CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-753

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA	21-753
Submission Date	3/31/2004, 7/12/2004
Brand Name	Differin®
Generic Name	Adapalene
Reviewer	Lei Zhang, Ph.D.
Team Leader	Raman K Baweja, Ph.D.
OCPB Division	DPE III
OND Division	DDDDP (HFD-540)
Applicant	Galderma Laboratories
Relevant IND	IND 61,085
Type of Submission; Code	505 (b)(1); 3S
Formulation; Strength(s)	Gel; 0.3%
Indication	Treatment of acne vulgaris

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1 EXECUTIVE SUMMARY

Adapalene is a naphthoic acid derivative with retinoid activity that is used as an anti-acne agent. It acts on retinoid receptors. The subject of this application, adapalene gel (0.3%), is the fourth

drug product of adapalene developed by the Sponsor and represents a higher strength dosage form of an approved product. NDAs for adapalene 0.1% solution (NDA 20-338) and adapalene 0.1% gel (NDA 20-380) were approved on May 31, 1996. Adapalene 0.1% cream (NDA 20-748) was approved on May 26, 2000. All these dosage forms of adapalene are indicated for once daily application at nighttime in the topical treatment of acne vulgaris. A higher concentration of adapalene than 0.1% may provide additional therapeutic benefit for acne patients and also provide for an alternative to adjust treatment according to clinical response.

To meet the Clinical Pharmacology and Biopharmaceutics requirements for this NDA, the sponsor submitted a total of 9 *in vitro* and *in vivo* studies and referenced 4 study reports submitted for the earlier NDA 20-380 (0.1% gel). These studies include *in vivo* PK, skin stripping, permeation and metabolism studies.

For this application, one *in vivo* PK study (RD.03.SRE.2690) is considered pivotal. The study evaluated plasma levels of adapalene on Day 10 in 16 patients—9 males and 7 females (19-30 years) with acne vulgaris. Application was to the face, chest and back with the to-be-marketed formulation (2 g adapalene 0.3% gel/day). Adapalene is detectable in 15 out of 16 patients (LOQ 0.1 ng/mL). C_{max} on Day 10 was 0.553 ± 0.466 ng/mL and AUC(0-24) was 8.37 ± 8.46 ng*h/mL. The maximum C_{max} and AUC(0-24) were 2 ng/mL and 36.1 ng*h/mL, respectively observed in a female subject.

A total of 1,441 subjects have been treated with adapalene 0.3%, gel. In the pivotal Phase 3 clinical trial (Study RD.06.SRE.18081) that was conducted in patients 12 to 52 years of age with acne vulgaris who applied the medication once daily in the evening for 12 weeks, adapalene 0.3% gel (N=227) was significantly more effective than its vehicle (N=120) based on success rate and all lesion counts. However, it was not superior to adapalene 0.1% gel. In terms of local safety, 0.3% gel is more irritable than the 0.1% gel.

Mean daily dose used in the three 12 week Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673) was approximately 0.6 to 0.9 g/day.

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, the Sponsor has evaluated systemic exposure of adapalene in patients following application of 2 g of adapalene 0.3%, gel per day to the diseased skin that covered a skin area of about 1000 cm^2 (~5-6% BSA) for 10 days. The dose was at the high end considering that mean daily dose used in the three 12 week Phase 2 and 3 studies was approximately 0.6 to 0.9 g/day. For a topical drug product, the measurement of drug in systemic circulation is one of safety assessment. The application is acceptable provided that the Division of Dermatological and Dental Drug Products determines that there is little systemic safety concern from the clinical trials. Recommendations for consideration for the final labeling were included in Section 3.

Comment to the Medical Officer:

It is noted that the patients in the PK study RD.03.SRE.2690 were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible (based on the amount of drug applied, the drug may have only been applied to 5-6% BSA of the diseased skin). The dose was, however, at the high end considering that mean daily application in the three 12 week Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673) was approximately 0.6 to 0.9 g/day. 2 g dose was used in the previous PK studies for the 0.1% adapalene products and was considered acceptable. However, because this application represents a higher dose of adapalene, safety will be of concern. If there is no systemic safety concern from the current clinical trials (where mean daily dose of 0.6 to 0.9 g were used) for this product, labeling needs to reflect the amount of drug applied in the clinical trials. If a larger than 2 g dose is expected to be used in patients (for patients with >6% BSA), additional PK studies that enroll patients with larger body surface areas may be necessary to link safety to adapalene exposure.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A total of 9 *in vitro* and *in vivo* studies were included in the human PK and bioavailability section of this NDA. These studies include *in vivo* PK, skin stripping, permeation and metabolism studies. In addition, 4 study reports submitted for the earlier NDA 20-380 (0.1% gel) and IND 31,997 were mentioned.

For this application, one *in vivo* PK study (RD.03.SRE.2690) is considered pivotal. The study evaluated plasma levels of adapalene on Day 10 in 16 patients—9 males and 7 females (19-30 years) with acne vulgaris. Application was to the face, chest and back with the to-be-marketed formulation (2 g adapalene 0.3% gel/day). Adapalene is detectable in 15 out of 16 patients (LOQ 0.1 ng/mL). C_{max} on Day 10 was 0.553 ± 0.466 ng/mL (N=15) and AUC(0-24) was 8.37 ± 8.46 ng*h/mL (N=15). The maximum C_{max} and AUC(0-24) were 2 ng/mL and 36.1 ng*h/mL, respectively observed in a female subject. It appears that female had higher adapalene exposure than male subjects. Mean C_{max} and $AUC_{(0-24h)}$ in females were 100% and 148% higher than in males, respectively. When data from Subject 8 (female) were excluded, mean C_{max} and $AUC_{(0-24h)}$ in females were 42% and 63% higher than mean data in males, respectively. Because of potential teratogenecity effects of retinoid-like compounds, probable higher exposure in female subjects needs to be taken into consideration for the safety assessment of this product in women. The mean terminal half-life was 17.2 hours; a previous single oral dose study of adapalene showed that the half-life of adapalene was 13 hours.

