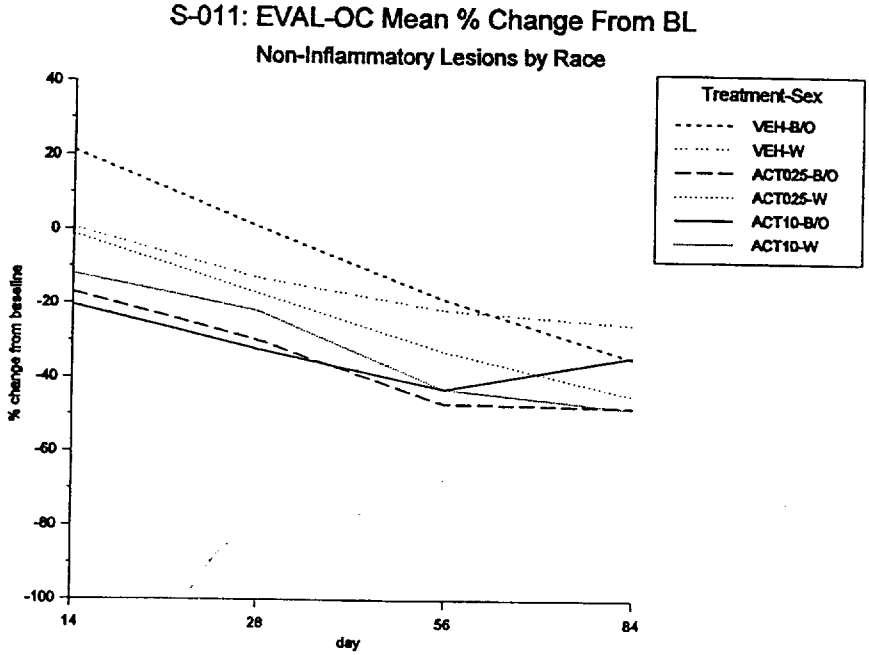


FIGURE 5: Study 011Non-Inflammatory Lesions by Age

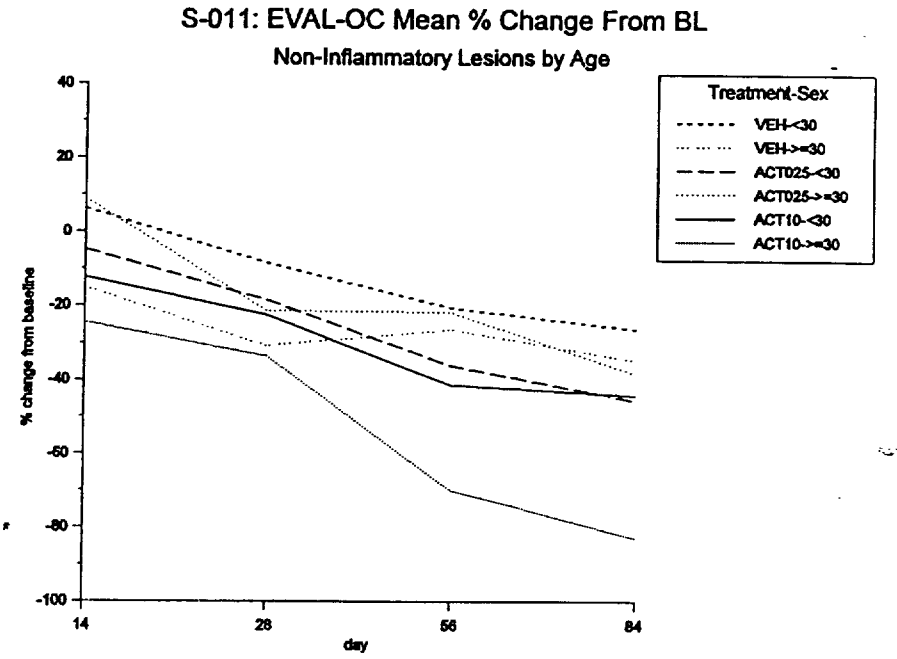
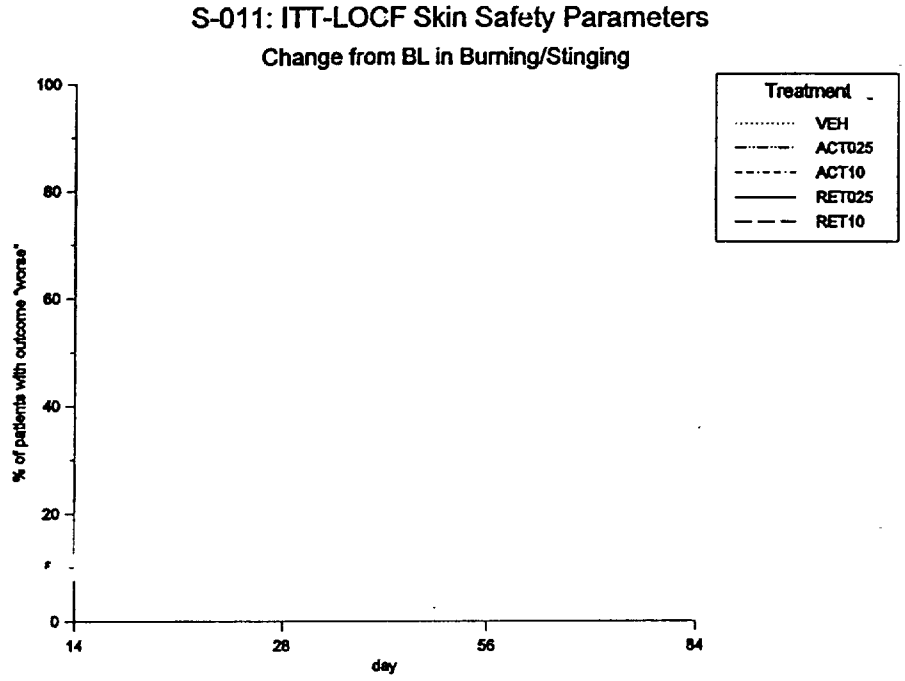


