CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-748

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 28 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-748 **SUBMISSION DATE:** 3/9/2000
PRODUCT: Differin (adapalene) Cream, 0.1%
SPONSOR: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Fort Worth, Texas 76163
TYPE OF SUBMISSION: Amendment **REVIEWER:** Sue-Chih Lee, Ph.D.

Background

An approvable letter dated March 8, 2000 was issued to the sponsor for Differin Cream. The remaining issues pertain to labeling. This submission is the sponsor's response to the approvable letter.

Review

Sponsor's question:
Why the pharmacokinetic information from the multicenter safety and efficacy study was deleted from the FDA version of the Pharmacokinetics section of the labeling.

Reviewer's comment:
The multicenter safety and efficacy study was conducted using a different formulation than the market image in that the former contains [redacted] Whether this formulation difference will impact on the study outcome is not clear. In addition, only one blood sample per subject was collected in the study and there appears no records of dose, dosing area and sampling time for each individual making it impossible to interpret the data. Because of these reasons, the information was not included in the FDA proposed label.

Recommendation

The above comment should be communicated to the sponsor.

LSL 4/27/00
Sue-Chih Lee, Ph.D.
Pharmacokinetics Evaluation Branch III

RD/FT Initialed by Dennis Bashaw, Pharm.D. LSL

CC:
NDA 20-748
HFD-540 (Div. File)
HFD-540 (CSO/Cintron) comment faxed to sponsor on 4/28/00.
HFD-880 (Bashaw)
LSL

HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

JAN 28 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-748 **SUBMISSION DATES:** 09/07/99
PRODUCT: Differin (adapalene) Cream, 0.1% 01/21/00, 1/27/00
SPONSOR: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Fort Worth, Texas 76163
TYPE OF SUBMISSION: Amendment **REVIEWER:** Sue-Chih Lee, Ph.D.

I. BACKGROUND

Adapalene, a naphthoic acid derivative, possesses retinoid-like activities, i.e., modulation of cellular differentiation, keratinization and inflammatory processes. The proposed product, Differin Cream 0.1%, is intended for the treatment of acne vulgaris. This amendment is in response to the Not Approvable letter dated July 9, 1998, in which the sponsor was requested to conduct, among other studies, a multiple dose study in patients with large surface area of diseased skin using the to-be-marketed formulation (Formulation #CDP) to determine the maximal systemic absorption. Included in the submission was a study entitled "Pharmacokinetic Evaluation of Differin (adapalene cream) Cream, 0.1% Following Maximal Exposure with Multiple Applications in Subjects with Acne Vulgaris" (Protocol # 1.GUS.04.SPR.18036).

II. REVIEW

STUDY #1.GUS.04.SPR.18036: Pharmacokinetic Evaluation of Differin (adapalene cream) Cream, 0.1% Following Maximal Exposure with Multiple Applications in Subjects with Acne Vulgaris

INVESTIGATORS AND LOCATIONS:

OBJECTIVES:
To determine the maximal systemic absorption of adapalene following multiple topical applications of the cream formulation.

STUDY DESIGN:
This is a single-center study. Six acne patients (4M & 2F; age: 23.5±4.9 yrs.; wt: 69.5±12.8 kg) received treatment at the clinic with a 2-gram application (weighed and applied by study staff) of adapalene cream 0.1% to the facial area and the chest or back and/or shoulders (an area of approximately 1000 cm^2) once a day in the morning for five days. Subjects were allowed to wash their backs and chests 1-2 hours prior to application of test material while face was washed 10 minutes prior to the application of test material. All subjects were required to

have approximately 1000 cm^2 of acne involved skin. Blood samples were collected prior to morning dosing on Days 1, 2, 3, 4 and 5 and on Day 5 at 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours after the last application.

ASSAY:

Assay of adapalene in plasma samples was performed by Galderma in France. A [redacted] method with [redacted] was used. [redacted] of plasma was added an internal standard, which was then subject to [redacted], followed by extraction with [redacted]. The [redacted] for analysis. The validation results are as follows:

Linearity: [redacted] ng/mL ($r > 0.997$)
Precision (%CV): [redacted] (at 0.5, 1 and 2.5 ng/mL)
Accuracy: [redacted] (at 0.5, 1 and 2.5 ng/mL)
Stability: Acceptable after [redacted] at -20°C

The detection limit is [redacted] and the LOQ is [redacted] for a 2-mL sample. Note that some samples were received with quantities equal to 1.5 mL, consequently they were analyzed after dilution to 2 mL and the quantification limit for these samples were established at [redacted]

RESULTS:

The analysis results revealed that the concentration of adapalene was below quantifiable limit in all plasma samples (see the attached individual plasma concentrations), indicating a low systemic exposure of adapalene after 5 days of topical applications.

The sponsor stated that, of the 6 subjects enrolled in the study, 5 had reductions in acne count while one subject (#003) had slightly increased acne count on the face, back and chest at the end of the study. Acne grading was unchanged or reduced slightly for all subjects except Subject 002.

III. LABELING COMMENTS:

Pharmacokinetics: Absorption of adapalene from DIFFERIN Cream through human skin is low. In a pharmacokinetic study with six acne patients treated once daily for 5 days with 2 grams of DIFFERIN Cream applied to 1000 cm^2 of acne involved skin, there were no

[redacted]

IV. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is acceptable. Labeling comment should be conveyed to the sponsor.