It is noted that the patients in this study were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible (based on the drug applied, they may have only been applied to 5-6% BSA of the diseased skin). The dose was, however, at the high end considering that mean daily dose used in the three 12

week Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673) was approximately 0.6 to 0.9 g/day.

For this topical product, the site of therapeutic action is the skin and this action occurs earlier than the level of the drug seen in the blood. The measurement of drug in systemic circulation is therefore one of safety assessment. Additional PK studies that enroll patients with larger body surface areas may be necessary to link safety to adapalene exposure if there is systemic safety concern when a larger than 2 g dose is expected to be used in patients (for patients with >6% BSA).

As a note, previous PK studies with application of 2 g of 0.1% adapalene gel or cream to acne patients showed that levels of adapalene in patients were < 0.35 ng/mL.

The pivotal PK and clinical studies were conducted with the to-be-marketed gel product.

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

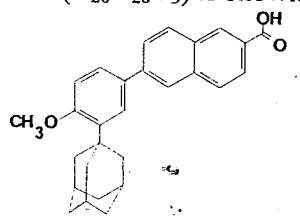
Raman K Baweja, Ph.D.
Clinical Pharmacology Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

2 QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What are the highlights of the physicochemical properties of adapalene?

The chemical name is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, and its molecular weight is 412.53. The structural formula ($C_{28}H_{28}O_3$) is shown below:



2.1.2. What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of adapalene gel, 0.3%?

Indication:
Adapalene Gel, 0.3% is indicated for the topical treatment of acne vulgaris.

Dosage and Route of Administration:
Apply to [redacted] the skin once daily, at nighttime. A thin film of the gel should be applied to the skin [redacted]

Mechanism of Action:
Adapalene acts on retinoid receptors. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.

Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

2.2. General Clinical Pharmacology

2.2.1. What is dose-response of adaplene gel? Why 0.3% dose was selected?

Dose-response in terms of safety and efficacy for adapalene gel was studied in Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673). In these studies, efficacy and safety of adapalene 0.3% gel, 0.1% gel and vehicle were compared. It is not clear how 0.3% dose was selected. In the pivotal Phase 3 clinical trial (Study RD.06.SRE.18081) that was conducted in patients 12 to 52 years of age with acne vulgaris who applied the medication once daily in the evening for 12 weeks, adapalene 0.3% gel (N=227) was significantly more effective than its vehicle (N=120) based on success rate and all lesion counts. However, it was not statistically superior to adapalene 0.1% gel, although a trend towards greater efficacy was shown in 0.3% gel. In terms of local safety, 0.3% gel is more irritable than the 0.1% gel.

Please refer to section 2.2.2 for exposure information of adapalene.

2.2.2. What studies have been conducted for bioavailability evaluation of the drug product? What are the outcomes of these studies?

Three studies included in the application evaluated the bioavailability of adapalene gel, 0.3% in acne patients with the to-be-marketed formulation: Study 1.CG.03.SPR.2649, Study RD.03.SRE.2690, and Study RD.06.SRE.18060.

There are two additional *in vivo* studies conducted in healthy subjects: Study RD.03.SPR.19027 and Study RDT.07.SRE.27001.P7T1.

In vivo studies in patients:

Study 1.CG.03.SPR.2649 (PK study) was not reviewed because this study utilized an analytical method that was less sensitive (LOQ 0.25 ng/mL) and there were considerable liquid-liquid extraction problems that did not yield reliable data. The study was repeated in Study 2690 with more subjects.

PK study RD.03.SRE.2690 is considered pivotal. The study evaluated plasma levels of adapalene on Day 10 in 16 patients—9 males and 7 females (19-30 years) with acne vulgaris. Application was to the face, chest and back with the to-be-marketed formulation (2 g adapalene 0.3% gel/day is equivalent to 6 mg adapalene/day). Adapalene is detectable in 15 out of 16 patients (LOQ 0.1 ng/mL). C_{max} on Day 10 was 0.553 ± 0.466 ng/mL (N=15) and AUC(0-24) was 8.37 ± 8.46 ng*h/mL (N=15). The maximum C_{max} and AUC(0-24) were 2 ng/mL and 36.1 ng*h/mL, respectively in one subject. The mean terminal half-life was 17.2 hours (Table 2.2.2.1). Exposure of potential circulating metabolites of adapalene was not measured.

Table 2.2.2.1. Adapalene pharmacokinetic parameters (Reviewer's Analysis).