FIGURE 6A: Study 011 Skin Safety Parameters



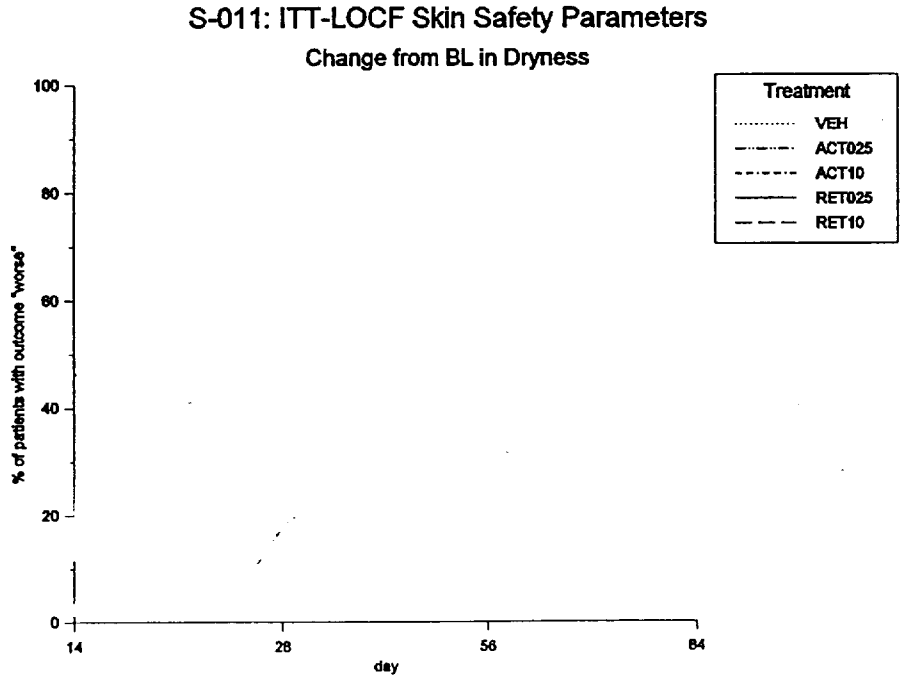
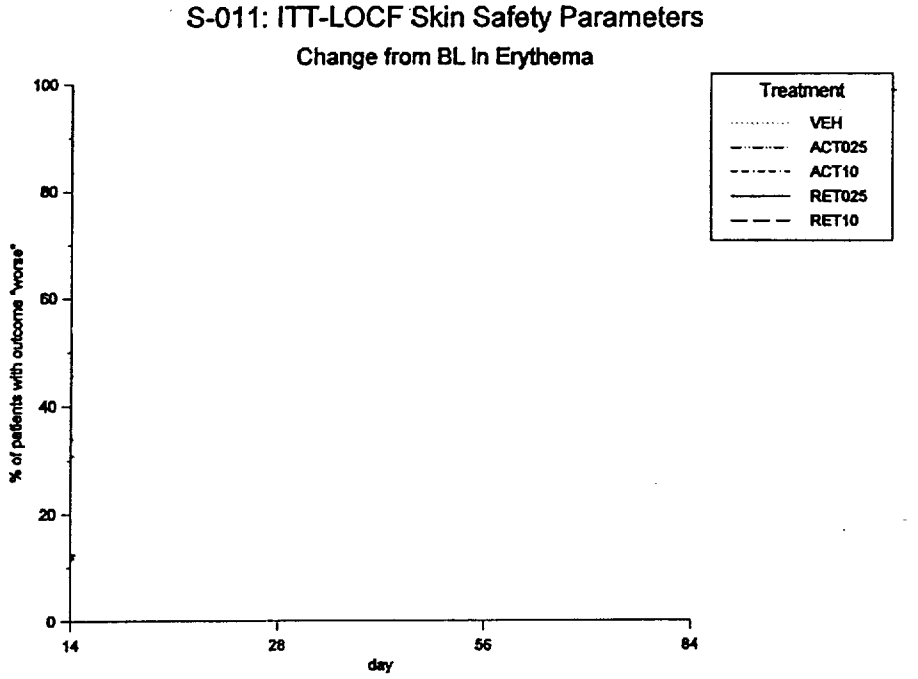