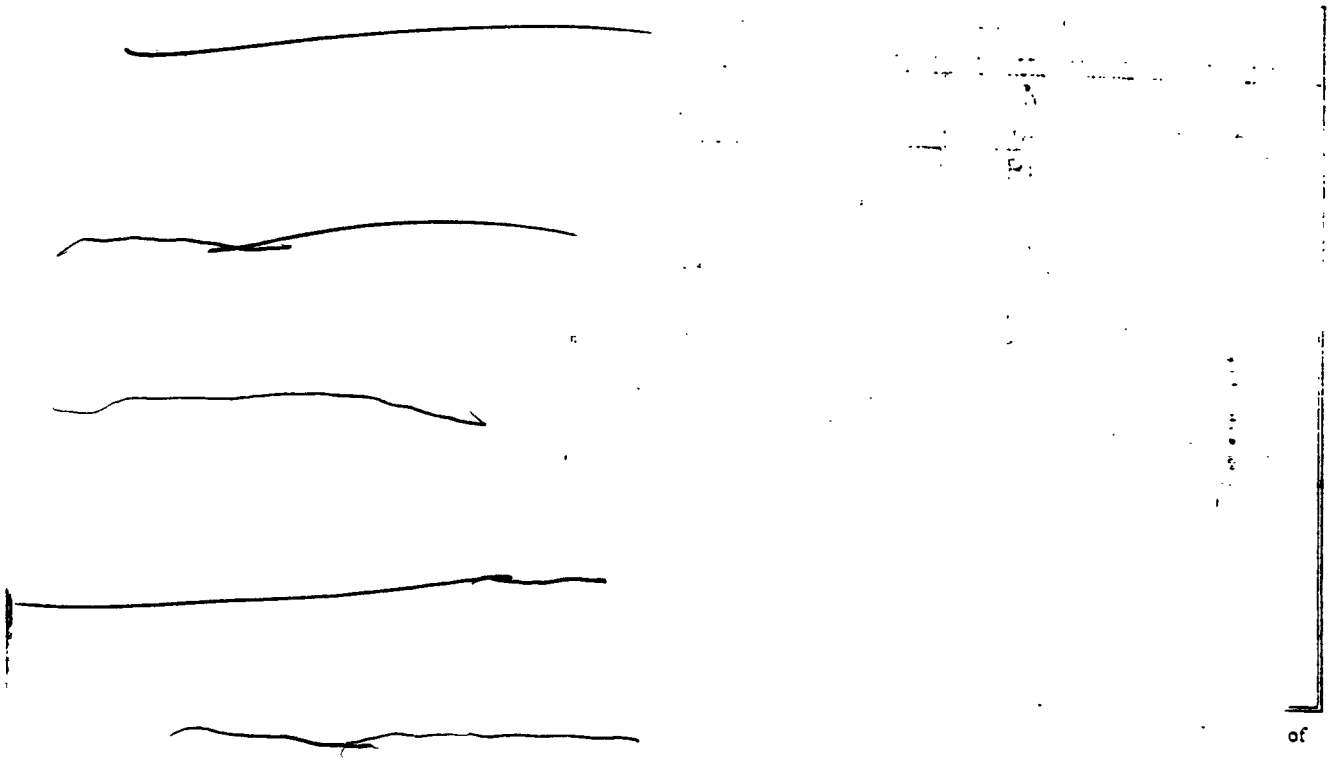
/S/ 1/28/2000

Sue-Chih Lee, Ph.D.
Pharmacokinetics Evaluation Branch III

RD Initialed by Dennis Bashaw, Pharm.D.
RD Initialed by Dennis Bashaw, Pharm.D. /S/ 1/28/00

CC:
NDA 20-748
HFD-540 (Div.File)
HFD-540 (CSO/Cintron)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

Attachment



of

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

FEB 27 1998

NDA: 20-748
PRODUCT: Differin (adapalene) Cream, 0.1%
SPONSOR: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Fort Worth, Texas 76163
TYPE OF SUBMISSION: Original NDA

SUBMISSION DATES: 07/16/97
12/03/97

REVIEWER: Sue-Chih Lee, Ph.D.

I. SYNOPSIS:

Adapalene, a naphthoic acid derivative, possesses retinoid-like activities, i.e., modulation of cellular differentiation, keratinization and inflammatory processes. The proposed product, Differin Cream 0.1%, is intended for the treatment of acne vulgaris. The adapalene solution and gel dosage forms were approved in 1996. The sponsor indicated that this formulation incorporates emollient and moisturizing characteristics and may be more appealing to a certain group of patients.

The sponsor submitted 3 studies (one PK, one skin stripping and one in vitro studies) for the cream dosage form but none used the to-be-marketed formulation. The PK information was basically plasma adapalene concentrations obtained during a clinical trial without information regarding dose, dosing area and sampling time. Several other studies with gel or oral dosage form were also provided. Some of these studies were conducted in an attempt to examine possible teratogenic risk and distribution of adapalene into adipose tissues. The study assessing the teratogenic risk has not been completed. Very low levels (range: undetectable to 5.5 ng/mL) of adapalene were found in adipose tissues. However, a drawback with these studies has been that healthy subjects rather than patients were used in the study. After one single oral dose of 10 mg or 25 mg, the half-life of adapalene was determined to be approximately 13 hours.