Subject (Gender)	C_{max}[1] (ng/mL)	T_{max}[1] (h)	$AUC_{(0-24h)}$[1] (ng.h/mL)	$t_{1/2}$[1] (h)	C_{min} (ng/mL)	Ratio C_{max}/C_{min}
1 (F)	0.506	6	8.01	14	BLQ	NA
2 (F)	0.666	8	9.87	13	0.209	3.2
3 (M)	BLQ	NA	NA	NA	BLQ	NA
4 (M)	0.274	16	4.07	15	BLQ	NA
5 (M)	1.08	16	14.9	14	0.387	2.8
6 (F)	0.346	4	5.72	19	0.131	2.6
7 (M)	0.269	6	3.13	24	BLQ	NA
8 (F)	2.00	16	36.1	13	0.662	3.0
9 (M)	0.511	6	5.56	10	BLQ	NA
10 (M)	0.336	12	4.37	11	BLQ	NA
11 (F)	0.629	10	11.2	16	0.323	1.9
12 (F)	0.289	0	5.67	14	0.191	1.5
13 (M)	0.129	0	0.37	51	BLQ	NA
14 (M)	0.434	12	6.99	19	0.160	2.7
15 (M)	0.203	12	3.51	19	BLQ	NA
16 (F)	0.624	12	6.04	7	0.115	5.4
Mean	0.553	9.07	8.37	17.2	NA	NA
SD	0.466	5.34	8.46	10.2		
CV (%)	84	58.9	101	59.5		

BLQ: Below the limit of quantification (0.1 ng/mL)
SD:Standard deviation
CV: Coefficient of variation
NA:Not applicable
[1]: The subjects with C_{max} reported BLQ or $AUC_{(0-24h)}$ reported NA were not included to calculate the mean values.

As a note, previous PK studies with application of 2 g of 0.1% adapalene gel or cream to acne patients showed that levels of adapalene in patients were < 0.35 ng/mL.

In a Phase 2 Study (RD.06.SRE.18060), plasma levels of adapalene were determined at weeks 2, 8, 12 in a subset of 78 patients who received either 0.3% adapalene gel, 0.1% adapalene gel or vehicle as once daily application for 12 weeks. All plasma adapalene levels which were collected 6-16 hours post drug application at Weeks 2, 8 and 12 were below 0.25 ng/mL (LOQ). The records of dose, dosing area and sampling time for each individual at Weeks 2, 8 and 12 were not clear.

In vivo studies in healthy subjects:

Study RD.03.SPR.19027 compared cutaneous absorption of 0.1% and 0.3% gel formulations via skin stripping method in healthy subjects. This study was not reviewed because this is a study for formulation development. In addition, the results are questionable due to variability of the assay and lack of validation.

Study RDT.07.SRE.27001.P7T1 examined the cutaneous safety of adapalene gel (0.3%, 0.1% and 0.03%) vs. gel vehicle and white petrolatum after application of one 50 mg dose under occlusion for 24 hours (photo-patch test) and 48 hours (safety test) in healthy male adults. Blood sampling was performed before application and at 24 hr after application. Because the study was performed in healthy subjects after a single dose under occlusion and the dose was lower than the anticipated clinical dose, the PK results were not reviewed. The irritation and phototoxicity aspects of the drug product are being reviewed by the Medical Reviewer.

2.2.3. What is protein binding of adapalene?

Results from Study DC/JF/91-143 that was submitted to NDA 20-380 for the 0.1% gel suggested that total binding of adapalene in blood was >99%. Adapalene binds primarily to lipoproteins and to human serum albumin.

2.2.4. What is in vitro metabolism of adapalene?

Metabolism of adapalene has been studied in previous submissions (Study CF/JF/92-080). Adapalene was found to be metabolized extensively in human hepatocytes. M2 and M6 were the major metabolites in human hepatocytes (Table 2.2.4.1).

Table 2.2.4.1. Interspecies Metabolism of 14C-Adapalene in Cultured Hepatocytes for 24 hours Incubation (% total sample radioactivity).

	Mice		Rats		Rabbits		Dog	Man	
	M	F	M	F	M	F	M	M	F
M0/M1	-	22/22*	-	34/20	-	-	-	-	-
M2	-	-	27/27	43/40	-	-	53/33	53/29	31/16
M6	-	-	-	-	-	-	3/27	16/41	34/44
M7	40/15	48/20	-	-	47/13	52/5	-	-	-
∑M	47/32	83/54	71/71	93/89	78/47	79/8	71/74	92/89	92/93
adapalene	53/68	17/46	29/29	7/11	22/53	21/92	29/26	8/11	8/7

* Before conjugate hydrolysis/after conjugate hydrolysis

In this submission, a study report (RDS.03.SRE.4518) for a study conducted from August to September 1994 was submitted. This study provided general qualitative information. The summary provided by the Sponsor was attached in Section 4.4.3. In this study, there were a total of 6 metabolite fractions (A-F; A being the most polar and F the least polar fraction) including conjugated metabolites detected in human hepatocyte media. Fractions A and C contained glucuronic conjugates. Fractions B and E contained mixtures of two or more molecules. Fraction F appeared to contain O-demethyl adapalene. The B fraction may contain a previously isolated metabolite M2, a dihydroxylated moeity with hydroxylation occurring on the adamantyl group. The E fraction may contain a previously isolated metabolite M6, a monohydroxylated moeity with hydroxylation occurring on the adamantyl group. The study failed to rigorously and completely characterize any of the metabolites.

