CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-748

MEDICAL REVIEW

MAY 18 2000

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CDER Stamp Date: 4/3/2000
Correspondence date: 3/31/2000

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-748

May 15, 2000

SPONSOR: Galderma Laboratories
Fort Worth, Texas

DRUG: Differin (adapalene) cream 0.1%

CLINICAL INDICATION: Acne

REASON FOR AMENDMENT: Safety Update report

The sponsor has provided a clinical safety update generated from foreign and domestic studies with the drug substance and topical formulations of adapalene since submission of the major amendment of 9/7/99.

Reviewer's evaluation: The adverse events reported with completed and ongoing studies with adapalene cream, 0.1%, are consistent with those reported in the NDA. There is no significant change in the safety profile of this drug product.

Phyllis A. Huene, M.D.

Cc: Orig NDA 20-748
HFD-540 Division Files
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Cintron

Not in DFS

MAY 18 2000

Correspondence date: April 24, 2000
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MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-748

May 9, 2000

SPONSOR: Galderma Laboratories

DRUG: Differin (adapalene) cream 0.1%

INDICATION: Acne

DATE OF AMENDMENT: April 24, 2000

REASON FOR AMENDMENT: Submission of revised labeling in response to the teleconference of April 10, 2000.

The sponsor has provided a revised draft of the clinical part of the package insert for Differin cream, pursuant to the discussion at the teleconference of April 10, 2000. The sponsor states that this includes mutually acceptable items that were discussed. In addition, the sponsor has revised or repositioned other information that was discussed, or has proposed wording that they feel is more appropriate.

This review concerns those clinical areas of the labeling in which the current revision submitted in this amendment differs from the labeling in the approvable letter of March 8, 2000. These are as follows, according to the labeling section. (The proposed labeling submitted in this amendment is referred to as the 'current revision.')

CLINICAL STUDIES

1. Instead of the sentence _____ the current revision states 'Patients were instructed to apply their treatment medication once daily at bedtime for 12 weeks'.

2. The statements in the approvable labeling that patients were provided with a soapless cleanser and were encouraged to forgo the use of a moisturizer, and that no other topical treatments were to be applied, have been deleted. The sponsor states that in only one of the studies were the patients provided with a soapless cleanser and the use of moisturizers was restricted.

3. A sentence has been added to the second paragraph of the approvable labeling (denoted by underline), as follows: ' Avoid contact with the eyes, lips, angles of the nose . . . As with other retinoids, use of waxing as a depilatory method should be avoided on skin treated with adapalene.'

The sponsor proposes to include this information in the labeling on the basis of published case reports with the use of oral isotretinoin and topical tretinoin (Retin-A), and post-marketing reports with Differin gel. Two cases of erosions following wax epilation of facial areas in patients on Retin-A were reported in the Archives of Dermatology. One case of erosions of the upper lip and chin following wax epilation in a patient on oral isotretinoin was reported in the British Journal of Dermatology. It was postulated that these skin reactions were related to the fragility of the skin following the use of retinoids. Additionally, three post-marketing reports of skin removal with waxing in connection with the use of Differin gel have been received by the sponsor.

Reviewer's comments: There are no objections to the changes in this section.

Information for patients

1. Wording has been added to Item 4 of the approvable labeling, (denoted by underline) to read: 'Cleanse affected area with a mild or soapless cleanser before applying this medication.'

2. The following sentences have been added:

; however, products containing alpha hydroxy or glycolic acids should be avoided.'

'Wax epilation should not be performed on treated skin.'

3. The following sentence in the approvable labeling has been deleted:

Reviewer's comments: There are no objections to these changes.

The sponsor states that their revision is based on adverse events that were judged by the investigators to be reasonably associated with the use of Differin cream, and that they omitted any events which were classified by the investigators as unlikely, definitely unrelated, or unknown. Also, [redacted] erythema, and pruritus have been omitted from this paragraph as the sponsor feels that these events have been sufficiently identified in the first paragraph of the section.

Reviewer's comments on the above items are as follows:

Item 1: The manner of presentation of the local symptomatology in the approvable labeling was felt by the Division in the labeling meeting to be the most appropriate. Therefore, the sponsor's revision of this section is not acceptable.

Item 2: In the first sentence of this paragraph the adverse events should be characterized as local cutaneous events, as in the approvable labeling; this sentence is otherwise acceptable. In regard to the second sentence, all adverse effects should be included in the labeling, not just the events that were considered possibly, probably, or definitely treatment-related. Therefore, the second sentence should remain as in the approvable labeling, with the exception that erythema and pruritus may be deleted, as these were described in the first paragraph of this section.

DOSAGE AND ADMINISTRATION

The following sentence has been added following the directions for application: 'A mild transitory sensation of warmth or slight stinging may occur shortly after the application of Differin Cream.'

Reviewer's comments: There is no objection to this statement.

Addendum to review: Subsequent to this amendment, the sponsor submitted additional revised labeling on 5/5/00; this is identical to the labeling in this amendment, except that the paragraph under Drug Interactions which was cited in this review as objectionable has been deleted. An internal meeting was held on 5/8/00 with all disciplines present to further discuss the labeling in this amendment; separate minutes of this meeting have been made. The labeling that was formulated at this meeting is to be conveyed to the sponsor.

Conclusions: Certain sections of the revised labeling which was submitted on April 24, 2000 in response to the approvable letter of March 8, 2000 are not acceptable, as described above, and as further discussed at the meeting of May 8, 2000. The labeling which has been formulated at this meeting is to be conveyed to the sponsor.

/S/

Phyllis A. Huene, M.D.

5/15/00

Cc: Orig NDA 20-748
HFD-540: Division files
HFD-540/Wilkin /S/
HFD-540/Walker
HFD-540/Huene
HFD-540/Cintron
HFD-540/DeCamp
HFD-540/Jacobs /S/

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APR 22 2000

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MEDICAL OFFICER'S REVIEW OF SUPPLEMENT TO NDA 20-748

April 19, 2000

SPONSOR: Galderma Laboratories

DRUG: Differin (adapalene) cream 0.1%

INDICATION: Acne

REASON FOR SUPPLEMENT: Objections to the revised labeling in the approvable letter of March 8, 2000.

The sponsor has submitted a number of questions and objections regarding the labeling attached to the approvable letter of March 8, 2000.

This review concerns the sponsor's questions in regard to the Adverse Reactions section of the labeling. A discussion of the other of the sponsor's concerns is reported in the minutes of the internal meeting held on April 10, 2000.

Adverse Reactions section

The vehicle controlled studies were #s 9111 and 18035; the positive controlled study was # 90087.

The local tolerance assessments in Study 18035, derived from the sponsor's data, as tabulated on page 14 of the MOR of 11/1/99, were as follows.

Local tolerance assessments Study 18035 Sponsor's data		
Severity	Differin cream	Vehicle
Erythema		
None	73 (64%)	83 (72%)
Mild	35 (30%)	28 (24%)
Moderate	7 (6%)	5 (4%)
Severe	-	-
Scaling		
None	71 (62%)	96 (83%)
Mild	38 (33%)	17 (15%)
Moderate	6 (5%)	3 (3%)
Severe	-	-
Dryness		
None	50 (44%)	75 (65%)
Mild	48 (42%)	36 (31%)
Moderate	16 (14%)	5 (4%)
Severe	1 (0.9%)	-
Pruritus		
None	83 (72%)	98 (85%)
Mild	22 (19%)	16 (14%)
Moderate	9 (8%)	2 (2%)
Severe	1 (0.9%)	-
Stinging/burning		
None	87 (76%)	106 (91%)
Mild	22 (19%)	10 (9%)
Moderate	5 (4%)	-
Severe	1 (0.9%)	-

The local tolerance assessments in Study 9111 and 90087, as derived from the sponsor's data and presented in the MOR of 11/10/97 were as follows. (The numbers are taken from the row showing the maximum reactions. It should be noted that pruritus was not evaluated in these studies.)

Local tolerance - Study 9111 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Erythema					
Differin	75 (44%)	73 (43%)	21 (12%)	1 (0.6%)	170
Vehicle	98 (57%)	68 (40%)	6 (4%)	0	172
Scaling					
Differin	95 (56%)	62 (37%)	12 (7%)	1 (0.6%)	170
Vehicle	144 (84%)	26 (15%)	2 (1%)	0	172
Dryness					
Differin	86 (51%)	73 (43%)	10 (6%)	1 (0.6%)	170
Vehicle	138 (80%)	30 (17%)	4 (2%)	0	172
Burning					
Differin	115 (68%)	47 (28%)	7 (4%)	1 (0.6)	170
Vehicle	156 (91%)	14 (8%)	2 (1%)	0	172

Local tolerance - Study 90087 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Erythema					
Differin	30 (23%)	72 (55%)	25 (19%)	4 (3%)	131
Retin-A	19 (14%)	74 (55%)	34 (25%)	7 (5%)	134
Scaling					
Differin	45 (34%)	62 (47%)	18 (14%)	6 (5%)	131
Retin-A	24 (18%)	65 (49%)	39 (29%)	6 (5%)	134

Local tolerance - Study 90087 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Dryness					
Differin	28 (21%)	78 (56%)	20 (15%)	5 (4%)	131
Retin-A	8 (6%)	77 (58%)	41 (31%)	8 (6%)	134
Burning					
Differin	111 (85%)	16 (12%)	3 (2%)	1 (0.8)	131
Retin-A	104 (78%)	19 (14%)	9 (7%)	2 (2%)	134

The tabulations in the labeling attached to the approvable letter compiled the results of Studies 9111 and 18035, as follows.