A study to determine the systemic absorption of adapalene from the to-be marketed cream formulation has not been conducted. Because of this, a teleconference was conducted on September 29, 1997 between the Agency and sponsor, in which we requested that the sponsor conduct a multiple-dose study in patients with large surface area of the involved skin using the to-be-marketed formulation. In their response dated December 3, 1997, the sponsor considered that they had adequate information to waive such a study. However, the response is considered not acceptable. (See Appendix 1: Memo by Dr. Dennis Bashaw.) At the present time, we do not have evidence to indicte that the extent of percutaneous absorption for a cream formulation is always less than that of a gel. Nor do we have evidence to indicate a correlation between the in vitro skin penetration and in vivo percutaneous absorption.

II. FORMULATION AND DOSAGE REGIMEN:

The cream is to be applied to affected areas of the skin once daily at nighttime. Several

formulations were tested during the drug development phases. The to-be-marketed formulation is designated as Formulation #CDP.

	Commercial Drug Product (Proposed Formulation)	Adapalene Cream Investigational Formulations				
Formulation Code Strength - w/w%	CDP 0.1	C1 0.1	C2 0.1	C3 0.1	C4 0.1	C5
INGREDIENTS = w/w%						
ACTIVE INGREDIENT: Adapalene	0.1	0.1[1]	0.1[2]	0.1	0.1	
INACTIVE INGREDIENTS: Carbomer 934P, Carbomer 934P Propylparaben, NF Phenoxyethanol, BP Methylparaben, NF Edetate Disodium, USP Glycerin, USP PEG-20 Methyl Glucose Sesquistearate Methyl Glucose Sesquistearate Cyclomethicone Squalane, NF Trolamine, NF Purified Water						
Lot (Batch) No. - used in clinical and human biopharmaceutic studies		ELDP-2	AKEI-0054	524.827/F1 [^{14}C]-524.827/R11	553.109/2F1	524.894/E1

1 Includes excess to compensate for loss during production. Subsequent evaluation of batch records and analysis revealed no significant losses occurred, thus the excess was dropped from the proposed commercial formulation.

2 Includes excess to compensate for loss during production.

	Adapalene Cream Investigational Formulations				Cream Vehicle Formulations	
Formulation Code Strength - w/w%	C6	C7	C8	C9	CV1	CV2
INGREDIENTS = w/w%						
ACTIVE INGREDIENT: Adapalene						
INACTIVE INGREDIENTS: Carbomer 934P, Carbomer 934P Propylparaben, NF Phenoxyethanol, Methylparaben, NF Edetate Disodium, USP Glycerin, USP PEG-20 Methyl Glucose Sesquistearate Methyl Glucose Sesquistearate Cyclomethicone Squalane, NF Trolamine, NF Purified Water						
Lot (Batch) No. - used in clinical and human biopharmaceutic studies	524.865/E2	553.113/2F1	524.864/F1	553.113/2F1	524.827/MF1	ELDN-2

III. PK STUDIES:

Besides the various studies previously submitted to the gel and solution NDAs, the following new studies are provided in the Clinical Pharmacology and Human Pharmacokinetic section:

Cream formulations:

a) PK study using cream formulation C2 (Clinical study #CR 90087).

b) Tape-stripping study comparing three strengths of adapalene in a cream formulation (Formulation C4) (Study #1.CG.03.SRE.2042)

Gel formulation:

c) PK study with 0.1% gel to examine adapalene distribution into adipose tissue (Study #1.CG.03.SRE.2019)

d) PK study using — adapalene in 0.1% gel to characterize the extent of absorption (Study #1.CG.03.SRE.4529)

e) Absorption and Excretion under maximized exposure conditions using 0.1% gel (Study #1.CG.03.SRE.2005)

Oral administration:

f) Oral ADME study with single dose of 10 mg or 25 mg of adapalene in sesame oil (Study #1.CG.03.SRE.4515)

IV. IN VITRO STUDY:

A brief summary of an in vitro percutaneous absorption study (PK Study #91005) comparing three dosage forms (lotion, gel and cream) was provided. The formulation for the cream was not indicated.

V. COMMENTS:

1. The only PK study that assess the systemic exposure to adapalene after topical application of the cream dosage form was conducted as part of a clinical study (Clinical study #CR 90087). The formulation used (#C2) differs from the proposed formulation in that it contains ———— Whether this formulation difference will impact on the study outcome is not clear. Further, only one blood sample per subject was collected in the study and there appears no records of dose, dosing area and sampling time for each individual.

   The sponsor is required to conduct a multiple-dose study in patients with large surface area of the involved skin using the to-be-marketed cream formulation to determine the maximal systemic exposure. A radio-labeled study may be conducted for this purpose. This study cannot be waived based on the existing information for the gel dosage form because we do not have evidence to indicate that the extent of percutaneous absorption for a cream formulation is always less than that of a gel, nor do we have evidence to indicate a correlation between the in vitro skin penetration and in vivo percutaneous absorption results.

2. The formulation used in tape-stripping study (C4) contains — carbomer while the

proposed formulation has [redacted] carbomer. This difference may affect the study results.

3. The new studies with topical gel formulation were mostly conducted in healthy subjects. In the study to assess the adapalene distribution into the adipose tissue, the inclusion criteria allows healthy subjects to participate in the study. It is unclear how many subjects in this study had acne lesions, and of those subjects with acne, it is not known how much surface area was involved. Because the diseased skin may increase the systemic absorption, studies in patients with maximal surface area of the involved skin are most informative.