2.2.5. What is in vivo metabolic fate of adapalene?

Adapalene is shown to be metabolized extensively *in vitro*. Low exposure of adapalene in the PK study was not necessarily due to low absorption of adapalene through skin. It is important to determine the *in vivo* metabolic fate of adapalene following topical application. Excretion and plasma kinetics of radioactivity in man following topical administration of 0.1% ^{14}C-adapalene gel (Study 1.CG.03.SRE.4529) was submitted to NDA 20-748 (0.1% cream). Level of radioactivity in all plasma, urine or fecal samples were below the limit of quantitation, indicating very little radioactivity (adapalene plus possible metabolites) was absorbed through the skin after topical application of the gel formulation. The study was conducted in healthy male subjects. Absorption in patients with diseased skin may be different.

2.3 Intrinsic Factors

2.3.1. Is there a gender difference in adapalene exposure after application of 0.3% Differin (adapalene) gel?

It appears that female had higher adapalene exposure than male subjects (Table 2.3.1.1). Mean C_{max} and $AUC_{(0\text{-}24h)}$ in females were 100% and 148% higher than in males, respectively. When data from Subject 8 (female) were excluded, mean (± SD) C_{max} and $AUC_{(0\text{-}24h)}$ in females were 0.51 ± 0.16 ng/mL and 7.75 ± 2.36 ng·h/mL, respectively, which were 42% and 63% higher than mean data in males. Because of potential teratogenecity effects of retinoid-like compounds,

probable higher exposure in female subjects needs to be taken into consideration for the safety assessment of this product in women.

Table 2.3.1.1. Adapalene Exposure (Mean ± SD) between Female and Male Subjects.

	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng.h/mL)
Female (N=7)	0.72 ± 0.58	11.8 ± 10.9
Male (N=9)	0.36 ± 0.31	4.77 ± 4.40

2.5 General Biopharmaceutics

2.5.1. What is quantitative composition of 0.3% Differin (adapalene) gel?

Table 2.5.1.1 shows the composition of the drug product. The composition of the drug product is the[ ] as the approved 0.1% gel, except that the concentration of the active is three times that of the 0.1% gel.

Table 2.5.1.1. Formulation of Adapalene Gel, 0.3%.

Formulation Code:	To-be-marketed Drug Product BOH-1**	557.301*
Active Ingredient:		
Adapalene	0.3%	0.3%
Excipients:		
Carbomer 940 (1), NF	[ ]	[ ]
Carbomer 940, NF		
Edetate Disodium, USP		
Methylparaben, NF		
[ ]		
Poloxamer 124, NF		
[ ]		
Propylene Glycol, USP		
Sodium Hydroxide, NF		
[ ]		
Hydrochloric Acid, NF		
Purified Water, USP		
Lot (Batch) No. – used in clinical and human biopharmaceutic studies	PLE RIGT-3 RIGW-4	557.301/2F3 Y9271

* Galderma Laboratories R&D formulation code
** DPT Laboratories, Ltd. formulation code
(1) [ ]

2.5.2. Are there any differences between the clinical and to-be-marketed formulations?

All batches utilized in clinical and human biopharmaceutic studies to support this application were the to-be-marketed formulation.

2.6 Analytical

2.6.1. What bioanalytical methods are used to assess the amount of adapalene in plasma? Have the analytical methods been fully validated?

Yes, validated analytical methods were used for plasma samples collected in Study RD.03.SRE.2690 and Study RD.06.SRE.18060 (See Table 2.6.1.1).

Study RD.03.SRE.2690: The analysis was carried out in the Bioanalysis Laboratory of Galderma Research Development, 635 Route des Lucioles, BP87, 06902 Sophia Antipolis Cedex, France. The plasma concentrations of adapalene were determined following [ ] [ ] high performance liquid chromatography (HPLC), and fluorescence detection according to the validation method (Report RDS.03.VRE.34016).

Results: Quantifiable amounts of adapalene were found in 15 out of 16 patients (LOQ 0.1 ng/mL).

Study RD.06.SRE.18060: Plasma samples were analyzed at [ ] [ ] The plasma concentrations of adapalene were determined following [ ] [ ], high performance liquid chromatography (HPLC), and fluorescence detection with an excitation wavelength of [ ] nm and an émission wavelength at [ ] nm using [ ] as the internal standard according to the validation method (1.CG.03.ATP.4024.R01 and [ ] No. 40349).

Results: Levels of adapalene were below LOQ (0.25 ng/mL) in all 209 samples analyzed.

Table 2.6.1.1. Summary of Analytical Methods used for the Determinations of Adapalene in Human Plasma.

Study	RD.03.SRE.2690	RD.06.SRE.18060
Assay Method	[ ] HPLC with fluorescent detection	
Analytical Site	Bioanalysis Laboratory of Galderma Research Development in France	[ ]
Internal Standard	[ ]	
Matrix	Human Plasma	
Accuracy (%)	92.0-108.7%	-2.35-0.74% (% bias) *between-run*
Precision (CV%)	5.4-7.7%	2.34-4.79% *between-run*
Standard Curve Range	0.10-10.0 ng/mL (R > 0.996)	0.25-2.5 ng/mL (R > 0.99)
Sensitivity (LOQ)	0.10 ng/mL	0.25 ng/mL
QC Samples (ng/ml)	0.20, 1.00, 8.00	0.25, 0.5, 1, and 2
Stability	Adapalene has been shown to be stable for at least 7 weeks in human plasma stored at approximately -20°C. Analysis occurred between June 24, 2002 and July 12, 2002 that was within 7 weeks of study initiation.	Analysis occurred between July 31, 2001 and Sept 11, 2001. Sample collection for PK samples were started around Feb 13, 2001. There is a 7 month lapse between sample collection and sample analysis.