At least mild reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	95	42	137/289 = 47%
Scaling	75	44	119/289 = 41%
Dryness	84	65	149/289 = 52%
Pruritus	-	32	32/119 = 27%
Burning	55	28	83/289 = 29%

At least mild reactions - Vehicle Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=172	Study 18035 n=118	Total n=290
Erythema	74	33	107/290 = 37%
Scaling	28	20	48/290 = 17%
Dryness	34	41	75/290 = 26%
Pruritus	-	18	18/118 = 15%
Burning	16	10	26/290 = 9%

At least moderate reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	22	7	29/289 = 10%
Scaling	13	6	19/289 = 7%
Dryness	11	17	28/289 = 10%
Pruritus	-	10	10/119 = 8%
Burning	8	6	14/289 = 5%

At least moderate reactions - Vehicle Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=172	Study 18035 n=118	Total n=290
Erythema	6	5	11/290 = 4%
Scaling	2	3	5/290 = 2%
Dryness	4	5	9/290 = 3%
Pruritus	-	2	2/118 = 2%
Burning	2	0	2/290 = <1%

Severe reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	1	0	1/289 = < 1%
Scaling	1	0	1/289 = < 1%
Dryness	1	1	2/289 = < 1%
Pruritus	-	1	1/119 = < 1%
Burning	1	1	2/289 = < 1%

Study 90087 n=131 Compiled by clinical reviewer	
At least mild reactions	
Erythema	101/131 = 77%
Scaling	86/131 = 66%
Dryness	103/131 = 79%
Burning	20/131 = 15%
At least moderate reactions	
Erythema	29/131 = 22%
Scaling	24/131 = 18%
Dryness	25/131 = 19%
Burning	4/131 = 3%
Severe reactions	
Erythema	4/131 = 3%
Scaling	6/131 = 5%
Dryness	5/131 = 4%
Burning	1/131 = < 1%

Reviewer's note: It is felt that pruritus could be omitted from these tables, as it was evaluated in only one of the three studies. Also, the word 'persistent' for burning could be deleted, as in only one of the studies was there a differentiation between persistent and transient burning.

In addition, the Safety Update submitted on 4/3/00, shows no significant events which differ from those reported in the original NDA.

Phyllis A. Huene, M.D.

N20748.ad3

4/19/00

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JAN 31 2000

HFD 540 # 994106
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MEDICAL OFFICER'S REVIEW OF NDA 20-748
RESUBMISSION

November 1, 1999

SPONSOR: Galderma Laboratories
Fort Worth, Texas

DRUG: Differin (adapalene) cream 0.1%

CLINICAL INDICATION: Acne

REASON FOR AMENDMENT: Response to the Not Approvable letter of 7/9/99.

INDEX
MEDICAL OFFICER'S REVIEW

The sponsor states that this submission is a complete response to correct the major deficiencies in NDA 20-748, as were listed in the Not Approvable letter of July 9, 1998.

Not approvable letter of July 9, 1998

The deficiencies as summarized in the Not Approvable letter are quoted as follows.

Clinical/Statistical:

Clinical study CR 90087 failed to demonstrate non-inferiority to its comparator, Retin-A Cream 0.05%. Please conduct an additional vehicle-controlled clinical trial to support safety and efficacy for the indication sought, using the to-be-marketed formulation.

Biopharmaceutics:

The pharmacokinetic study assessing the systemic exposure to adapalene after topical application of the cream dosage form is not adequate. Please conduct a multiple-dose study in patients with large surface area of diseased skin using the to-be-marketed formulation to determine the maximal systemic exposure. Please contact the Agency for guidance.

Microbiology:

The amendment of February 2, 1998, failed to adequately address requests for information in support of microbial quality of the subject drug. Please include the following additional information in the resubmission:

Microbial Limits Test:

1. References cited in Document #74.4110.00 for USP and the FDA Bacteriological Analytical Manual are not current and should be updated as provided for in Procedure #74.1001.01.

2. Establish an action limit for molds and yeasts and provide for this specification under Acceptance Criteria.

3. Provide a revised specification for Microbial Limits (Finished Product Tests and Specification, page 0006). The specification " .... and no detectable pathogens" should be replaced with those organisms required to be absent from the formulation. This change should also be made in procedure #74.4110.00 under Acceptance Criteria.

Chemistry:

We note that the safety and efficacy studies for Differin (adapalene cream) Cream 0.1% were conducted utilizing formulations different from the proposed to-be-marketed formulation (CDP). Specifically, Clinical Study 90087 utilized formulation C2. Formulation C2 contained a [redacted] overage of adapalene and [redacted] Clinical Study 9111-CD271C-EV utilized formulation C1 which contained a [redacted] overage of adapalene and no [redacted]. The [redacted] overage was eventually dropped as described in page 2 0075. Future clinical studies for Differin Cream should be conducted with the to-be-marketed formulation (CDP).

Additional requests were made by Chemistry that were to be addressed in the resubmission, although these were not the basis for the non-approval of the application.

Overview of clinical section of NDA resubmission

To satisfy the clinical deficiencies in the non-approvable letter, the sponsor has submitted two clinical studies. Study 1.GUS.04.SRE.18036 is a pharmacokinetic study, and Study 1.GUS.04.SRE.18035 is a comparison of the safety and efficacy of Differin cream with its vehicle.

Financial Disclosure statement

The sponsor has listed all investigators who have performed studies under Protocol 1.GUS.04.SRE.18035., and has certified that no financial arrangements have been made with any of these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor further states that each listed investigator required to disclose to the sponsor whether the investigator had a proprietary interset in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The sponsor also certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Study Report 1.GUS.04.SRE.18035

The Differin cream 0.1% formulation used in this study was the commercial drug product formulation. The study was conducted by the following investigators.

1) Study objective: The study objective was to assess the safety and efficacy of Differin cream as compared to its cream vehicle when applied once daily for 12 weeks in patients with mild to moderate acne.

2) Study design: This was a double blind, multicenter, randomized, parallel group comparison of Differin cream and its vehicle in patients with acne.

3) Inclusion criteria: Patients who met the following inclusion criteria were enrolled into the study.

   - Males and females between the ages of 12 and 30 years with mild to moderate acne vulgaris.
   - Acne of a Grade 1 through 5 on the Cunliffe Acne Grade scale for global facial severity.
   - Inflammatory lesion counts between 10 and 40, non-inflammatory lesion counts between 20 and 125, and no more than 3 nodules/cysts.
   - Females of childbearing potential and those with a tubal ligation must have had a negative pregnancy test at the beginning of the study, and had to have a urine pregnancy test at each visit if there had been no menstrual period during the preceding four weeks. If systemic birth control were used, the patient must have been taking the same type for at least three months prior to the study and must not change the method during the study. If patients had used systemic birth control and had stopped,

this should have been more than six months prior to the study.

4) Exclusion criteria: Patients with the following conditions were excluded from enrollment in the study.

- Pregnancy, lactation, or planning a pregnancy.
- Clinically important abnormal physical findings (other than acne) which might, in the opinion of the investigator, interfere with the objectives of the study.
- Acne conglobata, acne fulminans, secondary acne, or severe acne requiring more than topical treatment.
- Underlying diseases or other dermatological conditions that required the use of interfering topical or systemic therapy, such as atopic dermatitis, perioral dermatitis, or rosacea.
- Use of the following topical products during the specified washout periods, or a need for the concurrent use of any of these topical products on the face:

  Moisturizers, alpha hydroxy acid products, astringents, and other preparations, as follows:

Preparations with alcohol	1 day
Corticosteroids to the face	2 weeks
Antibiotics	2 weeks
Other anti-inflammatories	2 weeks
Other acne treatments	2 weeks
Retinoids	2 weeks

- Use of the following systemic products during the specified washout periods, or a need for the concurrent use of any of these systemic products:

Corticosteroids	4 weeks
Anti-inflammatories	2 weeks
Antibiotics (excluding penicillin)	2 weeks
Other acne treatments.	
(Including isotretinoin)	6 months

- Patients with known sensitivities to any of the study preparations.
- Patients with a beard or other facial hair that might interfere with study assessments.
- Patients (and parent/guardian if patient is under 18) who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

- Patients who had participated in another investigational drug or device research within 30 days of enrollment.

5) Treatment regimen: Applications of Differin Cream 0.1% or its cream vehicle were made once daily at bedtime for 12 weeks.

_____ was provided to each patient in an attempt to standardize washing procedures. If the patient did not wish to use _____ he/she could use a cleanser of his choice, provided that the product did not interfere with the study design; this was recorded on the CRF.

The patients were also encouraged to forgo the use of a moisturizer for as long as possible. If a moisturizer was added, this was noted as an adverse event. Also, if there were a need to temporarily decrease the frequency of dosing due to intolerance this was noted as an adverse event.

No other topical treatment was to be applied to the face during the study.

6) Efficacy parameters: The following evaluations were performed at baseline and at the return visits at weeks 2, 4, 8, and 12.

a. Facial lesion counts for inflammatory and non-inflammatory lesions.

b. Global evaluation of acne severity on the Cunliffe grading scale, as follows.

Global Evaluation scale		
I	0.25 0.5 0.75	Comedones are the main lesions. Papules and pustules may be present but are small and few in number.
II	1.0 1.25 1.5 1.75 2.0	Moderate number of papules and pustules, comedones are present.
III	3.0 4.0 5.0	Numerous papules and pustules with occasional larger, deeper inflamed lesions. Widespread affected areas usually involving face, back, and chest.
IV	6.0 7.0 8.0 9.0 10.0	Nodular-cystic acne and acne conglobata with severe lesions, mostly large, painful, and cystic.

The primary efficacy variables were considered to be the lesion counts for inflammatory and non-inflammatory lesions, the total lesion counts, and the investigator's assessment of global severity.

7) Safety parameters: At baseline and at each return visit the following signs and symptoms were noted and classified as mild, moderate, or severe: erythema, scaling, dryness, pruritus, and stinging/burning. The following descriptions of the categories were provided.

Erythema		
Severity	Score	Description
None	0	No erythema
Mild	1	Slight pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

Scaling		
Severity	Score	Description
None	0	No scaling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

Dryness		
Severity	Score	Description
None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness

Pruritus		
Severity	Score	Description
None	0	No itching
Mild	1	Slight itching; not really bothersome
Moderate	2	Definite itching that is somewhat bothersome, without loss of sleep
Severe	3	Intense itching that has caused pronounced discomfort; night rest interrupted and excoriation of the skin from scratching may be present.