FIGURE 6B: Study 011 Skin Safety Parameters



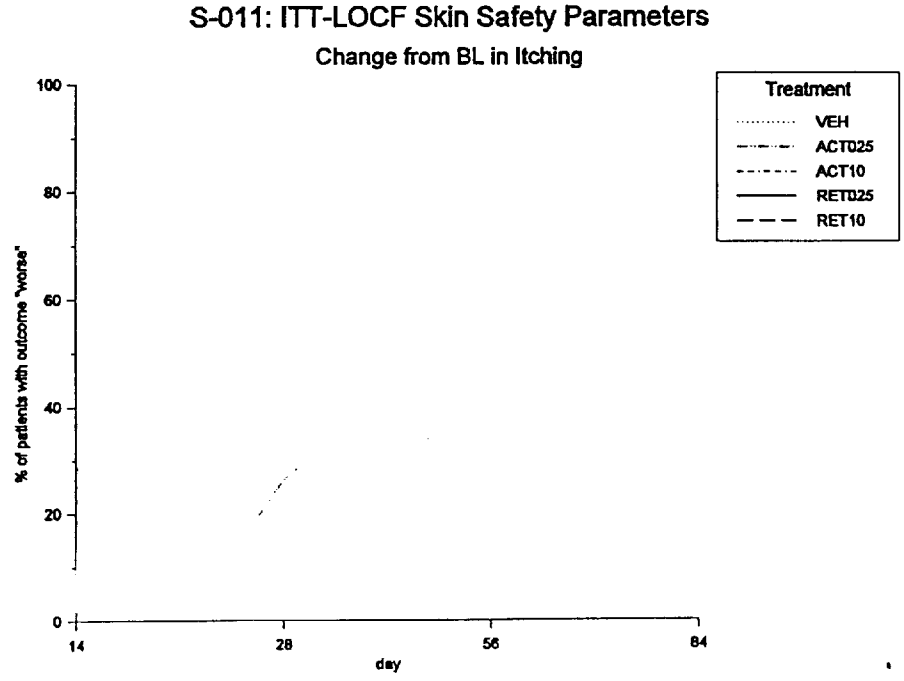
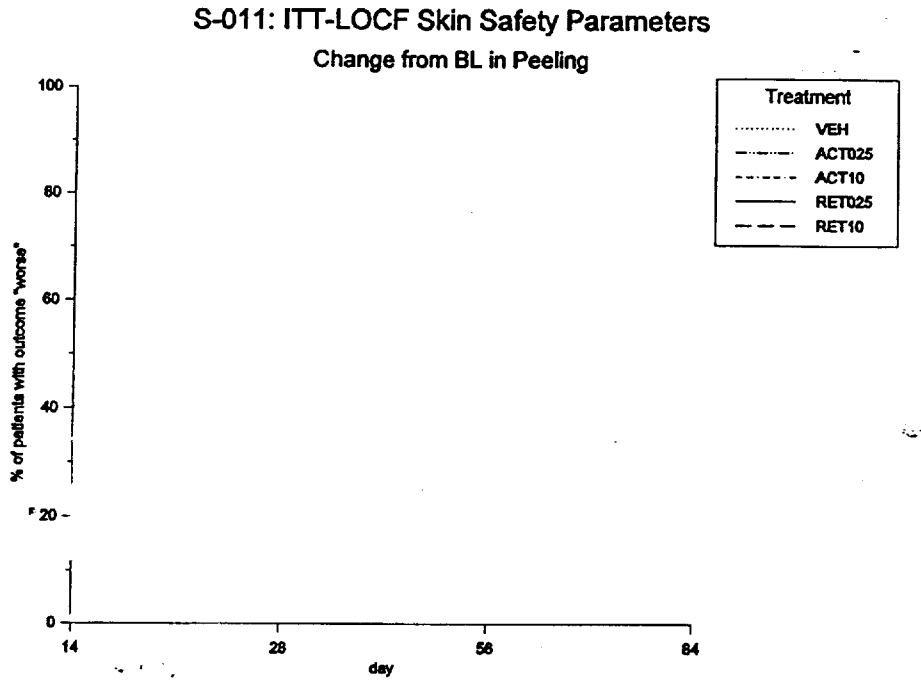
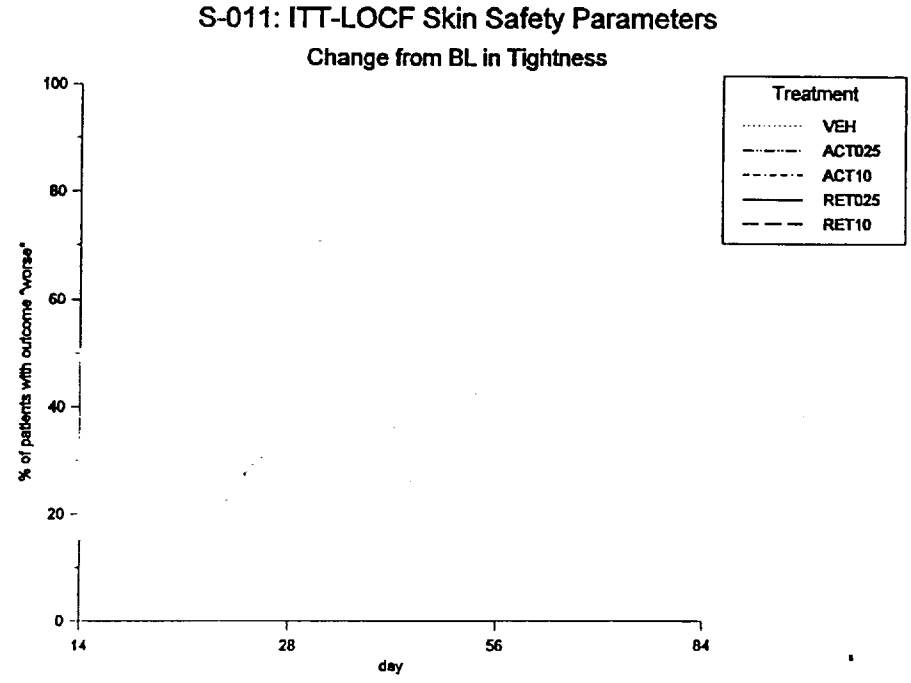