3 DETAILED LABELING RECOMMENDATIONS

Recommendations for changes to the proposed labeling are provided below (only affected sections relating to Clinical Pharmacology are listed).

CLINICAL PHARMACOLOGY

Pharmacokinetics: [ ]

[ ]

4 page(s) of draft labeling has been removed from this portion of the review.

Clinical Pharmacology / Biopharmaceutics Review #1

4.2 Individual Study Reviews

4.2.1 Study RD.03.SRE.2690: *Pharmacokinetics of adapalene after repeat topical applications of adapalene 0.3% gel on the face, back and chest of patients with acne vulgaris*

Objective: To determine the pharmacokinetics of adapalene 0.3% in a gel formulation when applied to subjects with acne vulgaris after 10 days of once daily application using a sensitive bioanalytical method with a quantification limit of 0.1 ng/mL for the determination of adapalene in plasma

Study Site: [redacted]

Investigator: [redacted] M.D.

Study Period: May 16, 2002 to June 11, 2002

Study Design: A single-center, open-label study to determine measurable blood levels of adapalene after 10 days of topical application of adapalene 0.3% gel. Sixteen male and female subjects with acne vulgaris (age 19-30 years) were enrolled in the study (Appendix, Table A1). 15 were Caucasians and 1 was Asian. Subjects received a once daily 2 g-application of the test product in the morning on the face, upper part of chest and back (0.5 g on the face, 0.5 g on the chest and 1 g on the back). The study product was applied to approximately 1000 cm^2 of the body surface (~5-6% BSA), corresponding to approximately 2 mg/ cm^2. The gel formulation was delivered with a syringe and the precise amount applied was measured by weighing the syringes before and after application.

All subjects received the full and correct dose. Blood samples for determination of adapalene level in plasma were drawn before morning application on Day 10 and 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the last application (Day 10). The quantification limit of the assay was 0.1 ng/ml.

Duration of treatment: 10 days
(Reviewer's Note: The report states that in a prior pharmacokinetic study with adapalene 0.3% cream (1[RD.03.SPR.2657]), mean trough adapalene plasma levels did not display any tendency to increase with the treatment duration between Day 4 and Day 10. Therefore, 10 days of treatment were considered sufficient.)

Investigational product:
Adapalene 0.3% gel
Formula number/Batch number: 557.301/RIGT-3 (DPT Laboratories, Ltd., United States)

Analytical Method: The plasma concentrations of adapalene were determined following [redacted] high performance liquid chromatography (HPLC), and fluorescence detection according to the

validation method (Report RDS.03.VRE.34016). The limit of quantitation (LOQ) is 0.1 ng/mL. The bioanalytical report RDS.03.SRE.34051 was attached in Appendix 16.4 of the study report.

Results:

Adapalene individual and mean plasma concentrations on Day 10 are listed in Appendix, Table A2. The plasma profiles in all subjects are shown in Figure 1. The plasma level of adapalene was less than 0.1 ng/mL (LOQ) at all timepoints for one male subject (Subject 3). Adapalene peak plasma concentrations (C_{max}) on Day 10 ranged from < 0.1 ng/mL (subject 3) to 2 ng/ml (Subject 8). The mean C_{max} on Day 10 of adapalene in all subjects (n = 16) was 0.52 ± 0.47 ng/mL (mean ± SD) with undetectable level for Subject 3 set as 0. The mean C_{max} on Day 10 of adapalene in subjects with measurable adapalene levels (n = 15) was 0.55 ± 0.47 ng/mL (mean ± SD) (Table 1). Tmax ranged from 0 to 16 hours with a mean of 9 hours. The concentration ratio C_{max}/C_{min} in subjects with quantifiable C_{min} ranged from 1.5 to 5.4 (Table 1). Mean $AUC_{(0\text{-}24h)}$ over a 24-h dosing interval on Day 10 for all subjects (n = 16) was 7.82 ± 8.46 ng.h/mL (mean ± SD) with uncalculable AUC set as 0 for Subject 3. In other subjects, $AUC_{(0\text{-}24h)}$ was determined using the data points. Mean $AUC_{(0\text{-}24h)}$ over a 24-h dosing interval on Day 10 for these subjects with AUC values (n = 15) amounted to 8.37 ± 8.46 ng·h/mL (mean ± SD). The maximum $AUC_{(0\text{-}24h)}$ was 36.1 ng·h/ml in subject 8 (Table 1). In Sponsor's analysis, AUC was not calculated for Subject 13 (male) because there are only detectable levels at three timpoints that were very close to LOQ, 0.1 ng/mL (0, 1 and 10 hr). Mean AUC without Subjects 3 and 13 was 8.94 ± 8.99 ng·h/mL (mean ± SD, N=14) (Appendix, Table A3).

Subject 8 (female, Caucasian)had plasma concentrations notably higher than that seen in other subjects. No cutaneous or systemic adverse events were recorded for this subject. Adapalene was no longer found in plasma at 72 h after the last application in all but one subject (Subject 8). In the Sponsor's analysis, the terminal apparent half-life was determined in 7 of the 16 enrolled subjects. It ranged from 13 to 16 h (Appendix, Table A3). The reviewer reanalyzed the terminal half-lives by determining the slope from the last three measurable timepoints. The mean terminal half-life was 17.2 hours, which suggested that a pharmacokinetic steady-state was reached before Day 10. Mean plasma concentration at 0 hr was 0.178 ng/mL (N=16) and at 24 hr was 0.292 ng/mL (N=16).