Stinging/burning		
Severity	Score	Description
None	0	No stinging/burning
Mild	1	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	2	Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe	3	Hot, tingling/stinging sensation that has caused definite discomfort

The patients were also queried as to other adverse events.

Results were as follows.

1) Patient enrollment and demographic characteristics: 237 patients were enrolled into the study and constituted the ITT population; of these 119 were in the Differin cream 0.1% group and 118 were in the vehicle group. The ITT population consisted of all patients who were enrolled in the study and were randomized.

The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics - all patients enrolled		
	Differin cream 0.1%	Vehicle
Sex		
Male	59 (50%)	66 (56%)
Female	60 (50%)	52 (44%)
Race		
White	89 (75%)	87 (74%)
Black	7 (6%)	7 (6%)
Mongoloid	3 (3%)	1 (1%)
Hispanic	18 (15%)	21 (18%)
Other	2 (2%)	2 (2%)
Age (mean)	17.5	17.3

The reasons for patient discontinuations were as follows.

Patient discontinuations		
	Differin cream	Vehicle
Adverse event	1	0
Patient request	9	6
Protocol violation	0	1
Lost to followup	3	4
Other	0	1

2) Efficacy parameters: The results are tabulated at the return visits and at endpoint, with endpoint defined as the last observation recorded for a patient. Results for the ITT population were as follows.

a. Lesion counts.

The mean non-inflammatory lesion counts and the mean change from baseline in non-inflammatory lesion counts at each evaluation time were as follows.

Mean non-inflammatory lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Baseline	45.0	45.7	0.7525
Week 2	39.4	41.1	0.2118
Week 4	35.3	37.3	0.1565
Week 8	32.4	39.1	0.0053
Week 12	28.3	35.6	0.0037
Endpoint	29.1	36.7	0.0045

Mean percent change in non-inflammatory lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Week 2	- 15.4	- 8.6	0.1328
Week 4	- 23.6	- 16.9	0.0355
Week 8	- 30.5	- 13.7	0.0031
Week 12	- 38.0	- 19.8	0.0050
Endpoint	- 35.2	- 18.8	0.0054

The mean inflammatory lesion counts and the mean change from baseline in inflammatory lesion counts at each evaluation time were as follows.

Mean inflammatory lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Baseline	20.6	20.2	0.8451
Week 2	18.3	17.1	0.3530
Week 4	17.0	17.2	0.4371
Week 8	16.0	15.3	0.9759
Week 12	13.8	17.1	0.0030
Endpoint	14.3	17.2	0.0056

Mean percent change in inflammatory lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Week 2	- 11.0	- 15.5	0.4314
Week 4	- 18.5	- 16.1	0.2894
Week 8	- 26.8	- 25.5	0.8594
Week 12	- 35.5	- 18.9	0.0040
Endpoint	- 31.9	- 16.2	0.0070

The mean total lesion counts and the mean change from baseline in total lesion counts at each evaluation time were as follows.

Mean total lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Baseline	65.8	66.0	0.8748
Week 2	57.9	58.4	0.4559
Week 4	52.4	54.6	0.1419
Week 8	48.6	54.6	0.0229
Week 12	42.4	52.9	0.0007
Endpoint	43.6	54.2	0.0011

Mean percent change in total lesion counts ITT population			
Visit	Differin cream	Vehicle	p value
Week 2	- 14.9	- 11.4	0.3751
Week 4	- 23.7	- 16.9	0.0537
Week 8	- 29.9	- 17.7	0.0084
Week 12	- 37.9	- 19.8	0.0013
Endpoint	- 35.2	- 18.4	0.0013

b. Investigator's global assessment of severity.

The investigator's mean scores for acne severity were as follows.

Investigator's global assessment scores ITT population			
Visit	Differin cream	Vehicle	p value
Baseline	1.76	1.67	0.5310
Week 2	1.61	1.63	0.1340
Week 4	1.49	1.53	0.0960
Week 8	1.30	1.37	0.1471
Week 12	1.21	1.36	0.0565
Endpoint	1.28	1.38	0.0572

3) Safety.

The incidence and severity of local erythema, scaling, dryness, pruritus, and stinging/burning were as follows.

Local tolerance assessments		
Severity	Differin cream	Vehicle
Erythema		
None	73 (64%)	83 (72%)
Mild	35 (30%)	28 (24%)
Moderate	7 (6%)	5 (4%)
Severe	-	-
Scaling		
None	71 (62%)	96 (83%)
Mild	38 (33%)	17 (15%)
Moderate	6 (5%)	3 (3%)
Severe	-	-
Dryness		
None	50 (44%)	75 (65%)
Mild	48 (42%)	36 (31%)
Moderate	16 (14%)	5 (4%)
Severe	1 (0.9%)	-
Pruritus		
None	83 (72%)	98 (85%)
Mild	22 (19%)	16 (14%)
Moderate	9 (8%)	2 (2%)
Severe	1 (0.9%)	-
Stinging/burning		
None	87 (76%)	106 (91%)
Mild	22 (19%)	10 (9%)
Moderate	5 (4%)	-
Severe	1 (0.9%)	-

The adverse events which appear to this reviewer to be possibly related to treatment, and the investigator's assessment of the treatment relationship, are as follows.

Adverse events					
Event	Total # pts	Investigator evaluation of treatment relationship			
		Definitely related	Probably related	Possibly related	Unrelated/ unlikely
Dermatitis					
Differin	1 (0.8%)		1 (0.8%)		
Vehicle	0				
Desquamation					
Differin	2 (2%)		2 (2%)		
Vehicle	0				
Dry skin					
Differin	24 (20%)	2 (2%)	15 (13%)	7 (6%)	
Vehicle	4 (3%)	1 (0.8%)	3 (3%)		
Erythema					
Differin	1 (0.8%)		1 (0.8%)		
Vehicle	1 (0.8%)			1 (0.8%)	
Pruritus					
Differin	2 (2%)		1 (0.8%)	1 (0.8%)	
Vehicle	0				
Skin discoloration					
Differin	1 (0.8%)			1 (0.8%)	
Vehicle	0				
Skin discomfort					
Differin	4 (4%)		1 (0.8%)	3 (3%)	
Vehicle	1 (0.8%)				
Contact dermatitis					
Differin	0				
Vehicle	1 (0.8%)				1 (0.8%)

One patient withdrew from the study due to apparent treatment related adverse events; this patient was on Differin cream, and experienced dryness, burning, and discoloration of the skin, which subsequently resolved.

Reviewer's comments: In summary, this was a double blind, multicenter comparison of Differin cream 0.1% and the cream vehicle in 237 patients with mild to moderate acne, with applications once daily for 12 weeks. The effectiveness parameters were lesion counts for inflammatory and non-inflammatory lesions, total lesion counts, and an investigator's global evaluation.

The results showed that Differin cream was significantly superior to the vehicle at week 12 and at endpoint in the mean non-inflammatory lesion counts, the mean percent change in non-inflammatory lesion counts, the mean inflammatory lesion counts, the mean percent change in inflammatory lesion counts, the mean total lesion counts, and the mean percent change in total lesion counts. Differin cream, however, was not significantly superior to the vehicle in the investigator's global evaluation.

Local tolerance assessments with Differin cream were mild to moderate erythema and scaling in about one-third of patients, mild to moderate dryness in about one-half of patients, and mild to moderate pruritus and stinging/burning in about one-fourth of patients. There were single cases each of severe dryness, pruritus, and stinging/burning. Reported as adverse events with Differin cream were dry skin in 20%, skin discomfort in 4%, and 1-2 cases each of dermatitis, desquamation, erythema, pruritus, and skin discoloration.

Adverse events in the controlled studies

The adverse events which occurred in the three controlled studies, presented in the original submission and in the current submission, have been tabulated by this reviewer as follows.

Adverse event reports - controlled studies				
	Study 9111-CD271C-EV	Study CR 90087	Study 1GUS04SR E18035	Total
Dry skin		1	26	27 (6%)
Discomfort (burning/stinging)		1	4	5 (1%)
Irritation	1	4	1	6 (1%)
Edema of face	1			1
Acne flare	1	1		2
Erythema	1	2	1	4
Sunburn	7			7 (2%)
Contact dermatitis	4			4
Rash	1			1
Pruritus	1		2	3
Conjunctivitis	1			1
Eczema		1		1
Edema of eyelid		2		2
Skin discoloration			1	1

Summary: This resubmission of NDA 20-748 for Differin cream provides an additional clinical study for the demonstration of safety and effectiveness in the treatment of acne. The initial submission provided two controlled clinical studies, one of which was a comparison with the cream vehicle, and the other a comparison with Retin-A cream 0.05%. The results of the first study showed a significant superiority of Differin cream over the vehicle in the mean percent change in non-inflammatory lesion counts and total lesion counts, and in the investigator's global evaluation. However, the results of the positive controlled study

showed that Retin-A cream was significantly superior to Differin cream in the effect on all efficacy parameters.

A non-approvable letter was issued on 7/9/98, which stated that an additional vehicle controlled clinical study is needed to support the safety and effectiveness fot the proposed clinical indication.

The present clinical study was a double blind, multicenter comparison of Differin cream 0.1% and the cream vehicle in 237 patients with mild to moderate acne, with applications once daily for 12 weeks. The effectiveness parameters were lesion counts for inflammatory and non-inflammatory lesions, total lesion counts, and an investigator's global evaluation.

The results showed that Differin cream was significantly superior to the vehicle at week 12 and at endpoint in the mean non-inflammatory lesion counts, the mean percent change in non-inflammatory lesion counts, the mean inflammatory lesion counts, the mean percent change in inflammatory lesion counts, the mean total lesion counts, and the mean percent change in total lesion counts. Differin cream, however, was not significantly superior to the vehicle in the investigator's global evaluation.

Local tolerance assessments with Differin cream were mild to moderate erythema and scaling in about one-third of patients, mild to moderate dryness in about one-half of patients, and mild to moderate pruritus and stinging/burning in about one-fourth of patients. There were single cases each of severe dryness, pruritus, and stinging/burning. Reported as adverse events with Differin cream were dry skin in 20%, skin discomfort in 4%, and 1-2 cases each of dermatitis, desquamation, erythema, pruritus, and skin discoloration.