FIGURE 6C: Study 011 Skin Safety Parameters





MAR 1 1995

NDA:	20,404	**SUBMISSION DATE:**	March 28, 1994 June 03, 1994 June 08, 1994
PRODUCT:	Acticin Cream 0.025%,	(NDA 20,404)	
SPONSOR:	Penederm 320 Lakeside Drive, Suite A Foster City, CA 94404		
TYPE OF SUBMISSION:	Resubmission	**REVIEWER:**	HE SUN, Ph.D.

BIOPHARMACEUTICS REVIEW

NDA 20,404

I. SYNOPSIS.

The sponsor re-submitted these two New Drug Application (NDA 20,404) to support two new topical formulations-Acticin Gel and Cream. Two types of studies are included: *in vitro* percutaneous absorption studies and *in vivo* pharmacokinetic studies. The *in vitro* percutaneous absorption studies include 6 major studies to determine the absorption of tritiated tretinoin from Acticin and Retin-A Gel or Cream formulations, absorption of polyolprepolymer-2 (PPP-2) from neat material, Gel vehicle and Cream vehicle; and 6 supportive studies. The *in vivo* absorption studies include the absorption of PPP-2 from neat material, from Cream vehicle and a bioavailability study of Acticin Gel and Retin-A Gel formulation.

Based on these studies, the sponsor concluded the following:

(1) Acticin Gel and Cream offers lower or similar low systemic exposure to tretinoin (<0.3%) when compared to the commercial Retin-A Gel and Cream product.

(2) A very small amount (< 0.3% of the applied dose) of PPP-2 penetrates excised human cadaver skin *in vitro* and the predominant component that penetrates is the lower molecular weight polyol, PPG-725. The higher molecular weight oligomers, comprising at least 80% (GPC peak area) of PPP-2, are retained in the upper layers of the stratum corneum and readily be removed from the skin surface by washing and/or tape stripping after topical application.

(3) There were no statistical differences between Retin-A 0.025% Gel and Acticin 0.025% Gel in the plasma pharmacokinetic parameters for tretinoin and isotretinoin.

II. RECOMMENDATIONS

II.1. For the Gel 0.025% formulation (NDA)

A. Due to problems found (see specific comments), the *in vitro* percutaneous absorption studies #PD168-60, #PD34-21, #PD24-77, #PD37-21, #PD37-25 (Gel, PDT004-002) are only of informative value. The *in vivo* plasma pharmacokinetic study of tretinoin and isotretinoin for Retin-A 0.025% Gel (Gel, PDT004-002) and Acticin 0.025% Gel is acceptable. Therefore, the Biopharmaceutics Section of the Gel 0.025% formulation (NDA is acceptable.

B However, the higher resistance of Acticin Gel formulation to stripping suggests deeper skin penetration which may results in higher local skin irritation rate of Acticin Gel 0.025% compared to Retin-A 0.025% (although washing with alcohol, soap and water is able to remove all drug residual). The significance of such higher resistance to stripping should be evaluated with other clinical observations

C. The sponsor should evaluate gender effect in tretinoin and isotretinoin absorption for Retin-A 0.025% Gel (Gel, PDT004-002) and Acticin 0.025% Gel.

II.2. For the Cream 0.025%, 0.05% and 0.1% formulations (NDA 20,404),

The *in vitro* data alone is unable to support the formulation. The sponsor should test, at least for the 0.1% strength, *in vivo* pharmacokinetics profiles and local skin reactions of the Cream formulation. Therefore, the Cream formulation (NDA 20,404) is not fully supported by studies submitted and is not acceptable to the Division of Biopharmaceutics.

II.3. For PPP-2 polymer

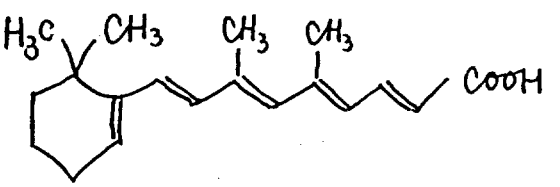
The *in vitro* studies of PPP-2 (PDT002-002) used for supporting both NDAs, #PD168-33, #PD168-21 and #PD-168-27, and the *in vivo* studies #PD112-18 (PDT002-002) and #TOX002-020 (Cream vehicle, PDT004-054) are acceptable.

TABLE OF CONTENTS:

III. BACKGROUND:

III.1. THE DRUG

Tretinoin, also known as retinoic acid or all-trans-retinoic acid, is a metabolite formed from all-trans-retinol, vitamin A, via conversion to all-trans-retinaldehyde.