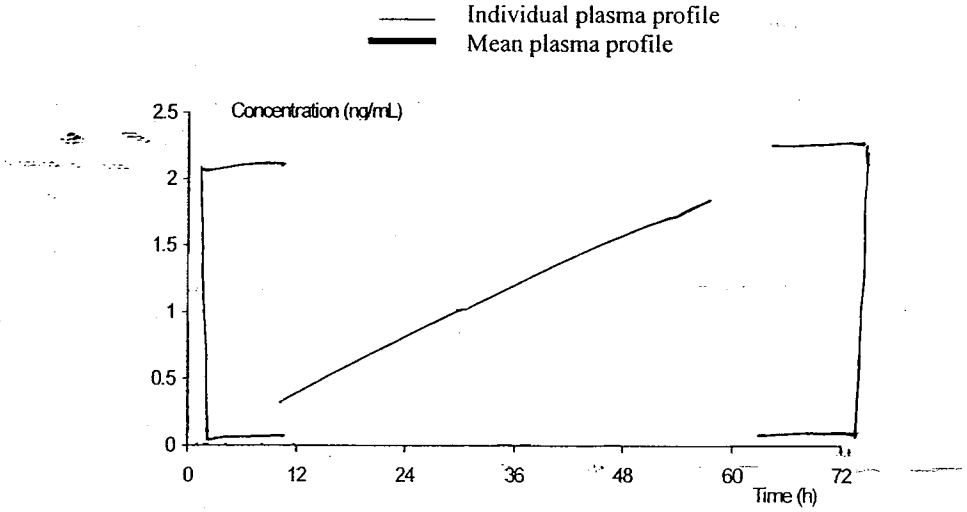


Figure 1. Adapalene individual and mean plasma profiles over 72 h.

Table 1. Adapalene pharmacokinetic parameters (Reviewer's Analysis).

Subject (Gender)	C_{max}[1] (ng/mL)	T_{max}[1] (h)	$AUC_{(0-24h)}$[1] (ng.h/mL)	$t_{1/2}$[1] (h)	C_{min} (ng/mL)	Ratio C_{max}/C_{min}
1 (F)	0.506	6	8.01	14	BLQ	NA
2 (F)	0.666	8	9.87	13	0.209	3.2
3 (M)	BLQ	NA	NA	NA	BLQ	NA
4 (M)	0.274	16	4.07	15	BLQ	NA
5 (M)	1.08	16	14.9	14	0.387	2.8
6 (F)	0.346	4	5.72	19	0.131	2.6
7 (M)	0.269	6	3.13	24	BLQ	NA
8 (F)	2.00	16	36.1	13	0.662	3.0
9 (M)	0.511	6	5.56	10	BLQ	NA
10 (M)	0.336	12	4.37	11	BLQ	NA
11 (F)	0.629	10	11.2	16	0.323	1.9
12 (F)	0.289	0	5.67	14	0.191	1.5
13 (M)	0.129	0	0.37	51	BLQ	NA
14 (M)	0.434	12	6.99	19	0.160	2.7
15 (M)	0.203	12	3.51	19	BLQ	NA
16 (F)	0.624	12	6.04	7	0.115	5.4
Mean	0.553	9.07	8.37	17.2	NA	NA
SD	0.466	5.34	8.46	10.2		
CV (%)	84	58.9	101	59.5		

BLQ: Below the limit of quantification (0.1 ng/mL)
SD:Standard deviation
CV: Coefficient of variation
NA:Not applicable
[1]: The subjects with C_{max} reported BLQ or $AUC_{(0-24h)}$ reported NA were not included to calculate the mean values.

Mean C_{max} and $AUC_{(0-24h)}$ were calculated based on gender (Table 2). It appears that female had higher exposure than male subjects. Mean C_{max} and $AUC_{(0-24h)}$ in females were 100% higher and 148% higher than in males, respectively. When data from Subject 8 (female) were excluded, mean (± SD) C_{max} and $AUC_{(0-24h)}$ in females were 0.51 ± 0.16 ng/mL and 7.75 ± 2.36 ng·h/mL, respectively which were 42% and 63% higher than mean data in males. Because of potential teratogenecity effects of retinoid-like compounds, probable higher exposure in female subjects needs to be taken into consideration for the safety assessment of this product in women.

Table 2. Adapalene Exposure (Mean ± SD) between Female and Male Subjects.

	C_{max}[1] (ng/mL)	$AUC_{(0-24h)}$[1] (ng.h/mL)
Female (N=7)	0.72 ± 0.58	11.8 ± 10.9
Male (N=9)	0.36 ± 0.31	4.77 ± 4.40

[1]: Zero was used in Subject 3 (male) who had C_{max} reported BLQ and $AUC_{(0-24h)}$ reported NA to calculate the mean values.

Discussion and Conclusions:

For this NDA, Study RD.03.SRE.2690 is considered pivotal to determine systemic exposure of adapalene in acne patients. The study evaluated plasma levels of adapalene on Day 10 after

applying 2 g per day for 10 days in 16 patients—9 males and 7 females (19-30 years) with acne vulgaris. Application was to the face, chest and back with the to-be-marketed formulation. Adapalene is detectable in 15 out of 16 patients (LOQ 0.1 ng/mL). C_{max} on Day 10 was 0.553 ± 0.466 ng/mL (N=15) and AUC(0-24) was 8.37 ± 8.46 ng*h/mL (N=15). The maximum C_{max} and AUC(0-24) were 2 ng/mL and 36.1 ng*h/mL in one subject. Mean C_{max} and $AUC_{(0-24h)}$ in females were 100% higher and 148% higher than in males, respectively.