<u>Reviewer's evaluation</u>: It is felt that, although a superiority of Differin cream over its vehicle in the investigator's global evaluation has not been shown in this study, the overall results in the two vehicle controlled studies adequately demonstrate the effectiveness of Differin cream in the treatment of mild to moderate acne. In the first study (in the original submission) there was a highly significant superiority of Differin cream over the vehicle in the mean percent change in non-inflammatory lesion counts and total lesion counts, and in the investigator's global evaluation. In the current study there is also a highly significant superiority of Differin cream in the mean percent change in non-inflammatory and total lesion counts.

Conclusions: It is felt that the two vehicle controlled clinical studies adequately demonstrate the safety and effectiveness of Differin cream, 0.1%, in the treatment of mild to moderate acne, when used once daily for 12 weeks.

Recommendations: It is recommended that the application be approved for the use of Differin Cream for the topical treatment of acne.

Phyllis A. Huene, M.D.

1/24/00

Cc: Orig NDA 20-748
HFD-540 Division Files
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Cintron
HFD-540/DeCamp
HFD-540/Jacobs

8 pages redacted from this section of the approval package consisted of draft labeling

MEDICAL OFFICER'S REVIEW OF NDA 20-748
ORIGINAL SUBMISSION

November 10, 1997

SPONSOR: Galderma Laboratories
Fort Worth, Texas

JUN 5 1998

DRUG: Differin (adapalene) cream 0.1%

CLINICAL INDICATION: Acne

DOSAGE AND ADMINISTRATION:

FORMULATION:

Adapalene	0.1%
Carbomer 934P	
Propylparaben	
Phenoxyethanol	
Methylparaben	
Edetate disodium	
Glycerin	
PEG-20 methyl glucose sesquistearate	
Methyl glucose sesquistearate	
Cyclomethicone	
Squalene	
Trolamine	
Purified water —	

DATE OF SUBMISSION: July 16, 1997

RELATED SUBMISSIONS: NDA 20-338 for Differin solution 0.1%; NDA 20-380 for Differin gel 0.1%.

PHARMACOLOGY AND CONTROLS REVIEW: These are currently pending.

Pharmacologic class and scientific rationale

In a variety of *in vivo* and *in vitro* pharmacological and biochemical model systems designed to identify retinoid compounds with anti-acne potential, adapalene, a napthoic acid derivative, demonstrated activity equal to or superior to tretinoin and isotretinoin. The pharmacological profile of topically applied adapalene appears to be that of a potent retinoid-like substance with

regard to its comedolytic, hyperplasia, keratinization, and cellular differentiation activities. Topical adapalene also exhibits anti-inflammatory activity in experimental models. Adapalene has shown an affinity for human nuclear retinoic acid receptors, and it is believed that the retinoid-like activity of adapalene is mediated by its specific action on these receptors.

Marketing history

The NDAs for Differin Gel 0.1% and Differin Solution 0.1% were approved in May, 1996. Commercial distribution of Differin Gel in the US began in August 1996; marketing of Differin Solution has not been initiated. Differin Cream 0.1% was approved in Canada in June 1997. The drug has not been withdrawn in any dosage form from marketing in any foreign country.

Overview of clinical studies

A summary of the clinical studies performed on 0.01% Adapalene cream is as follows.

Summary of Clinical studies			
Study No.	Description	Treatment	# subjects
Phase I Studies			
CR 90080	Cumulative irritation and sensitization potential	Adapalene cream 0.01%, 0.03%. 0.1%**, 0.3%, and cream vehicle	25
CR.U9605	Contact sensitization	Adapalene cream 0.1%*, and cream vehicle	230
CR.U9424	Phototoxicity	Adapalene cream 0.1%*, and cream vehicle	12
CR.U9425	Photosensitization	Adapalene cream 0.1%*, and cream vehicle	30
1.CG.03.SRE.2042	Stratum corneum quantification	Adapalene cream 0.1%, 0.2%, 0.3% Adapalene gel 0.1%	12
Phase III studies			
9111-CD271C-EV	Safety and efficacy	Adapalene cream 0.1% * Adapalene cream vehicle	175 175
CR 90087	Safety and efficacy	Adapalene cream 0.1%*** Tretinoin cream	136 140

* same formulation as the NDA formulation except for — excess adapalene to compensate for loss during production.

** differed from the NDA formulation as follows: contained — propylparaben, — no phenoxyethanol or—

*** differed from the NDA formulation as follows: contained — excess adapalene to compensate for loss during production; also — propylparaben, — no phenoxyethanol or —

Phase I studies

1. Cumulative irritancy. (Study CR 90080)

This was conducted by [redacted] in 25 subjects. Five test articles were used in this study, as follows.

Adapalene cream 0.01%
Adapalene cream 0.03%
Adapalene cream 0.1%
Adapalene cream 0.3%
Adapalene cream vehicle

The test materials were applied in a double blind, randomized manner to the lower back of each subject, using a Finn chamber,. then attached to the skin with adhesive tape. The patches were applied daily to the same skin sites for 24 hours on weekdays and for 48 or 72 hours on weekends, for 18 consecutive days. After each patch removal the test site was graded for reactions on the following scale.

0	=	no erythema
0.5	=	equivocal erythema
1	=	slight erythema, with or without edema
2	=	moderate erythema, edema with or without papules
3	=	severe erythema, edema with or without papules
4	=	severe erythema, edema with vesicles or blisters

After a two week rest period challenge patches were applied to new skin sites for 48 hours. The test sites were examined for reactions at 30 minutes and at 24, 48, and 72 hours after patch removal. Reactions to the challenge patch were graded on the following scale.

0	=	no reaction
0.5	=	erythema on part of the test area
1	=	erythema covering the test area
2	=	erythema with edema
3	=	erythema with vesicles or blisters in part of the test area
4	=	erythema with vesicles or blisters covering all the test area

Results were as follows.

a. Individual scores. During the induction phase, Adapalene cream 0.1% produced a Grade 2 reaction in one subject on the last 2 days. There were no scores with Adapalene cream 0.1% above a Grade 1 in the other subjects. In the challenge phase, one subject had a Grade 2 reaction at 48 hours with 0.01% and 0.1% Adapalene cream, and one subject had a Grade 2 reaction at 48 hours with 0.01% Adapalene cream and the cream vehicle; these reactions decreased during later

readings to a Grade 0 on the last evaluation. Both subjects were re-challenged, and no reactions occurred which were greater than Grade 1.

b. Mean scores. The mean total irritancy scores were as follows.

Mean total irritation scores	
Test product	Score
Untreated patch	0.08
Vehicle cream	0.06
Adapalene cream 0.01%	0.12
Adapalene cream 0.03%	0.12
Adapalene cream 0.1%	0.12
Adapalene cream 0.3%	0.14

2. Contact sensitization. (Study CR.U9605)

This study was conducted by [redacted] Enrolled into the study were 230 subjects, of which 209 subjects completed the study.

In the induction phase, applications of Adapalene cream 0.1% and the cream vehicle were made in a randomized, investigator blinded manner to the back of each subject under occlusive patches, three times weekly for three weeks. The patches remained in place for 48 hours after the Monday and Wednesday applications, and for 72 hours after the Friday application. At patch removal the reactions were graded on the following scale.

0	=	no sign of irritation
1	=	slight erythema
2	=	noticeable erythema with slight infiltration
3	=	erythema with marked edema
4	=	erythema with edema and blistering

After a two week rest period challenge applications were made to naive skin sites for 48 hours. Reactions were evaluated at 48 and 72 hours after application. A subject was considered to be sensitized when a challenge site showed signs of erythema, edema, papules, and/or vesicles. Reactions of grade 2, 3, or greater (apparently on the above scale) along with increasing severity or sequential scores were considered to be indicative of sensitization. If the results could not be definitely interpreted as either irritation or sensitization, a rechallenge was performed.

Results were as follows.

Twenty-one subjects were withdrawn from the study; the reasons for withdrawal included one adverse event, 15 protocol violations, and 5 patient requests. The adverse event consisted of hives, itching and swelling of the hands and feet during week 3 of the induction period, which resolved a few hours later after treatment with Benadryl; this was considered to be possibly related to the test materials. The protocol violators were 14 patients who missed two study visits and were dropped from the study, and one patient who was discontinued because of concomitant anti-inflammatory medication.

The means of the cumulative irritation scores were as follows.

Mean cumulative irritation scores	
Test product	Score
Adapalene cream 0.1%	5.52
Vehicle cream	3.93

The individual scores showed numerous Grade 1 and 2 reactions for both test materials. The number of Grade 3 and 4 scores was as follows.

Occurrence of Grade 3 and 4 scores (# of scores)		
	Adapalene cream 0.1%	Vehicle
Grade 3	3	1
Grade 4	2	2

The conclusion was that both Adapalene cream 0.1% and its vehicle were mild irritants.
The challenge reactions were as follows. For the cream vehicle, reactions were mostly Grade 0, with a few Grade 1 reactions. With Adapalene cream the reactions were scored as Grade 0 or 1, with the exception of two subjects. These two had Grade 2 reactions at challenge, and were re-challenged, with the result that one subject had a Grade 2 reaction at 48 and 72 hours and a Grade 1 reaction at 96 hours, and the other subject had a 0 score at 48 hours, missed the 72 hour reading, and had a Grade 1 score at 96 hours. The conclusion was that neither Adapalene cream 0.1% nor its vehicle showed a potential for contact sensitization.

3. Phototoxicity. (Study CR.U9424)

This study was conducted on 12 subjects by [redacted] Duplicate applications of Adapalene cream 0.1% and the cream vehicle were made under occlusive patches to contralateral skin sites of the back in a double blind manner. An untreated control patch was applied to an adjacent site. After 24 hours all patches were removed and one set of patch sites were irradiated with [redacted] radiation from a [redacted] with a filtered light source. The other set of patch sites served as non-irradiated control sites. The patch sites were scored immediately after irradiation and at 24 and 72 hours post-irradiation, using the following scale.