Tretinoin was reported by Stuttgen in 1962 to be effective topically in disorders of keratinization; and by Kligman, et. al. in 1969 to be effective topically in acne. This early

work led to the development of a family of marketed products, Retin-A Cream, Gel, and liquid (Ortho Pharmaceutical Co.).

Retinoic acids and their derivatives exert substantial effects on epithelial growth and differentiation. In high oral doses, retinoic acids and some retinoic acid deriavatives are known to be human teratogens. Topical formulations of retinoic acid have not been shown to be human teratogens, however, evaluation of the potential risk associated with retinoic acid includes analysis of the results of percutaneous absorption of this drug on endogenous blood levels in order to identify any potential systemic effects.

Previous studies in humans with radioactive retinoic acid in both Gel and Cream formulations indicated minimal systemic absorption of the drug following topical administration.

III.2. THE ANDA/NDA APPLICATION HISTORY

Acticin was originally submitted as an ANDA for a generic equivalent to Ortho Pharmaceutical Corporation's Retin-A Gel. Since the limited systemic absorption of topical tretinoin does not lend itself to development of ANDA bioequivalence data by the simple measurement of blood drug levels, a protocol (#PDC 004-003) was developed to evaluate the therapeutic equivalence of the Acticin formulation versus vehicle and the innovator product, Retin-A Gel, in the treatment of acne vulgaris over a twelve-week period. In addition, a second twelve-week study (#PDC 004-015) was conducted to evaluate the Acticin formulation in comparison to vehicle only. The sponsor obtained the Agency's concurrence on the general design of bioequivalence protocol #PDC 004-003 on September 26, 1990. The subsequent study protocol, #PDC 004-015, was developed based on this prior concurrence and was submitted to the Agency on September 14, 1992.

The bioequivalence data were compiled and submitted in an ANDA application on May 29, 1991 to the Office of Generic Drugs. The ANDA was accepted for filing on August 9, 1991. Subsequently, at a meeting held on August 13, 1992 with representatives of the Office of Generic Drugs and the Division of Anti-Infective Drug Products, CDER. The Agency refused to accept the application for continuing review as an ANDA, due to the inclusion of an excipient in the Acticin formulation which is not present in the innovator's product. This ingredient is the sponsor's proprietary excipient, , which has not been previously approved for use in pharmaceutical products.

A non-approvable letter was sent by the Office of Generic Drugs because of the presence of on February 4, 1993. ANDA application was officially withdrawn by the sponsor and acknowledged by the Agency (Office of Generic Drugs) on April 8, 1993.

On February 11, 1993, a letter from the Division of Anti-Infective was sent defining additional requirements to allow substantive review of the tretinoin Gel application as an NDA. A determination was sent out from the Agency on April 26, 1993 that the ANDA application would require reformatting as an NDA submission.

The original NDAs 20,404) were submitted to the Agency on Oct. 24, 1993 and were refused to be filed by the Agency (RTF) after initial review.

The sponsor then resubmitted NDA and NDA 20,404 in March and June, 1994 to the Agency.

IV. DRUG FORMULATION

The Acticin Gel and Cream formulation are listed on the following pages.

3. Composition

1. Statement of Composition

A complete description of the quantitative composition of the drug product including any applicable range of inactive ingredients follows:

Acticin (tretinoin) Gel, 0.025%
Penederm formulation PDT 004-002

mg/g	Ingredient	% w/w
	✓ Tretinoin, USP	
	✓ Polyolprepolymer-2	
	✓ Hydroxypropyl cellulose, NF	
	✓ Butylated hydroxytoluene, NF or F.C.C.	

* The sponsor will manufacture the drug product with a 10% overage of tretinoin.

** The concentration range is %.

† concentration to be adjusted based on concentration of butylated hydroxytoluene decided prior to manufacture.

Composition

1. Statement of Composition

A complete description of the quantitative composition of the drug products including any applicable range of inactive ingredients follows:

Acticin (tretinoin) Cream, 0.025%
Penederm formulation PDT 004-044

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

* The sponsor will manufacture the drug product with a % overage.

1. Statement of Composition (continued)

Acticin (tretinoin) Cream, 0.05%
Penederm formulation PDT 004-045

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

* The sponsor will manufacture the drug product with a)% overage.

1. Statement of Composition (continued)

Acticin (tretinoin) Cream, 0.1%
Penederm formulation PDT 004-046

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

* The sponsor will manufacture the drug product with a % overage.

V. GENERAL SUMMARY OF STUDIES.

V. 1. Study list

1, Studies in #PD94-71 are *in vitro* percutaneous absorption studies of tritiated tretinoin from Acticin (test) and Retin-A (reference) Cream formulations at tretinoin concentrations of 0.025%, 0.05% and 0.1% using dermatomed human skin.

2, Studies in #PD168-60 are *in vitro* percutaneous absorption studies of tritiated tretinoin from Acticin (test) and Retin-A (reference) Gel formulations at tretinoin concentrations of 0.025% using dermatomed human skin.

3, Studies #PD34-21, 24-77, 37-21 and 37-25 are supportive studies to assess the effect of rubbing, instead of detergent washing, on epidermal levels of tretinoin from Gel formulation.

4, Study #PD91-79 was to test the percutaneous absorption of PPP-2 from test materials and from Cream vehicle.