4. Regarding the formulations used in clinical trials (Formulations C1 and C2):
#C1 is identical to the proposed formulation except that it contains : [redacted] overage of the active ingredient. This is acceptable.
#C2 differs from the proposed formulation in that the former contains [redacted]
Whether this difference will result in different clinical outcome is not clear.

VI. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is not acceptable. However, if the Division of Dermatological and Dental Drug Products determines that there is sufficient safety data in the NDA and that the benefit outweighs the risk, the pharmacokinetic study as described under Comment #1 may be conducted as a Phase IV commitment. Comments #1, 2 and 3 should be conveyed to the sponsor.

[redacted]

Sue-Chih Lee, Ph.D.
Pharmacokinetics Evaluation Branch III

RD Initialed by Dennis Bashaw, Pharm.D. _
RD Initialed by Dennis Bashaw, Pharm.D. _ [redacted]

CC:
NDA 20-748
HFD-540 (Div.File)
HFD-540 (CSO/Cintron)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

TABLE OF CONTENTS:

APPENDIX 2: INDIVIDUAL STUDIES

1) Study CR 90087:

Clinical Safety and Efficacy Evaluation of 0.1% CD 271 Cream Versus 0.05% Retin-A Cream (Vol. 1.13, p. 58)

INVESTIGATORS AND LOCATIONS:

OBJECTIVES:
The primary objective is to compare the safety and efficacy of Differin Cream 0.1% versus Retin-A cream 0.05% in a 12-week treatment of acne vulgaris. On the side, plasma samples were collected from several patients for the determination of adapalene concentration.

FORMULATION: #C2
The formulation is similar to the proposed formulation except that it contains

STUDY DESIGN:
This is a multi-center study. A total of 277 patients with mild to moderate acne vulgaris were entered into the study and were randomized to receive either 0.1% Differin Cream or 0.05% Retin-A Cream. Forty-eight patients had one blood sample drawn at the end of the treatment. Of these patients, 24 were under treatment with Differin Cream and 24 under Retin-A cream treatment.

ASSAY: Plasma was analyzed by for adapalene content before (Center #1 only) and after using a The detection limit is ng/mL and the LOQ is

RESULTS:
Sixteen samples were analyzed before and all except Patient 129 had no detectable adapalene concentrations. Samples (n=48) from all study centers were analyzed post . Forty-four samples were found to be below the detection limit and four samples (patients 102, 109, 114 and 115) had detectable adapalene concentrations but were still lower than the LOQ. These 4 samples had no detectable adapalene concentrations before However, after decoding, it was found that Patients 109, 115 and 129 had been treated with Retin-A.

COMMENTS:
1. The adapalene cream formulation used in the study is not the to-be-marketed formulation.
2. All plasma samples had adapalene concentrations below the limit of quantitation. However, no information was given regarding the dose, dosing surface area and blood sampling time for each individual patient, which makes any judgment of the data impossible.

2) **Study 1.CG.03.SRE.2042:**

Assessment of the Dose Relationship of Adapalene by its Quantification in the Stratum corneum after a Single Topical Application of Adapalene 0.1%, — and — Creams in Healthy Volunteers (Vol. 1.13, p. 68)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

1) To study the dose-effect relationship of adapalene by its quantification in the stratum corneum using the stripping method after a single application of three cream formulations containing 0.1%, — and — of adapalene (w/w).
2) To compare two methods for measuring stratum corneum uptake: stripping of the stratum corneum and extraction of the drug by a turbine apparatus.
3) To determine the adapalene concentration in the cream formulation which is equivalent to a 0.1% gel formulation in terms of stratum corneum uptake.

DOSAGE FORMS:

Adapalene creams, 0.1%, — and —; Formulation #C4
Adapalene gel, 0.1% (reference product)

STUDY DESIGN:

This is a randomized, open study in twelve healthy subjects (3M, 9F; age: 20-50 yrs.). A single application of adapalene cream or gel was given to each subject without occlusion and was left on the skin for an hour. Each formulation was applied simultaneously on both arms for the two methods of stratum corneum sampling and in the same sequence.

Application:

Four sites were delineated symmetrically on each forearm of each volunteer. The sites located on the right forearm were used for the stripping method while those located on the left arm were used for the turbine (extraction) method. The sites of application for the four formulations were assigned using a randomization procedure identical for both arms. A micropipette was used to apply 25 mg of each formulation to the center of a 5.7 cm^2 hole previously cut in a self adhesive label applied to the skin (about 4.4 mg/cm^2). The formulations were rubbed in with a gloved finger and each application site was massaged for 1 minute.

Drug removal:

One hour after application, excess formulation was removed with a paper tissue and with one tape strip.

Stratum corneum sampling:

A. Stripping method

Ten tape-strips were successively applied with pressure on each of the four sites on the right arm. They were pooled into two groups of five placed in pre-labeled vials at 4°C until

analysis. Five tape-strips were performed on an untreated area to provide for controls.

B. Extraction method

The apparatus, is composed of a able to receive the extraction solvent and containing a for agitating liquids. The extraction solvent contains: . To extract adapalene from skin, , of the extraction solvent was introduced into this apparatus with syringe. The apparatus, with the agitation system turned on, was then applied with slight pressure in a vertical position for exactly on a skin surface area of on each of the four tested sites. An untreated area was extracted to provide for controls. The method has not been validated.