It is noted that the patients in this study were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible (based on the drug applied, they may have only applied to 5-6% BSA of diseased skin). The dose was, however, at high end considering that mean daily exposure levels in the three 12 week Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673) was approximately 0.6 to 0.9 g/day. 2 g dose was used in the previous PK studies for the 0.1% adapalene products and was considered acceptable. However, because this application represents a higher dose of adapalene, safety will be of concern. Depending on whether there is systemic safety concern from the clinical trials (especially whether there is safety database for adapalene 0.3%, gel applied to patients with larger areas of diseased skin), additional PK study may be necessary. Labeling needs to reflect the amount of drug applied in the clinical trials.

Labeling suggests that the drug be applied in the evening. In this PK study, drug was applied in the morning. It is not clear whether there is diurnal difference in PK of adapalene.

Adapalene is metabolized extensively in human hepatocyte. The metabolic fate of adapalene after topical application is not clear. Exposure of potential circulating metabolites of adapalene was not measured.

Appendix (RD.03.SRE.2690)

Table A1. Summary of Demographics

		Adapalene 0.3% gel N= 16
Age (years)	Mean ± SD	23.6±4.1
	Min	19.1
	Max	30.1
Gender		
Male	n (%)	9 (56.3%)
Female	n (%)	7 (43.8%)
Race		
White	n (%)	15 (93.8%)
Black	n (%)	0 (0%)
Other	n (%)	1 (6.3%)
Skin Phototype		
II	n (%)	4 (25.0%)
III	n (%)	12 (75.0%)
Height (cm)	Mean ± SD	169.50±7.78
	Min	158.0
	Max	180.0

Weight (kg)	Mean ± SD Min Max	62.94±10.54 45.0 84.0

Table A2. Adapalene plasma concentrations (ng/mL)

Time (h)	Subject 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Mean	SD
0																	0.178	0.206
1																	0.177	0.233
2																	0.179	0.218
4																	0.259	0.252
6																	0.343	0.317
8																	0.331	0.281
10																	0.363	0.338
12																	0.386	0.343
16																	0.399	0.495
24																	0.292	0.429
36																	0.116	0.205
48																	BLQ	NA
72																	BLQ	NA

BLQ:Below the limit of quantification (0.1 ng/mL)
SD:Standard deviation
NA:Non applicable

Table A3. Adapalene pharmacokinetic parameters (Sponsor's Analysis)

Subject	C_{max}[1] (ng/mL)	T_{max} (h)	$AUC_{(0\text{-}24h)}$[1] (ng.h/mL)	$t_{1/2}$ (h)	C_{min} (ng/mL)	Ratio C_{max}/C_{min}
1	0.506	6	8.01	14	BLQ	NA
2	0.666	8	9.87	13	0.209	3.2
3	BLQ	NA	NA	NA	BLQ	NA
4	0.274	16	4.07	15	BLQ	NA
5	1.08	16	14.9	14	0.387	2.8
6	0.346	4	5.72	NA	0.131	2.6
7	0.269	6	3.13	NA	BLQ	NA
8	2.00	16	36.1	13	0.662	3.0
9	0.511	6	5.56	NA	BLQ	NA
10	0.336	12	4.37	NA	BLQ	NA
11	0.629	10	11.2	16	0.323	1.9
12	0.289	0	5.67	14	0.191	1.5
13	0.129	0	NA	NA	BLQ	NA
14	0.434	12	6.99	NA	0.160	2.7
15	0.203	12	3.51	NA	BLQ	NA

16	0.624	12	6.04	NA	0.115	5.4
Mean	0.553	NA	8.94	NA	NA	NA
SD	0.466		8.99			
CV (%)	84		101			

BLQ: Below the limit of quantification (0.1 ng/mL)
SD:Standard deviation
CV: Coefficient of variation

4.2.2. Study RD.06.SRE.18060: *The Safety and Efficacy of Adapalene Gel, 0.3% as Compared to its Vehicle and Adapalene Gel, 0.1% in the Treatment of Acne Vulgaris*

Objectives: 1) To determine the treatment differences between Adapalene Gel, 0.3% and the gel vehicle and assess the magnitude of treatment differences between the 0.3% and 0.1% gels, and 2) To determine the local tolerability and systemic safety profile of Adapalene Gel, 0.3% compared to Adapalene Gel, 0.1%.

(Reviewer's Note: This review will focus on adapalene exposure determination as part of systemic safety evaluation for 0.3% adapalene gel.)

Study Sites: 11 centers in the U.S.

Investigators: Scott Clark, MD, *et. al.*

Study Period: January 15, 2001 to July 26, 2001

Study Design: This study was conducted as a multicenter, randomized, investigator-blinded, vehicle-controlled, balanced parallel group comparison study involving subjects with moderate to moderately severe facial acne vulgaris meeting the following inclusion/exclusion criteria: male and female subjects aged 12 to 40 years (one 45-year-old subject was enrolled) with a minimum of 20 inflammatory and 20 non-inflammatory lesions (maximum of two cysts/nodules) and a global facial severity grade of 4 to 8 according to the Leeds Revised Acne Grading System 1 (Appendix, Table A1). Efficacy was determined by the reduction in the number of acne lesions and the change in global severity from baseline *(Note: Facial and truncal lesions could be treated; however, only facial lesions were assessed for efficacy)*. Safety was assessed by evaluating adverse events (AEs). At 5 specified centers, laboratory analyses included CBCs, serum chemistries, urinalyses, and obtaining adapalene plasma concentrations. Subjects were treated once daily for 12 weeks and evaluated at Baseline, and at Weeks 1, 2, 4, 8, and 12.