5, Study #PD168-33 was to test the percutaneous absorption of PPP-2 from Gel vehicle.

6, Studies #PD168-21 and #PD168-27 were to develop methods to evaluate the localization of PPP-2 and its higher molecular weight polyol component in human skin.

7, Study #PD11-01 was to evaluate the localization of PPP-2 *in vivo*.

8, Study #TOX002-020 was to evaluate the localization of PPP-2 from Cream vehicle

9, Study #PDC004-017 was an *in vivo* clinical study to determine the effect of multiple applications of tretinoin-containing formulation on plasma levels of tretinoin in normal volunteers.

V. 2. The sponsor made following conclusions:

(1) The *in vitro* percutaneous absorption studies indicate that penetration of radiolabeled drug from two formulations never exceeded 0.3%. Acticin Gel and Cream offers similar low systemic exposure to tretinoin when compared to the commercial Retin-A Gel and Cream product, which have been used for many years.

(2) A very small amount (< 0.3% of the applied dose) of PPP-2 penetrates excised human cadaver skin *in vitro* and the predominant component that penetrates is the lower molecular weight polyol, PPG-725. The higher molecular weight oligomers, comprising at least 80% (GPC peak area) of PPP-2, are retained in the upper layers of the stratum corneum and readily removed from the skin surface by washing and/or tape stripping after topical application.

(3) Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal irritation response as

assessed by erythema, peeling and dryness. Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal physiological alteration of the stratum corneum as assessed by trans-epidermal-water-loss.

(4) There were no statistical differences between Retin-A 0.025% Gel and Acticin 0.025% Gel in the plasma pharmacokinetic parameters, decrease in AUC, Cmax and Css plasma tretinoin values from Study Day 7 to Study Days 14 and 28. There were no statistical differences in the plasma pharmacokinetic parameters for isotretinoin.

(5) There was a slight but statistically significant increase in Css tretinoin from Study Day 0 to Study Day 7.

V.3. Summary of studies

V.3.1. *in vitro* Percutaneous Absorption Studies

V.3.1.1. Percutaneous Absorption of tretinoin

The *in vitro* tretinoin percutaneous absorption was determined using radiotrace method for the assessment of potential systemic toxicity following topical exposure. In these studies, test formulations (Gel and Cream, Acticin, Penederm) and reference formulations (Gel and Cream, Retin-A, Ortho) were evaluated in human skin for *in vitro* percutaneous absorption and penetration using modified Franz flow-through diffusion cells. Three concentrations (0.1%, 0.05%, and 0.025%) of tretinoin were investigated (test formulations: PDT 004-046, PDT 004-045 and PDT 004-044 and control formulations: PDT 004-031, PDT 004-030 and PDT 004-024, respectively). Dermatomed human cadaver skin was used. Each formulation was applied to the epidermal surface of the skin at a surface dose of 10.0 ± 1.1 mg over the 0.64 cm^2 test area. After the 48-hour exposure period, each skin surface was washed. The skin and washing were saved for analysis of radiolabeled drug content.

Results of Cream:

The penetration of radiolabel from the Acticin formulations never exceeded 0.3%. Furthermore, receptor phase data indicate that the Acticin Creams, at concentrations of 0.025% and 0.1%, deliver statistically equivalent amounts of tretinoin compared to the corresponding Retin-A Creams. The Acticin 0.05% Cream formulation, however, delivered statistically less tretinoin to the receptor phase compared to the Retin-A 0.05% Cream.

Tretinoin skin levels, although generally greater from the Acticin Cream formulations than from the Retin-A formulations, were not statistically different at any of the corresponding tretinoin concentrations.

Results of Gel:

The absolute epidermal levels of radiolabeled tretinoin varied in magnitude among these studies, especially for Acticin Gel, whereas Retin-A Gel was relatively constant across studies. When the wipe and tape strip procedures were used, higher epidermal levels of the

radiolabel were observed following topical application of Acticin Gel compared to Retin-A Gel. This suggests a greater resistance to the rub off of tretinoin following topical application of Acticin Gel than Retin-A Gel. In contrast, when a detergent washing procedure was employed, lower epidermal levels of tretinoin are observed following topical application of Acticin Gel compared to Retin-A. This suggests that washing with detergent is more efficacious in the removal of tretinoin from the skin following topical application of Acticin Gel when compared to Retin-A Gel.

V.3.1.2.Percutaneous Absorption of PPP-2

Method

The test materials were applied (3-6 mg/cm^2) to the epidermal surface of dermatomed human skin mounted on Franz static diffusion cells. The dermal surface of the skin was perfused with phosphate buffered saline containing % sodium azide and % Oleth 20 equilibrated at 37 °C. At 48 hours, the skin surface was washed with one soap:water (50:50, v/v) cotton swab, 3 consecutive ethanol swabs and one dry swab. Along with each individual wash sample, skin samples were solubilized and assayed for radioactivity.

The individual polyol components of PPP-2, tritiated higher molecular weight oligomers and tritiated PPG-725, were incorporated separately into neat PPP-2 and into Acticin Gel (PDT 004-006) to characterize the percutaneous absorption of each component into and through human skin.

Acticin Cream vehicle (PDT 004-054), a research Gel vehicle, and an ethanol vehicle, each containing 10% PPP-2, were tested for its effect on the *in vitro* percutaneous absorption of tritiated PPP-2. The penetration of the polyol components, oligomers and PPG-725, were measured simultaneously.