ASSAY:

The quantification of adapalene was performed using the The assay for tape-strips was validated but not the assay for the extraction samples.
Limit of quantitation: (Stripping Method)

DATA ANALYSIS:

The quantities of adapalene in tape strips or extraction solvent was subject to ANOVA analysis with subject, zone and product as factors.

RESULTS:

After one-hour application, the quantity of adapalene present in the stratum corneum is proportional to the concentration in the cream formulation (Table 1 & Figure 1). The 90% confidence interval for the slope is 0.712-1.022 for the tape stripping method, indicating a significant dose (strength)-effect relationship. There was no significant difference between the 0.1% cream and 0.1% gel formulations. The two methods for measuring the skin uptake of adapalene gave similar results but the intersubject variability was higher for the exploratory turbine method than for the reference stripping method. The adapalene concentration in the cream formulation equivalent in terms of stratum corneum uptake to a 0.1% concentration of adapalene in the gel is close to 0.1% with the two methods: namely 0.09% with the strippings method and 0.13% with the turbine method.

COMMENTS:

1. The cream formulations contain carbomer vs. carbomer in the proposed formulation.
2. To determine the quantity of adapalene in the stratum corneum, the formulation was removed from the application site one hour after application. The application site was then wiped with tissue and tape-stripped once before further tape-stripping or extraction. The procedure to remove the drug on the skin surface is very important. The adequacy of the procedure presented in this study is unclear. Generally, it is considered more appropriate to discard the first two tape-strippings to adequately remove the surface excess of the drug. Because of this, the results have some uncertainties.
3. The ANOVA results regarding the test site (zone), subject and formulation for the overall data were not provided.

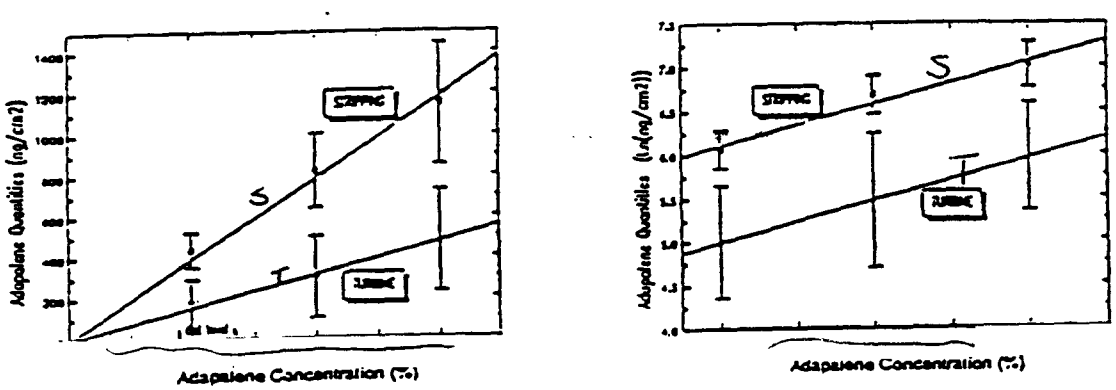
TABLE I:

ADAPALENE QUANTITIES MEASURED IN THE STRATUM CORNEUM BY METHODS OF STRIPPING AND TURBINE, expressed in ng / cm^2 and $Log(ng/cm^2)$ respectively

		MEAN	STD
Stripping	0.1 % cream	440.09	85.80
	— cream	822.72	181.14
	— cream	1147.57	296.07
	0.1 % gel	402.81	175.22
Turbine	0.1 % cream	179.92	116.01
	— cream	304.36	199.59
	— cream	476.89	352.31
	0.1 % gel	220.83	143.20
Ln(Stripping)	0.1 % cream	6.07	0.22
	— cream	6.69	0.22
	— cream	7.02	0.26
	0.1 % gel	5.92	0.39
Ln(Turbine)	0.1 % cream	5.00	0.65
	— cream	5.47	0.78
	— cream	5.97	0.62
	0.1 % gel	5.15	0.80

FIGURE I

DOSE EFFECT RELATIONSHIP OF ADAPALENE



S: Stripping method ; T: Turbine method

3) **Study PK 91005:**

Comparison of the In Vitro Liberation-Penetration of CD271 from Three 0.1% Formulations on Human Dermatomed Skin (Vol. 1.15, p. 753)

(Note: A brief summary is provided in this NDA. The study was previously submitted to NDAs 20-338 and 20-380.)

EXPERIMENTAL:

The in vitro penetration of adapalene from three different formulations (lotion, gel and cream) was investigated using human dermatomed skin from 6 different donors.

Apparatus: Flow-through diffusion cells
Receptor fluid: aqueous solution containing a surfactant.
Flow rate/cell volume ratio: 1 (per minute?)

Twelve cells were used for each formulation. For each cell, 20 μL of formulation was applied onto skin surface (2 cm^2) and left on the skin for 15 hours.

RESULTS:

The distribution of radioactivity after 15 hours was presented in the table below. The percent of adapalene present in the receptor fluid were low for all three formulations (——, —— and —— for the lotion, gel and cream formulations, respectively). The gel formulation showed the highest penetration of adapalene into the skin (6.7% for gel vs. 1.8% for both the lotion and cream formulations).