0	=	negative, no response
+/-	=	equivocal reaction, barely perceptible erythema with no clearly defined border
1	=	mild but definite erythema with clearly defined border
2	=	moderate clearly defined erythema
3	=	strong erythema or edema
4	=	bulla or vesiculation

The reactions with Adapalene cream 0.1% and the vehicle ranged from 0 to +/- at both UVA treated sites and non-UVA sites. One subject had a Grade 1 reaction in the UVA-treated Adapalene cream site; however, it was felt that the subject had been inadvertently exposed to UVB. On rechallenge all reactions were less than grade 1. It was concluded that under the conditions of this study there was no evidence of potential for phototoxicity with either Adapalene cream 0.1% or its vehicle.

4. Photosensitization. (Study CR.U9425)

This study was conducted on 29 evaluable subjects by [redacted] Applications of Adapalene cream 0.1% and the cream vehicle were made in a double blind manner under occlusive patches to skin sites on the back of each subject, remaining in place for 24 hours. After patch removal the sites were irradiated with 3 MEDs of UVA + UVB radiation. This procedure was repeated six times over a three week period. After a 14 day rest period duplicate challenge patches with each material were applied to naive skin sites for 24 hours. At patch removal one set of skin sites was irradiated with [redacted] radiation from a [redacted]. An additional untreated patch site was irradiated and served as an irradiated control site. The sites were scored for reactions at 24, 48, and 72 hours post-irradiation, using the following scale.

0	=	no visible erythema
+/-	=	barely perceptible erythema
1	=	mild erythema (faint pink to definite pink)
2	=	moderate erythema (definite redness)
3	=	severe erythema (very intense redness)

E	=	edema
P	=	papules
V	=	vesicles
B	=	bullae
S	=	spreading
W	=	weeping

Results were as follows.

Of 30 subjects enrolled in the study, 29 completed the study. One subject was discontinued due to an adverse event unrelated to the study treatment.

The erythema grades observed at two days post-application of each induction patch were as follows.

Reactions during induction phase - Adapalene cream 0.1%					
Erythema grade	Number of reactions observed at induction visit number				
	3	5	7	9	11
0	0	0	0	0	0
+/-	0	0	0	0	0
1	1	13	12	14	3
2	29	14	17	14	20
3	0	0	0	0	0
NR	0	3	1	1	6

Reactions during induction phase - Cream vehicle					
Erythema grade	Number of reactions observed at induction visit number				
	3	5	7	9	11
0	0	0	0	0	0
+/-	0	0	2	0	0
1	1	10	9	9	2
2	29	17	17	19	22
3	0	0	1	0	0
NR	0	3	1	1	5

The reactions during the challenge phase at sites treated with Adapalene cream 0.1% and were as follows.

Challenge reactions Adapalene cream 0.1%			
Grade	24 hour	48 hour	72 hour
0	26	29	29
+/-	3*	0	0
1	0	0	0
2	0	0	0
3	0	0	0
*Tape sensitivity			

The conclusion was that under the study conditions Adapalene cream 0.1% and its cream vehicle did not induce photoallergy in any of the study participants.

5. Stratum corneum quantification (Study 1.CG.03.SRE.2042)

This study was conducted in Nice, France on 12 subjects. After a one hour application of Adapalene cream at concentrations of 0.1, 0.2, and 0.3% to designated skin sites, the stratum corneum was stripped and the amount of adapalene was measured. The conclusion was that the adapalene quantities present in the stratum corneum were proportional to the concentration in the cream formulation.

Reviewer's comments: In summary, the Phase I studies performed on Differin cream 0.1% include cumulative irritancy, contact sensitization, phototoxicity, and photosensitization. It is felt that the studies were adequately performed, and showed little or no potential for contact sensitization, phototoxicity, or photosensitization under these test conditions. Significant irritation (erythema with edema and blistering) occurred in a few subjects under these conditions of exaggerated exposure, but this would not be expected to occur under conditions of clinical usage.

Phase III studies

I. Study 9111-CD271C-EV.

This study was conducted by the following investigators.

1. Study objective: The study objective was to assess the safety and effectiveness of Adapalene cream 0.1% as compared with the Adapalene cream vehicle in patients with mild and moderate acne vulgaris.

2. Study design: This was a double blind, randomized, parallel group, multicenter study of Adapalene cream 0.1% and its vehicle in patients with acne.

3. Patient inclusions: Patients who met the following inclusion criteria were enrolled into the study.

   a. males or females between that ages of 12 and 30 years.
   b. acne of Grade 1 to 5 on the Cunliffe scale, with 30 or more facial comedones (open and closed) and 10 or more inflammatory facial lesions. (papules/pustules).

4. Patient exclusions: Patients with the following conditions were excluded from enrollment in the study.

   a. acne conglobata, fulminans, or secondary acne.
   b. another dermatological condition or underlying disease that required the use of interfering topical or systemic therapy.

c. initial administration of birth control pills less than 3 months prior to the study, or discontinuance of birth control pills less than 6 months prior to the study.
d. use of topical acne treatment within 2 weeks prior to the study, systemic antibiotics (except penicillin) within 4 weeks prior to the study, or systemic retinoids within 6 months prior to the study.

5. Treatment regimen: Applications of the test products were made once daily, at bedtime, to the face for 12 weeks.

6. Effectiveness parameters. The following evaluations were performed at baseline and at weeks 2, 4, 8, and 12.

a. Facial lesion counts for open and closed comedones, papules and pustules.

b. Global evaluation on a scale of from 0 to 10, based on a series of representative photographs of acne patients. The evaluation used was described as the Leeds technique by Burke and Cunliffe, in the British Journal of Dermatology, 1984. The scale was as follows.

Global Evaluation scale	
0.25 0.5 0.75	Comedones are the main lesions. Papules and pustules may be present but are small and less than 10 are present.
1.0 1.25 1.5 1.75 2.0	Moderate number of papules and pustules (greater than 10). Comedones are present (greater than 30).
3.0 4.0 5.0	Numerous papules and pustules with occasional larger deeper inflamed lesions. Widespread affected areas usually involving face, back, and chest.
6.0 7.0 8.0 9.0 10.0	Nodular-cystic acne and acne conglobata with severe lesions, mostly large, painful, and cystic.

6. Safety parameters. At baseline and at each return visit the following signs and symptoms were noted and classified as mild, moderate, or severe: erythema, scaling, dryness, pruritus, and burning. The patients were also queried as to the occurrence of other adverse events.

Results were as follows.

1) Patient enrollment and demographic characteristics: 350 patients were enrolled into the study, of which 315 patients completed the study. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics - all patients enrolled		
	Adapalene cream 0.1%	Vehicle
Sex		
Male	104 (59%)	101 (58%)
Female	71 (41%)	74 (42%)
Race		
White	145 (83%)	140 (80%)
Black	6 (3%)	11 (6%)
Oriental	3 (2%)	9 (5%)
Other	21 (12%)	15 (9%)
Age (mean)	18.6	18.6

The reasons for patient discontinuations were as follows.

Patient discontinuations		
	Adapalene cream 0.1%	Vehicle
Patient request	9	8
Adverse event	3	1
Treatment failure	2	2
Lost to followup	4	2
Other	1	5

In addition, patients with the following protocol violations were not considered evaluable at any visit.

Protocol violations		
	Adapalene cream 0.1%	Vehicle
Less than 30 comedones at baseline	1	0
Interfering therapy	1	1
Missed more than 2 visits	10	6
Outside of age range	0	1
Less than 10 inflammatory lesions	0	1

The number of patients that were evaluable for efficacy at each evaluation time was as follows.

Patients evaluable for efficacy						
	Adapalene cream 0.1%			Vehicle		
	Evaluable	Unevaluable	Total	Evaluable	Unevaluable	Total
Baseline	162	13	175	167	8	175
Week 2	158	17	175	166	9	175
Week 4	159	16	175	167	8	175
Week 8	156	19	175	155	20	175
Week 12	153	22	175	157	18	175
Endpoint	158	17	175	164	11	175

The number of patients evaluable for safety and ITT analyses at each evaluation time was as follows.

Patients evaluable for safety and ITT analyses						
	Adapalene cream 0.1%			Vehicle		
	Evaluable	Unevaluable	Total	Evaluable	Unevaluable	Total
Baseline	175	0	175	175	0	175
Week 2	165	10	175	171	4	175
Week 4	161	14	175	169	6	175
Week 8	159	16	175	157	18	175
Week 12	159	16	175	162	13	175
Endpoint	175	0	175	175	0	175

3) Efficacy parameters: Results for the efficacy evaluable patients were as follows.

a. Lesion counts.

The mean total non-inflammatory lesion counts and the mean change from baseline in non-inflammatory lesion counts at each evaluation time were as follows.

Mean non-inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	162	74.8	167	69.1	0.37
Week 2	158	64.1	166	64.2	0.005
Week 4	159	55.6	167	57.7	0.006
Week 8	156	49.2	155	57.0	0.0001
Week 12	153	42.8	157	55.2	0.0001
Endpoint	158	43.2	164	55.4	0.0001

Mean percent change in non-inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	158	-13.6	166	-4.5	0.0065
Week 4	159	-23.3	167	-13.5	0.0169
Week 8	156	-32.1	155	-14.0	0.0008
Week 12	153	-36.8	157	-15.4	0.0003
Endpoint	158	-37.0	164	-14.4	0.0001

The mean total inflammatory lesion counts and the mean change from baseline in inflammatory lesion counts at each evaluation time were as follows.

Mean inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	162	25.8	167	26.0	0.47
Week 2	158	24.9	166	25.0	0.89
Week 4	159	21.8	167	22.8	0.89
Week 8	156	21.0	155	20.9	0.76
Week 12	153	19.2	157	22.2	0.24
Endpoint	158	20.1	164	22.7	0.26

Mean percent change in inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	158	6.6	166	6.4	0.86
Week 4	159	-6.6	167	-6.9	0.89
Week 8	156	-6.0	155	-7.8	0.81
Week 12	153	-14.8	157	-5.4	0.29
Endpoint	158	-12.9	164	-4.6	0.31

The mean total lesion counts and the mean change from baseline in total lesion counts were as follows.