In order to characterize the localization of PPP-2 in skin *in vivo*, the higher molecular weight polyol component of PPP-2 was radiolabeled and then incorporated into neat PPP-2. The radiolabeled polymer was applied to the dorsal forearm of two subjects (3-5 mg/cm2) under either occluded or semi-occluded, protected conditions. At 24 hours post-dosing, the chamber was removed and the skin surface was washed. The upper layers of the stratum corneum were removed with 10 tape-strips and each tape-strip was analyzed for radioactivity.

The *in vivo* localization of PPP-2 in human skin was characterized by FTIR-ATR spectrophotometric method. Cotton pads were saturated with a test solution of 10% PPP-2 in ethanol:water (60:40 v/v) and applied to the dorsal forearm of two subjects under occluded conditions. At 3 hours post-dosing, the pads were removed and the test area was lightly wiped with two cotton swabs. The skin was tape-stripped eight times and after each tape-strip, analyzed by FTIR-ATR for the presence of PPP-2.

Results

The results indicate that the higher molecular weight oligomers of PPP-2 do not penetrate

the skin. The lower molecular weight PPG-725 penetrates the skin from both vehicles, but levels are very low (< 0.35% of the applied dose). Skin levels of each component, from both vehicles, are very low (< 0.30%), with the majority of the polyols localized in the epidermis. In addition, the soap/water and ethanol wash employed readily removes both components of PPP-2 from the skin. The majority of the radiolabeled PPP-2 in the test materials was readily removed from the skin surface by washing with soap/water and ethanol (96±9%). Receptor fluid data indicated that only a very small amount, less than 0.30% of the applied dose of PPP-2, penetrated through the skin from all three vehicles. In addition, PPP-2 skin levels were very low from all three vehicles (<0.40%).

Approximately 95% of the applied radiolabeled dose was readily removed from the skin surface by washing with soap and water. In addition, all of the radiolabeled oligomers were removed from the skin surface after the sixth tape-strip, suggesting that minimal amounts of the higher molecular weight oligomers of PPP-2 were localized in the upper layers of the stratum corneum (< 0.2% of the applied dose).

The results reveal that PPP-2 is localized in the upper layers of the stratum corneum under the conditions employed. In addition, all detectable PPP-2 is completely removed from the skin surface by five repetitive tape-strips, *in vivo*.

IV.3.1.3 In vivo absorption studies

The objectives of the study were to answer two primary questions: (1) does the topical application of either 0.025% tretinoin Gels alter endogenous plasma concentration of tretinoin and/or isotretinon; and (2) is there any difference in plasma concentration between the Retin-A Gel formulation and the Acticin Gel formulation? The irritation parameters, trans-epidermal water loss (TEWL) and plasma concentration provide various measures to compare the two test formulations.

Pharmacokinetic studies

This is a double blind comparison study. Eighteen subjects (9 males and 9 females), free of any skin disease, were enrolled. The subjects were carefully advised to avoid Vitamin A supplements. 20 gm tube of either Retin-A 0.025% Gel or Acticin 0.025% Gel were provided. Application was to the forehead and both cheeks (125-175 cm^2), excluding the nose, around the eyes and chin. Applications commenced on study day 1 and thereafter on each evening 30-40 minutes prior to bed. At each study visit day, the tubes were collected and tube weights recorded. Target application was to be 2 mg/cm^2 Gel over 150 cm^2. Tube weights demonstrated that mean daily usage over 28 days was 0.307±0.066 gms (Mean±SD) for Retin-A Gel and 0.312±0.057 gms for Acticin Gel. On the morning of study days 7, 14, and 28, the subjects washed their face with soap and water (Purpose Soap, Johnson and Johnson, Skillman, NJ). Thirty minutes after the face wash a weighed application was performed by the investigator to each subject. Subjects remained in a darkened room lighted only by low wattage yellow tungsten lamps for four hours after Gel application. Blood samples were collected at 15 minutes prior to and at 2, 4, 8, 10, 12, and 24 hours after Gel application. After-the 24 hour blood sample the tubes of medication were returned to the subject for subsequent evening applications until the next study day. Tretinoin and

isotretinoin were assayed by a sensitive HPLC beam/mass spectrometry method.

Irritation and TEWL

On day 0, 7, 14, and 28, prior to the face wash, subject's forehead and both cheeks were first evaluated for signs of cutaneous irritation defined as erythema, peeling, and dryness. Each factor was graded on a 3 point scale (O = none, 1= light, 2 = moderate, 3 = severe) with 0.5 unit increments. In addition, trans-epidermal water loss (TEWL) was measured from the center of the forehead and both cheeks simultaneously using a multi-probe Courage+Khazaka Tewameter (Germany). No adverse events occurred during this study.

Data were collated by subject, sample hour and day, and by formulation. For continuous data (AUC, Css, Cmax, TEWL), a repeated measures analysis was used. For scaled data (erythema, dryness and peeling), nonparametric analyses were used (Kruskal-Wallis test and Wilcoxon Signed Rank test).