COMMENTS:

1. The cream formulation was not indicated but it is not expected to be the proposed formulation.
2. In this study, the gel formulation gave a higher adapalene concentration in the skin than the cream formulation 15 hours after application of the formulations onto the dermatomed skin. Another study showed comparable adapalene concentration in the stratum corneum for the gel and cream formulations one hour after application. It would have been more informative to sample the receptor fluid more frequently during the 15-hour experiment.

RESULTS.

FORMULATIONS	LOTION	GEL	CREAM
Surface excess	91.3 ± 8.8	101 ± 18	89.9 ± 12
Epidermis	0.6 ± 0.2	2.2 ± 1.2	1.1 ± 1.3
Dermis	1.2 ± 0.9	4.5 ± 3.8	0.7 ± 0.5
Total skin	1.8 ± 0.9	6.7 ± 4.9	1.8 ± 0.9
Receptor fluid	0.12	0.01	0.03
Mass balance	93.2 ± 8.6	110.6 ± 17.1	92.0 ± 12.8

4) **Study 1.CG.03.SRE.2019:** (Note: This is a new study with gel formulation.)

Assessment of Adapalene Distribution in Adipose Tissue After Repeated Topical Applications of 0.1% Gel in Female Volunteers (Vol. 1.13, p. 173)

INVESTIGATOR AND LOCATION:

OBJECTIVES:
To assess the distribution of adapalene in the adipose tissue of women after repeated topical application of a 0.1% gel for three months.

FORMULATION: 0.1% Adapalene Gel; No cream formulation was used in this study.

STUDY DESIGN:
This is an open study in 6 female subjects (age: 22-36 yrs; wt: 48-65 kg) with healthy or acne skin. Two grams of adapalene gel 0.1% was applied topically once a day for 3 months by the subjects themselves on the face, upper chest and upper back.

Sample collections -
Blood and adipose tissue samples were collected prior to first application, at 3 months (12 hours after last application) and 4 months after first dose. Adipose tissues were collected from abdominal area, gluteal folds and hips under local anesthesia.

ASSAY: Samples were subject to either
samples) hydrolysis before assay by Galderma using
detection to determine total adapalene (free plus conjugated). The validation data summary is provided. Linearity range: (plasma samples)
(fatty tissue)

RESULTS:
The mean quantity of gel applied was 2.11±0.26 g/day. All plasma samples had adapalene concentrations below the detection limit ( ). Of all the adipose tissues analyzed, only 3 samples had detectable adapalene concentrations (/g, respectively). These were samples collected from the three different sites of one subject (subject #1) at the end of the three-month treatment.

COMMENT:
The results indicated very low plasma or adipose tissue concentrations after 3 months of topical application of adapalene gel. However, the inclusion criteria allows healthy subjects to participate in the study. It is unclear how many subjects in this study had acne lesions, and of those subjects with acne, it is not known how much surface area was involved. (Note: No cream formulation was used in this study.)

5) Study 1.CG.03.SRE.4529: (Note: This is a new study with the gel formulation.)

The Excretion and Plasma Kinetics of Radioactivity in Man Following Topical Administration of 0.1% [^{14}C]-Adapalene Gel

INVESTIGATOR AND LOCATION:

OBJECTIVE:
To investigate the rate and routes of excretion and the plasma kinetics of total radioactivity following topical administration of [redacted] Adapalene 0.1% gel to 8 male volunteers

FORMULATION:
[redacted] Adapalene 0.1% gel and non-radiolabeled adapalene gel

STUDY DESIGN:
Nine healthy male subjects (age: 44±6.5 yrs; wt: 76.7 ±8.2 kg) participated in the study. Five subjects (Group 1) received non-radiolabeled adapalene gel (approximately 0.5 g) once a day for 14 days as a pre-treatment. On the 15th day, 4 of the subjects received one single application of radio-labeled dose. Another 4 subjects (Group 2) received a single application of the radiolabeled gel (ca 0.5 g).

The dose was applied to a clearly defined area (10 cm x 25 cm) on the back of each subject. No clothing was worn over the dosed area for 6 hrs and care was taken to avoid the area coming in contact with anything during this time. Subjects remained fasted for 3 ½ hours after dosing. At 6 hrs post-dose, a protective gauze dressing was placed over the dosing area and each subject put on a T-shirt.

At 24 hrs post-dose, the dressing was removed and the dosing site was washed 4 times with cotton swab soaked in a mixture of [redacted] followed by a dry cotton swab. The area was dried and covered with a fresh dressing. Every 24 hours for up to 168 hours post-dose, the dressing was removed, the site was wiped once with the swab mixture and a new dressing was applied. At 336 hrs post-dose, skin stripping (15 strips) was performed at the site of application and the chest.

Sample collections -
Blood samples: Samples were collected at 0, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, 144, 168 and 336 hrs post-dose.

Urine samples: Samples were collected for the following intervals:
0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hr

Fecal samples: Samples were collected every 24 hours for 14 days.

ASSAY: All samples were assayed by [redacted] after sample preparations.

Comment: The assay validation results were not provided.

RESULTS:
Levels of radioactivity in all plasma, urine or fecal samples were below the limit of quantitation.

The recovery at 24 hr post-dose was [redacted] of the applied dose. Approximately [redacted] of the dose was recovered in the 0-24 hr post-dose gauze dressings, [redacted] was recovered from the 0-24 hr dose site swabs and [redacted] was from the T-shirt.

A further [redacted] of the dose was recovered in the 24-48 hr post-dose dressings, dose site and T-shirts. At 168 hr post-dose, the total recovery ranged from [redacted] of the applied dose.