Mean total lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	162	100.7	167	95.1	0.345
Week 2	158	88.9	166	89.2	0.016
Week 4	159	77.4	167	80.4	0.019
Week 8	156	70.2	155	77.9	0.0006
Week 12	153	61.9	157	77.4	0.0001
Endpoint	158	63.2	164	78.1	0.0001

Mean percent change in total lesion counts Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	158	- 10.6	166	- 3.8	0.0059
Week 4	159	- 20.1	167	- 13.4	0.047
Week 8	158	- 27.4	155	- 14.3	0.005
Week 12	153	- 31.9	157	- 14.6	0.001
Endpoint	158	- 31.8	164	- 13.6	0.0003

. Investigator's global assessment.

The investigator's mean global evaluation scores were as follows.

Investigator global assessment Efficacy evaluable patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	162	1.50	167	1.51	0.88
Week 2	158	1.46	166	1.47	0.94
Week 4	159	1.37	167	1.40	0.53
Week 8	156	1.28	155	1.26	0.93
Week 12	153	1.13	157	1.26	0.0048
Endpoint	158	1.15	164	1.27	0.0049

4) Efficacy parameters: The results for the intent-to-treat patients were as follows.

a. Lesion counts.

The mean total non-inflammatory lesion counts and the mean change in non-inflammatory lesion counts at each evaluation time were as follows.

Mean non-inflammatory lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	175	74.6	175	69.3	0.38
Week 2	164	64.1	171	64.9	0.005
Week 4	161	55.8	169	57.5	0.007
Week 8	159	48.5	157	56.5	0.0001
Week 12	159	42.0	162	54.4	0.0001
Endpoint	174	44.5	175	55.2	0.0001

Mean percent change in non-inflammatory lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	164	-13.2	171	-4.1	0.008
Week 4	161	-23.7	169	-13.6	0.0136
Week 8	159	-32.6	157	-14.7	0.001
Week 12	159	-38.1	162	-16.7	0.0002
Endpoint	174	-36.0	175	-15.2	0.0001

The mean total inflammatory lesion counts and the mean change in inflammatory lesion counts at each evaluation time were as follows.

Mean inflammatory lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	175	26.2	175	25.6	0.28
Week 2	164	25.2	171	24.6	0.79
Week 4	161	21.9	169	22.6	0.93
Week 8	159	20.9	157	21.1	0.99
Week 12	159	19.4	162	22.0	0.21
Endpoint	174	20.6	175	22.3	0.32

Mean percent change in inflammatory lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	164	6.0	171	5.5	0.82
Week 4	161	-6.6	169	-7.2	0.92
Week 8	159	-6.3	157	-4.7	0.76
Week 12	159	-15.1	162	-5.8	0.27
Endpoint	174	-12.1	175	-5.2	0.42

The mean total lesion counts and the mean change in total lesion counts at each evaluation time were as follows.

Mean total lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	175	100.8	175	94.9	0.277
Week 2	164	89.3	171	89.5	0.018
Week 4	161	77.7	169	80.0	0.021
Week 8	159	69.4	167	77.6	0.0003
Week 12	159	61.4	162	76.5	0.0001
Endpoint	174	65.1	175	77.7	0.0001

Mean percent change in total lesion counts Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 2	164	- 10.6	171	- 3.6	0.0066
Week 4	161	- 20.4	169	- 13.5	0.0396
Week 8	159	- 27.7	157	- 14.5	0.0047
Week 12	159	- 32.8	162	- 15.9	0.0012
Endpoint	174	- 30.8	175	- 14.5	0.0009

b. Investigator's global assessment.

The investigator's mean global evaluation scores were as follows.

Investigator global assessment Intent-to-treat patients					
	Adapalene cream		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	175	1.5	175	1.5	0.73
Week 2	164	1.5	171	1.5	0.99
Week 4	161	1.4	169	1.4	0.57
Week 8	159	1.3	157	1.3	0.93
Week 12	159	1.1	162	1.2	0.004
Endpoint	174	1.2	175	1.3	0.008

5) Safety.

The incidence and severity of local erythema, dryness, scaling and burning were as follows.

Erythema					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	115 (66%)	51 (29%)	8 (5%)	1 (0.6%)	175
Vehicle	115 (66%)	55 (31%)	5 (3%)	0	175
Week 2					
Adapalene	87 (53%)	64 (39%)	13 (8%)	0	164
Vehicle	118 (69%)	49 (29%)	4 (2%)	0	171
Week 4					
Adapalene	101 (63%)	52 (32%)	7 (4%)	1 (0.6%)	161
Vehicle	126 (75%)	41 (24%)	2 (1%)	0	169
Week 8					
Adapalene	109 (69%)	40 (25%)	9 (6%)	1 (0.6%)	159
Vehicle	121 (77%)	34 (22%)	2 (1%)	0	157
Week 12					
Adapalene	120 (76%)	27 (17%)	11 (7%)	1 (0.6%)	159
Vehicle	130 (80%)	30 (19%)	2 (1%)	0	162
Maximum					
Adapalene	75 (44%)	73 (43%)	21 (12%)	1 (0.6%)	170
Vehicle	98 (57%)	68 (40%)	6 (4%)	0	172

Scaling					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	159 (91%)	15 (9%)	1 (0.6%)	0	175
Vehicle	163 (93%)	11 (6%)	1 (0.6%)	0	175
Week 2					
Adapalene	112 (68%)	45 (27%)	7 (4%)	0	164
Vehicle	154 (90%)	17 (10%)	0	0	171
Week 4					
Adapalene	132 (82%)	24 (15%)	5 (3%)	0	161
Vehicle	159 (94%)	9 (5%)	1 (0.6%)	0	169
Week 8					
Adapalene	135 (85%)	20 (13%)	3 (2%)	1 (0.6%)	159
Vehicle	150 (96%)	7 (5%)	0	0	157
Week 12					
Adapalene	143 (90%)	12 (8%)	4 (3%)	0	159
Vehicle	155 (96%)	6 (4%)	1 (0.6%)	0	162
Maximum					
Adapalene	95 (56%)	62 (37%)	12 (7%)	1 (0.6%)	170
Vehicle	144 (84%)	26 (15%)	2 (1%)	0	172

Dryness					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	159 (91%)	14 (8%)	2 (1%)	0	175
Vehicle	150 (86%)	25 (14%)	0	0	175
Week 2					
Adapalene	103 (68%)	56 (34%)	5 (3%)	0	164
Vehicle	153 (90%)	16 (9%)	2 (1%)	0	171
Week 4					
Adapalene	122 (76%)	34 (21%)	5 (3%)	0	161
Vehicle	154 (91%)	14 (8%)	1 (0.6%)	0	169
Week 8					
Adapalene	138 (87%)	17 (11%)	3 (2%)	1 (0.6%)	159
Vehicle	145 (92%)	12 (8%)	0	0	157
Week 12					
Adapalene	132 (83%)	24 (15%)	3 (2%)	0	159
Vehicle	149 (92%)	11 (74%)	2 (1%)	0	162
Maximum					
Adapalene	86 (51%)	73 (43%)	10 (6%)	1 (0.6%)	170
Vehicle	138 (80%)	30 (17%)	4 (2%)	0	172

Burning					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	172 (98%)	3 (2%)	0	0	175
Vehicle	174 (99%)	1 (0.6%)	0	0	175
Week 2					
Adapalene	120 (73%)	36 (22%)	7 (4%)	1 (0.6%)	164
Vehicle	163 (95%)	7 (4%)	1 (0.6%)	0	171
Week 4					
Adapalene	134 (83%)	27 (17%)	0	0	161
Vehicle	163 (97%)	5 (3%)	1 (0.6%)	0	169
Week 8					
Adapalene	143 (90%)	16 (10%)	0	0	159
Vehicle	151 (96%)	6 (4%)	0	0	157
Week 12					
Adapalene	150 (94%)	9 (6%)	0	0	159
Vehicle	158 (98%)	4 (3%)	0	0	162
Maximum					
Adapalene	115 (68%)	47 (28%)	7 (4%)	1 (0.6%)	170
Vehicle	156 (91%)	14 (8%)	2 (1%)	0	172

The adverse events which appear to this reviewer to be possibly related to treatment, and the investigator's assessment of the treatment relationship, are as follows.

Adverse events Investigator evaluation of treatment relationship					
Event	Total # pts	Definitely related	Possibly related	Unrelated	Unknown
Edema of face Adapalene Vehicle	 1 0		 1		
Acne flare Adapalene Vehicle	 1 1	 1		 1	
Rash - erythema Adapalene Vehicle	 1 0				 1
Sunburn Adapalene Vehicle	 7 6		 3 1	 4 4	 1
Contact dermatitis Adapalene Vehicle	 4 0		 2	 2	
Rash Adapalene Vehicle	 1 1			 1 1	
Skin irritation Adapalene Vehicle	 1 0	 1			
Pruritus Adapalene Vehicle	 1 0				 1
Conjunctivitis Adapalene Vehicle	 1 2		 1	 2	

The severity of the above adverse events was as follows.

Adverse events - Severity				
Event	Total # pts	Mild	Moderate	Severe
Edema of face				
Adapalene	1	1		
Vehicle	0			
Acne flare				
Adapalene	1		1	
Vehicle	1	1		
Rash - erythema				
Adapalene	1	1		
Vehicle	0			
Sunburn				
Adapalene	7	5	2	
Vehicle	6	5	1	
Contact dermatitis				
Adapalene	4	1	3	
Vehicle	0			
Rash				
Adapalene	1	1		
Vehicle	1		1	
Skin irritation				
Adapalene	1	1		
Vehicle	0			
Pruritus				
Adapalene	1	1		
Vehicle	0			
Conjunctivitis				
Adapalene	1		1	
Vehicle	2	2		

Two patients, both on Adapalene cream, discontinued prematurely due to dermatological adverse events; one event was felt by the investigator to be possibly related, and the other was felt to be unrelated to treatment. These were as follows.