Study results

(1) There were no statistically significant changes in the plasma levels of tretinoin or isotretinoin relative to baseline for either treatment as measured by AUC, C_{max} and C_{ss}, except for a statistically significant increase in tretinoin C_{ss} on Study Day 7 (1.75±0.27 vs. 1.49±0.39 ng/ml) for both treatments.

(2) AUC, C_{max} and C_{ss} values on days 14 and 28 were significantly lower than values on day 7 regardless of formulation.

(3) There were no statistical differences observed in AUC, C_{max} and C_{ss} for the isotretinoin data.

(4) In addition, there was no statistically relevant correlation between these three parameters and the clinical observation data.

(5) Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal irritation response as assessed by erythema, peeling and dryness. Retin-A 0.025% Gel and Acticin 0.025% Gel demonstrated equal physiological alteration of the stratum corneum as assessed by trans-epidermal-water-loss.

VI. SPECIFIC COMMENTS

Need not to be sent to the sponsor:

1. Many experimental problems are noticed in the *in vitro* percutaneous absorption studies submitted for both NDAs. Therefore, *in vitro* percutaneous absorption studies submitted are unable to support these NDAs.

2. In vivo pharmacokinetics study of Gel formulation was performed and is acceptable, which resolved some questions raised in review of percutaneous absorption studies. Therefore, the

Gel 0.025% formulation was supported by submitted studies.

3. The higher resistance of Acticin Gel formulation to skin stripping suggests deeper skin penetration which resulted in higher local skin irritation rate of Acticin Gel 0.025% over Retin-A 0.025% (although washing with alcohol, soap and water was able to remove all drug residuals), which should be considered with other clinical observations for its clinical significance. This negative influence due to, most probably, PPP-2 should be evaluated and analyzed in combination with clinical studies in which same formulations were used.

Need to be sent to the sponsor

4. Some deficiencies were noticed in the ***in vitro*** percutaneous absorption studies submitted. The dose per unit area should be equivalent to that normally applied in a single application (~ 5 mg of formulation/cm^2). The exact nature of the skin preparation used for these studies should be carefully documented (the manner of preparation of the membranes from tissue, for example). Any treatment of the cadaver skin prior to harvesting should be recorded. In comparing drug absorption from two formulations using human skin, twelve experiments for each formulation should be run.

5. To ensure the safety of application of the drug, *in vivo* studies are needed for determining the acceptance of these NDAs. An *in vivo* pharmacokinetic study of Gel formulation was performed and is acceptable which resolved some questions raised in review of percutaneous absorption studies. The low systemic absorption (<0.3%) of the Acticin from the Gel 0.025% formulation and the similarity with Retin-A were supported by study #PDC004-017. However, the gender difference of tretinoin absorption from Acticin 0.025% Gel and Retin-A 0.025% Gel in clinical study #PDC004-017 should be analyzed.

6. With similar considerations stated in comments 4 and 5, the characteristics of systemic absorption and potential skin reaction of 0.025%, 0.05% and 0.1% Cream formulation can not be determined without *in vivo* studies. The sponsor should, at least for the 0.1% strength, perform *in vivo* pharmacokinetics studies for the Cream formulation.

Comments on Label:

7. The outcome of study #PDC004-017 should be described in the 0.025% Gel formulation labeling. Such information is needed for clinical situations in which co-administration of vitamin A is implemented. Suggested addition: "In a single center, double-blind, parallel pharmacokinetics study to determine the effect of multiple applications of Acticin Gel 0.025% on plasma levels of tretinoin in 18 normal volunteers, the average steady-state concentration (C_{ss}) of tretinoin and isotretinoin ranged between 1.49 ng/ml (baseline) to 3.39 ng/ml and 1.10 ng/ml (baseline) to 1.91 ng/ml, respectively".

NDA 20,404

3/1/95

He Sun, Ph.D.
Pharmacokinetics Evaluation Branch II

Biopharm-Day Mar.1, 1995. Attendees: Drs. Ludden, Malinowski, ChenM, Fleischer, Hepp, Gillespie, Hussian, Pelsor and Sun.

RD/FT Initialed by Frank Pelsor, Pharm. D. F. Pelsor 3/1/95

cc: NDA 20,404, HFD-540 (Clinical), HFD-427(ChenML, Pelsor), HFD-426(Fleischer), Chron, Drug, HFD-19(FOI), HFD-340(Viswanathan), Reviewer.

CDE NDA 20-404

ANDA: 74-071, -238, -239, -240

MEETING WITH SPONSOR
MEETING DATE: April 4, 1993

0.025% TRETINOIN GEL

Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404

REVIEWER: Ene Ette, M.S., Ph.D.

==========

BIOPHARM. ISSUES:

The Division of Biopharm. recommends that the Sponsor should carry out a pharmacokinetic study in healthy volunteers to determine the penetration of tretinoin. Given the variability in the population at large (and blood supply to the skin in the in vivo system), in vitro studies cannot completely predict the in vivo situation.

The Sponsor should also provide evidence via simulation using physiologically-based modelling to evaluate fetal exposure of all-trans retinoic acid.

Ene Ette, M.S., Ph.D.

FT initialed by N. Fleischer, M.S.,Ph.D. 4/27/93

cc: ANDA 74-071, -238, -239, -240, HFD-520 (Clinical Division), HFD-426 (E. I. Ette, N. Fleischer), Chron, Drug, Reviewer's file.

Recommendations
comment to
Penederm 6-1-93