The radioactivity in the skin stripping samples collected at 336 hours post-dose was below the limit of quantitation.

COMMENTS:
The results indicated very little radioactivity (or adapalene) was absorbed through the skin after topical application of the gel formulation. However, this study was conducted in healthy male subjects.

6) **Study 1.CG.03.SRE.2005:** (Note: This is a new study with the gel formulation.)

Assessment of the Maximized Absorption of Adapalene and Adapalene Metabolites After Topical Application - Assessment of the Embryotoxicity Potential (Vol. 1.14, p. 468)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

1) To quantitate adapalene in blood (plasma and erythrocytes), in feces and in the stratum corneum after topical application under maximized conditions.
2) to quantitate metabolites in plasma.
3) To assess the embryotoxicity potential of adapalene by the measure of the teratogenic activity of blood extracts in an in-vitro embryotoxicity model

FORMULATION: Adapalene gel, 0.1%
Gel vehicle (placebo)

STUDY DESIGN:

Six healthy male subjects (age: 18-30 yrs.; wt: 55-90 kg) participated in the study. Five subjects received adapalene gel while one subject served as a control. Approximately thirty grams (mean: 27.82±0.61 g/day) of the test article was applied once daily in the morning for 7 days to the back, chest, arms and legs (1.8 m^2) by the subjects themselves under supervision. (Application to the back was conducted by the nurse.)

Sample collections -
Blood samples: pre-dose, and at 12-hour intervals on Days 1, 2, 7 and 8, and once daily on Days 3, 5, 9, 10, 14 and 21. Additional serum samples for in vitro embryotoxicity evaluation were taken once daily on Days -1, 7, 8 and 21.

Urine samples: not collected

Fecal samples: collected over 24-hour intervals just prior to treatment, throughout treatment and for a further 14 days after treatment.

Stratum corneum strips: Samples of stratum corneum were obtained by stripping 8 different sites of the volunteer's back on Days -1, 8, 9, 10, 11, 12, 13, 14 and 21. Fifteen stripping was performed at each site and 5 strippings were pooled together for analysis (3 pools from each site).

ASSAY:

All samples except the stratum corneum strippings were subject to prior to analysis to measure total adapalene levels. A was used.

RESULTS:

Plasma levels of adapalene (Table 1) were below the detection limit (~~~~) in all samples with the exception of 2 quantifiable levels of ~~ and ~~ in subjects #3 and #4 on Days 1 and 3, respectively, and four trace levels (0.15 ≤trace<0.25 ng/mL) in subjects 4, 5, 6 and 3 on Days 1, 2, 2 and 5, respectively. Erythrocyte analysis is ongoing.

The level of adapalene in the tape-stripped samples of stratum corneum taken 24 hours after the last application (Day 8) ranged from ~~ (mean: 557±339 ng/cm^2). No detectable levels (≤25 ng per pool of 5 strips) were found in samples taken 5 days after the last application (Table 2).

Adapalene was first detected in Day 2/3 fecal samples in all subjects treated with adapalene, except for subject #4 who had detectable level in the Day ½ fecal samples (Table 3). The quantities of fecal adapalene increased until Day 5/6 and was present in all of the subsequent fecal samples collected during the treatment period. No adapalene could be detected in the fecal samples after 9th day following the last application. After 7 days of application, the mean quantities of adapalene excreted in the feces was 15.14 ±6.66 μg (range: ~~ μg), which is equivalent to approximately 0.008% of the applied dose.

COMMENTS:

1. The sponsor did not describe how embryotoxicity will be assessed. The study has not been completed. Embryotoxicological assessment is still ongoing and the adapalene levels in erythrocytes has not been determined.
2. The study used a high dose (30 g of gel per day). The results indicated very low adapalene levels in plasma. However, the study was conducted in healthy subjects.
3. The fecal samples gave some indication about systemic absorption. These values, however, do not represent total absorption since not all metabolites are taken into account. Besides, renal excretion was not accounted for.

Table 1 : Plasma levels of ADAPALENE (ng mL^{-1}) after ~~

SAMPLE PERIOD Days	Hours	VOLUNTEER N° 1	2	3	4	5	6
D-1	9 H						
D1	9 H						
D1	21 H						
D2	9 H						
D2	21 H						
D3	9 H						
D5	9 H						
D7	9 H						
D7	21 H						
D8	9 H						
D8	21 H						
D9	9 H						
D10	9 H						
D14	9 H						
D21	9 H						

ILD = inferior to the limit of detection ~~
T = traces (0.15 ng.mL^{-1} ≤ T < 0.25 ng.mL^{-1})

Table 2 : Levels of adapalene in stratum corneum
(expressed in ng/5.7 cm^2)

Sampling Time	Volunteers 1	2	3	4	5	6
D-1						
D8						
D9						
D10						
D11						
D12						
D13						
D14						
D21						

The stratum corneum content expressed in ng per cm^2, 24 hours after treatment cessation (D8) is the following:

Vol. 1	Vol. 2	Vol. 3	Vol. 4	Vol. 5	Vol. 6	Mean ± Stdev
						557 ± 339

Table 3 : Fecal levels of Adapalene (ng)
after

Sampling Time	Volunteers 1	2	3	4	5	6
D-1/1						
D1/2						
D2/3						
D3/4						
D4/5						
D5/6						
D6/7						
D7/8						
D8/9						
D9/10						
D10/11						
D11/12						
D12/13						
D13/14						
D14/15						
D15/16						
D16/17						
D17/18						
D18/19						
D19/20						
D20/21						
Total amount (ug)	ILD	5.99	15.71	24.31	16.95	12.74