1. Patient 8105: This patient developed moderately severe contact dermatitis 12 days after the initial application of the drug, which resolved with topical steroids. This was considered by the investigator to be caused by benzophenone in a sunscreen, unrelated to the study treatment.

2. Patient 8608: This patient developed a moderately severe contact dermatitis 9 days after initial application of the drug. Both cheeks were irritated, particularly on one side which was blistered following exposure to poison oak. The condition resolved after two weeks with treatment. The investigator felt that this was possibly related to treatment.

Reviewer's comments: In summary, this was a double blind, multicenter comparison of Adapalene cream 0.1% and the cream vehicle in 322 evaluable patients with mild and moderate acne, with applications once daily for 12 weeks. The effectiveness parameters were lesion counts for inflammatory and non-inflammatory lesions, the total lesion counts, and an investigator's global evaluation.

The results showed that Adapalene cream was significantly superior to the vehicle at week 12 and at endpoint in the mean non-inflammatory lesion counts, the mean percent change in non-inflammatory lesion counts, the mean total lesion counts, the mean percent change in total lesion counts, and the investigator's global evaluation. However, it is noted that the clinical significance of the difference in mean scores in the global evaluation is debatable; a difference between scores of 1.15 and 1.27 on the scale as defined might not even be clinically discernible. Adapalene cream was not significantly superior to the vehicle in the mean inflammatory lesion counts or the mean percent change in inflammatory lesion counts.

Local adverse effects with Adapalene cream were mild to moderate erythema and dryness in about half of the patients, and mild to moderate scaling and burning in about one-third of the patients. One case of severe persistent erythema, and one case each of severe transient scaling, dryness, and burning were reported. Other adverse effects which were considered to be definitely related to Adapalene cream were acne flare in one and skin irritation in another patient. Effects which were felt to be possibly related to Adapalene cream were edema of the face in one, sunburn in three, contact dermatitis in two, and conjunctivitis in one patient.

II. Study CR 90087

The investigators for this study were as follows.

1. Study objective: The study objective was to assess the safety and efficacy of Adapalene cream 0.1% as compared with Retin-A cream 0.05% in the treatment of patients with mild to moderate acne.

2. Study design: This was an investigator blinded, randomized, parallel group, multicenter study of Adapalene cream 0.1% and Retin-A cream 0.05% in patients with acne.

3. Patient inclusions: Patients enrolled into the study were males and females, aged 12 to 30 years, with mild to moderate facial acne of grades 1 to 5 on a scale described below, with a minimum of 20 non-inflammatory lesions and 10 inflammatory lesions.

4. Patient exclusions: Patients with the following conditions were excluded from enrollment in the study.

   a. Acne of greater than grade 5 or less than grade 1, with fewer than 20 comedones or fewer than 10 inflammatory lesions.
   b. acne conglobata, fulminans, or secondary acne.
   c. another dermatological condition or underlying disease that required the use of interfering topical or systemic therapy.
   d. use of birth control pills free of cyproterone acetate for less than 3 months, or use of cyproterone acetate birth control pills for less than 12 months.

e. use of topical acne treatment within the 2 weeks prior to the study, systemic antibiotics (except penicillin) within 4 weeks prior to the study, systemic retinoids within 6 months prior to the study, or topical or systemic chronic anti-inflammatory treatment within the 4 weeks prior to the study.

5. Treatment regimen: Applications of the test products were made once daily for 12 weeks.

6. Effectiveness parameters. The following evaluations were performed at baseline and at weeks 2, 4, 8, and 12.

   a. Facial lesion counts for closed comedones, open comedones, papules, pustules, nodules, and cysts.

   b. Global evaluation on a 0 to 10 scale based on a series of representative photographs of acne patients. The evaluation used was the Leeds technique by Burke and Cunliffe, reported in the British Journal of Dermatology, 1984. The scale was as follows.

Global Evaluation Scale		
Global acne grade	Definition	FDA severity acne grade*
0	Clear	0
0.25 0.5 0.75	Comedones are the main lesions. Papules and pustules may be present but are small and less than 10 are present.	I
1.0 1.25 1.5 1.75 2.0	Moderate number of papules and pustules (greater than 10). Comedones are present (greater than 30).	II
3.0 4.0 5.0	Numerous papules and pustules with occasional larger deeper inflamed lesions. Widespread affected areas usually involving face, back, and chest.	III
6.0 7.0 8.0 9.0 10.0	Nodular-cystic acne and acne conglobata with severe lesions, mostly large, painful, and cystic.	IV
* This was designated as the FDA severity acne grade in the protocol; in actuality there are no FDA acne grades		

6. Safety parameters. At baseline and at each return visit the following signs and symptoms were noted and classified as mild, moderate, or severe: erythema, scaling, dryness, pruritus, and burning.

Results were as follows.

1) Patient enrollment and demographic characteristics: 277 patients were enrolled into the study, of which 261 patients completed the study. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics - all patients enrolled		
	Adapalene cream 0.1% (n=136)	Retin-A cream 0.05% (n=141)
Sex		
Male	69	63
Female	67	77
Race		
White	113	117
Black	1	0
Hispanic	22	21
Asian	0	2
Age (mean)	19	20

The reasons for patient discontinuations were as follows.

Patient discontinuations		
	Adapalene cream 0.1%	Retin-A cream 0.05%
No data	0	1
Condition clear	1	0
Treatment failure	2	2
Adverse event	7	8
Interfering therapy	0	1
Lost to followup	1	4
Non- compliance	8	5

The number of patients that were evaluable for efficacy at each evaluation time was as follows.

Patients evaluable for efficacy						
	Adapalene cream 0.1%			Retin-A cream 0.05%		
	Evaluable	Unevaluable	Total	Evaluable	Unevaluable	Total
Baseline	130	0	130	131	0	131
Week 2	129	1	130	128	3	131
Week 4	127	3	130	127	4	131
Week 8	118	11	130	125	6	131
Week 12	110	20	130	112	19	131

3) Efficacy parameters: The following analyses were done on those patients who were evaluable for efficacy.

a. Lesion counts.

The mean total non-inflammatory lesion counts and the mean change from baseline in non-inflammatory lesion counts at each evaluation time were as follows.

Mean non-inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Baseline	130	66.6	131	65.3	0.37
Week 2	129	49.2	128	47.4	0.98
Week 4	127	39.6	127	33.6	0.02
Week 8	119	31.0	125	24.1	0.03
Week 12	110	21.4	112	17.3	0.009
Endpoint	130	23.4	131	17.5	0.002

Mean percent change in non-inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Week 2	129	-25.1	128	-25.3	0.65
Week 4	127	-38.3	127	-47.8	0.009
Week 8	119	-50.3	125	-61.7	0.027
Week 12	110	-64.4	112	-71.5	0.003
Endpoint	130	-59.8	131	-69.5	0.00

The mean total inflammatory lesion counts and the mean change from baseline in inflammatory lesion counts at each evaluation time were as follows.

Mean inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Baseline	130	29.3	131	29.8	0.95
Week 2	129	26.0	128	26.8	0.95
Week 4	127	20.8	127	21.8	0.72
Week 8	119	18.9	125	17.5	0.13
Week 12	110	15.7	112	12.7	0.001
Endpoint	130	16.2	131	13.0	0.006

Mean percent change in inflammatory lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Week 2	129	-7.2	128	-5.6	0.57
Week 4	127	-24.6	127	-22.2	0.80
Week 8	119	-30.0	125	-36.6	0.36
Week 12	110	-42.6	112	-55.5	0.004
Endpoint	130	-40.6	131	-52.5	0.008

The mean total lesion counts and the mean change from baseline in total lesion counts at each evaluation time were as follows.

Mean total lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Baseline	130	96.0	131	95.1	0.80
Week 2	129	75.1	128	74.2	0.81
Week 4	127	60.4	127	55.5	0.16
Week 8	119	49.9	125	41.6	0.03
Week 12	110	37.2	112	30.0	0.002
Endpoint	130	39.7	131	30.5	0.001

Mean percent change in total lesion counts Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Week 2	129	- 20.1	128	- 20.3	0.35
Week 4	127	- 35.7	127	- 41.1	0.21
Week 8	119	- 46.4	125	- 56.1	0.02
Week 12	110	- 59.3	112	- 67.4	0.001
Endpoint	130	- 55.1	131	- 65.0	0.000

b. Investigator's global evaluation.

The investigator's mean global grades were as follows.

Investigator mean global grade Efficacy evaluable patients					
	Adapalene cream		Retin-A cream 0.05%		p value
	# pts	Mean	# pts	Mean	
Baseline	130	1.6	131	1.6	0.35
Week 2	128	1.4	128	1.5	0.34
Week 4	127	1.2	127	1.2	0.43
Week 8	118	1.1	125	1.0	0.17
Week 12	109	0.8	111	0.7	0.05
Endpoint	130	0.8	131	0.7	0.07

5) Safety.

The incidence and severity of local erythema, dryness, scaling and burning were as follows.

Erythema					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	108 (79%)	20 (15%)	7 (5%)	1 (0.7%)	136
Retin-A	106 (76%)	27 (19%)	6 (4%)	1 (0.7%)	140
Week 2					
Adapalene	61 (47%)	51 (39%)	18 (14%)	1 (0.8%)	131
Retin-A	46 (35%)	56 (42%)	26 (20%)	4 (3%)	132
Week 4					
Adapalene	66 (51%)	50 (39%)	12 (9%)	1 (0.8%)	129
Retin-A	51 (39%)	65 (50%)	12 (9%)	2 (2%)	130
Week 8					
Adapalene	69 (57%)	46 (38%)	5 (4%)	2 (2%)	122
Retin-A	601 (48%)	55 (44%)	9 (7%)	1 (0.8%)	125
Week 12					
Adapalene	81 (69%)	35 (30%)	2 (2%)	0	118
Retin-A	72 (58%)	50 (40%)	3 (2%)	0	125
Maximum					
Adapalene	30 (23%)	72 (55%)	25 (19%)	4 (3%)	131
Retin-A	19 (14%)	74 (55%)	34 (25%)	7 (5%)	134

Scaling					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	128 (95%)	7 (5%)	0	0	135
Retin-A	128 (91%)	11 (8%)	1 (0.7%)	0	140
Week 2					
Adapalene	71 (54%)	47 (36%)	11 (8%)	2 (1.5%)	131
Retin-A	42 (32%)	60 (46%)	28 (21%)	2 (1.5%)	132
Week 4					
Adapalene	82 (64%)	41 (32%)	4 (3%)	2 (2%)	129
Retin-A	55 (42%)	58 (45%)	12 (9%)	5 (4%)	130
Week 8					
Adapalene	77 (64%)	35 (29%)	7 (6%)	2 (2%)	121
Retin-A	52 (42%)	59 (47%)	14 (11%)	0	125
Week 12					
Adapalene	84 (71%)	32 (27%)	2 (2%)	0	118
Retin-A	75 (60%)	42 (34%)	8 (6%)	0	125
Maximum					
Adapalene	45 (34%)	62 (47%)	18 (14%)	6 (5%)	131
Retin-A	24 (18%)	65 (49%)	39 (29%)	6 (5%)	134

Dryness					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	123 (91%)	12 (9%)	0	0	135
Retin-A	119 (85%)	17 (12%)	4 (3%)	0	140
Week 2					
Adapalene	53 (41%)	64 (49%)	12 (9%)	2 (2%)	131
Retin-A	34 (26%)	66 (50%)	26 (20%)	6 (5%)	132
Week 4					
Adapalene	58 (45%)	60 (47%)	10 (8%)	1 (0.8%)	129
Retin-A	36 (28%)	75 (58%)	14 (11%)	4 (3%)	129
Week 8					
Adapalene	64 (53%)	48 (40%)	7 (6%)	2 (2%)	121
Retin-A	48 (38%)	64 (51%)	12 (10%)	1 (0.8%)	125
Week 12					
Adapalene	78 (66%)	39 (33%)	1 (0.8%)	0	118
Retin-A	70 (56%)	47 (38%)	7 (6%)	1 (0.8%)	125
Maximum					
Adapalene	28 (21%)	78 (56%)	20 (15%)	5 (4%)	131
Retin-A	8 (6%)	77 (58%)	41 (31%)	8 (6%)	134

Burning (after application)					
	None	Mild	Moderate	Severe	Total # pts
Week 2					
Adapalene	101 (77%)	23 (18%)	7 (5%)	0	131
Retin-A	82 (63%)	41 (31%)	7 (5%)	1 (0.8%)	131
Week 4					
Adapalene	107 (83%)	19 (15%)	2 (2%)	1 (0.8%)	129
Retin-A	100 (77%)	23 (18%)	7 (5%)	0	130
Week 8					
Adapalene	108 (89%)	11 (9%)	3 (3%)	0	122
Retin-A	106 (85%)	16 (13%)	3 (2%)	0	125
Week 12					
Adapalene	107 (91%)	11 (9%)	0	0	118
Retin-A	113 (90%)	10 (8%)	2 (2%)	0	125
Maximum					
Adapalene	84 (64%)	36 (28%)	10 (8%)	1 (0.8%)	131
Retin-A	65 (49%)	54 (40%)	14 (10%)	1 (0.7%)	134

Burning (persistent)					
	None	Mild	Moderate	Severe	Total # pts
Baseline					
Adapalene	132 (97%)	4 (3%)	0	0	136
Retin-A	133 (95%)	7 (5%)	0	0	140
Week 2					
Adapalene	118 (90%)	11 (8%)	2 (2%)	0	131
Retin-A	116 (89%)	7 (5%)	7 (5%)	1 (0.8%)	131
Week 4					
Adapalene	124 (96%)	4 (3%)	0	1 (0.8%)	129
Retin-A	119 (92%)	7 (5%)	2 (2%)	1 (0.8%)	129
Week 8					
Adapalene	114 (94%)	7 (6%)	1 (0.8%)	0	122
Retin-A	116 (94%)	6 (5%)	2 (2%)	0	124
Week 12					
Adapalene	117 (99%)	1 (0.8%)	0	0	118
Retin-A	122 (98%)	2 (2%)	1 (0.8%)	0	125
Maximum					
Adapalene	111 (85%)	16 (12%)	3 (2%)	1 (0.8%)	131
Retin-A	104 (78%)	19 (14%)	9 (7%)	2 (2%)	134

Other adverse events of the skin and appendages which were reported were as follows.

Adverse events		
	Adapalene cream	Retin-A cream
Acne flare	1	1
Alopecia	0	1
Dermatitis	0	1
Eczema	1	0
Edema of eyelid	2	0
Erythema	1	2
Erythema/skin discomfort	1	0
Erythema/edema eyelid	0	1
Skin irritation	4	4
Skin discomfort	0	1
Dry skin	1	3

Reviewer's comments: In summary, this was an investigator-blinded, multicenter comparison of Adapalene cream 0.1% and Retin-A cream 0.05% in 261 patients with mild and moderate acne, with applications once daily for 12 weeks. The effectiveness parameters were lesion counts for inflammatory and non-inflammatory lesions, total lesion counts, and an investigator's global evaluation.

The results showed that Retin-A cream 0.05% was significantly superior to Adapalene cream 0.1% at week 12 and at endpoint in the mean non-inflammatory lesion counts, the mean percent change in non-inflammatory lesion counts, the mean inflammatory lesion counts, the mean percent change in inflammatory lesion counts, the mean total lesion counts, and the mean percent change in total lesion counts. Retin-A cream was also significantly superior to Adapalene cream in the investigator's global evaluation at week 12.

Local adverse effects with Adapalene cream were mild to moderate erythema, dryness, and scaling in 60% to 70% of the patients, and mild to moderate burning in about one-third of the patients. Four cases of severe erythema, four cases of severe scaling, five cases of severe dryness, and one case of severe burning were reported. The local tolerance to Adapalene cream was somewhat better than that with Retin-A cream.

Labeling review: *The draft package insert for Differin Cream provided in the NDA differs in some areas from the insert which was approved for Differin Gel in 1996. The draft Differin Cream label is not annotated to specify the differences between the two inserts, and the sponsor has been requested to provide such an annotated insert. Review of the labeling, however, is deferred, as the application is not approvable.*

Summary and evaluation: *Differin cream 0.1% is a line extension of Differin solution 0.1% and Differin gel 0.1%. For a demonstration of the safety and effectiveness of a line extension product the current policy requirement is for either two studies which compare the product to its vehicle, or one three arm study which compares the product to its vehicle and to the original product formulation. For a demonstration of effectiveness, superiority to the vehicle and equivalence to the original formulation must be shown in the percentage of patients who are cleared or almost cleared in the investigator's global evaluation, and in the percentage reduction from baseline in two or three of the following: inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts.*

Two studies on the clinical safety and effectiveness are provided in the application. The first study was a double blind, randomized, parallel group, multicenter comparison of Differin cream 0.1% with the cream vehicle in 322 patients with mild and moderate acne. Applications of the test products were made once daily for 12 weeks. The efficacy parameters were facial lesion counts for comedones, papules, and pustules, and an investigator's global evaluation of the acne condition.

The results showed that Differin cream was significantly superior to the vehicle at week 12 and at endpoint in the mean non-inflammatory lesion counts, the mean percent change in non-inflammatory lesion counts, the mean total lesion counts, the mean percent change in total lesion counts, and the investigator's global evaluation. (The investigator's evaluation was not analyzed as the percent of patients that were cleared or almost cleared.) Differin cream was not significantly superior to the vehicle in the mean inflammatory lesion counts or the mean percent change in inflammatory lesion counts.

In a second study Differin cream 0.1% was compared to Retin-A cream 0.05% in the treatment of patients with mild and moderate acne. The results showed that Retin-A cream 0.05% was significantly superior to Differin cream 0.1% in the effect on all parameters, namely, the mean counts and the percent change in mean counts for inflammatory lesions, non-inflammatory lesions, and total lesion counts, and in the investigator's global evaluation.

Local adverse effects with Differin cream in the first study were mild to moderate erythema and dryness in about half of the patients, and mild to moderate scaling and burning in about one-third of the patients. One case of severe persistent erythema, and one case each of severe transient scaling, dryness, and burning were reported. Other adverse effects which were considered to be definitely related to Adapalene cream were acne flare in one and skin irritation in another patient. Effects which were felt to be possibly related to Adapalene cream were edema of the face in one, sunburn in three, contact dermatitis in two, and conjunctivitis in one patient.

In the second study local adverse effects with Differin cream were mild to moderate erythema, dryness, and scaling in 60% to 70% of the patients, and mild to moderate burning in about one-third of the patients. Four cases of severe erythema, four cases of severe scaling, five cases of severe dryness, and one case of severe burning were reported. The local tolerance to Adapalene cream was somewhat better than that with Retin-A cream.

Additional safety studies which were performed on Differin cream 0.1% included cumulative irritancy, contact sensitization, phototoxicity, and photosensitization. These showed little or no potential for contact sensitization, phototoxicity, or photosensitization under the test conditions. Significant irritation (erythema with edema and blistering) occurred in a few subjects under conditions of exaggerated exposure, but this would not be expected to occur under conditions of clinical usage.

Conclusions: The effectiveness of Differin cream has been demonstrated in one study in which it was compared to its vehicle. However, Differin cream was found to be inferior to Retin-A cream in a second study. The conclusion is that the sponsor has not provided an adequate demonstration of the effectiveness of Differin cream.

Recommendations: It is recommended that the application not be approved.

LSI

Phyllis A. Huene, M.D.

As above. When an active control comparison study is employed as a pivotal study, the test product must be shown to be noninferior to the active control AND the design and conduct must assure a difference detecting ability. The active control must be an approved product for the indication used according to the approved labeling.

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cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cintron
HFD-540/DeCamp
HFD-540/Jacobs