15.14 ± 6.66

NS = no sample received
ILD = inferior to the limit of detection/quantification : ——— of dry feces)

7) **Study 1.CG.03.SRE.4515:**

A Single Dose Oral Administration of 10 and 25 mg of Adapalene to Healthy Male Volunteers: Clinical Tolerance and Plasma Pharmacokinetics (Vol. 1.15, p. 592)

INVESTIGATOR AND LOCATION:

OBJECTIVES:
1) To investigate the plasma kinetics and in particular to determine the terminal half-life of adapalene after a single oral administration in man.
2) To assess the safety of oral administration of adapalene in healthy human volunteers.

FORMULATION:
Adapalene (10 or 25 mg) suspended in 5 mL of sesame oil.
Lactose suspension as placebo

STUDY DESIGN:
This is a randomized, placebo-controlled, single rising dose study. Two groups (each of 6) of healthy male subjects (age: 18-35 yrs.; wt: 64.8-101.8 kg) were dosed immediately before breakfast in a randomized fashion (five active and 1 placebo per group) with 10 and 25 mg of adapalene, respectively.

Sample collections -
Blood samples: collected pre-dose, and at 1, 2, 3, 4, 6, 8, 16, 24, 48, 96 and 168 hours after dosing.

ASSAY:
Samples were subject to [redacted] is before analysis using [redacted] detection. The detection limit was [redacted] and the limit of quantification was [redacted].

DATA ANALYSIS: No information is given.

RESULTS:
After a single 10 mg oral dose, the mean peak plasma concentration was 60.2 $\pm$11.4 ng/mL and the mean AUC was 978 $\pm$249 ng-hr/mL. Following a 25 mg dose, the mean peak plasma concentration was 171$\pm$50 ng/mL and the mean AUC was 2232$\pm$603 ng-hr/mL. Tmax was around 4 hours post-dose and the half-life was approximately 13 hours.

Safety: All the physiological, hematological and biochemical measurements were within clinically acceptable limits. The oral doses were well tolerated. There were 3 adverse events reported for the 10 mg dose, but no adverse events were reported for the 25 mg dose.

COMMENT:
The information regarding data analysis is not provided. All AUC values presented in the

table were slightly lower than those calculated by this reviewer. However, this does not impact on the decision for this NDA. The only important information given by this study as related to the proposed product is the terminal half-life of adapalene, which is approximately 13 hours after one single oral dose. The determination of half-life would have been more accurate if blood samples were taken at 72 hrs post-dose as well.

Table . - 10 mg administration

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Arithmetic mean
Cmax ng.mL^{-1}						60.2 ± 11.4
Tmax Hrs						4 ± 1.2
AUC Hr.ng.mL^{-1}						979.6 ± 249.4
$T_{1/2}$ elim. Hrs						13.9 ± 2.9

Table - 25 mg administration

	Subject 7	Subject 9	Subject 10	Subject 11	Subject 12	
Cmax ng.mL^{-1}						171 ± 50.4
Tmax Hrs						6 ± 5.6
AUC Hr.ng.mL^{-1}						2232 ± 603
$T_{1/2}$ elim. Hrs						12.8 ± 2.9

Study samples

In all tables, results are expressed in ng of adapalene per mL of plasma. Results outside the highest calibration curve limit (> 2.5 ng.mL^{-1}) have been diluted before sample processing.

Table 1- 10 mg administration

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
Predose						
1 hour						
2 hours						
3 hours						
4 hours						
6 hours						
8 hours						
16 hour						
24 hour						
48 hour						
96 hour						
168 hours						

Table 2- 25 mg administration

	Subject 7	Subject 8	Subject 9	Subject 10	Subject 11	Subject 12
Predose						
1 hour						
2 hours						
3 hours						
4 hours						
6 hours						
8 hours						
16 hours						
24 hours						
48 hours						
96 hours						
168 hours						

B.D.
0.15 ng.mL^{-1} ≤ Tr.< 0.25 ng.mL^{-1}
M.S. missing sample

MAY 12 2000

TEAM LEADER MEMO

To: Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540

From: Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540

Date: May 12, 2000.

Re: NDA 20-748, Differin (adapalene) Cream, 0.1%
Submissions dated: 3/9/00, 4/28/00

Comments on Sponsor's proposed labeling submitted on 4/28/00:

The pharmacology and toxicology portion of the labeling should remain the same as transmitted in the approvable letter dated 3/8/00 with the following exceptions:

The doses in the carcinogenicity studies in mice should be revised to match the numbers in the Sponsor's version and the multiple of human exposure should change to 4 (from 5) in the following sentence. The first sentence in the carcinogenesis section should now read –"conducted in mice at topical doses of 0.4, 1.3, and 4 mg/kg " The second sentence should read, "

Per the CDER policy, doses are compared to human doses on a mg/m2 basis. The assessment of a clinical dose of 5 g per day is considered appropriate and thus calculations are based on 5 g.

Abby Jacobs, Ph.D., Pharm/Tox Team Leader, HFD-540

cc:

Original NDA 20-748
HFD-540/DivFile
HFD-540/Wilkin
HFD-540/Mainigi
HFD-540/Jacobs
HFD-540/Cintron