Single blood samples for determination of adapalene levels were drawn at Weeks 2, 8 and 12, approximately 6 to 16 hours after gel application from subjects at the five specified study centers.

Duration of treatment: 12 weeks (once application daily to the face and optionally to the trunk)

Product Indentity:

STUDY MEDICATION IDENTIFICATION			
Drug Name/ Formulation/ Concentration	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Adapalene Gel Vehicle
NAME OF ACTIVE INGREDIENT	adapalene	adapalene	Not applicable
Batch numbers	PLE	PLD	PLC
Expiration Date	October, 2002	October, 2002	October, 2002
Manufacturer	DPT Laboratories, Ltd.	DPT Laboratories, Ltd.	DPT Laboratories, Ltd.
Packaging	45 gram (g) tubes	45 g tubes	45 g tubes
Storage Requirements	20-25° C (68-77° F)	20-25° C (68-77° F)	20-25° C (68-77° F)
External Appearance	White gel	White gel	Translucent gel

Analytical Method: Plasma samples were analyzed at [ ] The plasma concentrations of adapalene were determined following [ ] high performance liquid chromatography (HPLC), and fluorescence detection with an excitation wavelength of [ ] nm and an emission wavelength at [ ] nm using [ ] as an internal standard according to the validation method (1.CG.03.ATP.4024.R01 and [ ] No. 40349). The limit of quantitation (LOQ) is 0.25 ng/mL. The limit of detection (LOD) was 0.15 ng/mL. The bioanalytical report RDS.03.SRE.4469 was attached in Appendix 16.4 of the study report.

Results:

Plasma adapalene levels were measured at Weeks 2, 8 and 12 by treatment group for the 78 subjects who had this measurement (24 patients received 0.3% adapalene gel, 26 patients received 0.1% adapalene gel and 28 patients received vehicle). Eight subjects had a total of 15 samples that were not drawn due to early discontinuation from the study and Subjects 219 and 220 had samples that hemolyzed and thus were not analyzed. Of the 209 plasma samples analyzed, adapalene concentrations were below the limit of detection of the bioanalytical method (0.15 ng/mL) in all samples except three, in which traces of adapalene below the limit of quantification (0.25 ng/mL) were found. One sample was from Subject 169 (Adapalene Gel, 0.3%), Week 12; and the other two were from Subject 174 (Adapalene Gel, 0.1%), Weeks 2 and 12. Subject 169 treated 3% BSA for eight weeks (thereafter, treating the face only). Subject 174 treated only the face for 12 weeks. Maximum %BSA values for each treatment group are listed in Table 1. Adapalene levels were under detection limit for these patients with maximum %BSA.

Average daily usage of 0.3% adapalene gel was 0.856 g/day (range 0.11 to 2.11 g/day) (Table 1 and Appendix, Table A2).

Table 1. Summary of Maximum BSA for PK Subset of Patients and Medication Usage for all the Patients.

PK Subset	0.3 % Adapalene Gel (N=24)	0.1 % Adapalene Gel (N=26)	Vehicle (N=28)
Maximum BSA (%)	23.5 at Week 2 (Subject 257)	40.5 at Week 2 (Subject 157)	58.5 at Week 2 (Subject 160)

Overall	0.3 % Adapalene Gel (N=56)	0.1 % Adapalene Gel (N=60)	Vehicle (N=61)
Total Medication Usage (g), Mean (Range)	63.96 (4.4, 206.9)	70.21 (7.0, 221.9)	83.12 (9.7, 243.3)
Daily Medical Usage (g/day), Mean (Range)	0.856 (0.11, 2.11)	0.865 (0.13, 2.61)	1.049 (0.13, 3.78)

Discussion and Conclusions:

All plasma adapalene levels from 78 subjects who received 0.3% adapalene gel, or 0.1% adapalene gel or vehicle 6-16 hours post drug application at Weeks 2, 8 and 12 were below 0.25 ng/mL. The records of dose, dosing area and sampling time for each individual at Weeks 2, 8 and 12 were not clear.

Appendix (Study RD.06.SRE.18060)

Table A1. Summary of Demographic

		Adapalene Gel, 0.3% (N = 70)	Adapalene Gel, 0.1% (N = 70)	Gel Vehicle (N = 74)
Gender				
Male	n (%)	38 (54.3)	43 (61.4)	45 (60.8)
Female	n (%)	32 (45.7)	27 (38.6)	29 (39.2)
Age (18 to 45 years)				
	Mean	17.8	16.5	17.6
	SD	6.02	4.51	4.55
	Min	12	12	12
	Max	40	45	35
Race				
Caucasian	n (%)	48 (68.6)	46 (65.7)	53 (71.6)
Black	n (%)	7 (10.0)	8 (11.4)	8 (10.8)
Oriental	n (%)	0 (0.0)	1 (1.4)	0 (0.0)
Hispanic	n (%)	15 (21.4)	14 (20.0)	12 (16.2)
Other/Mixed	n (%)	0 (0.0)	1 (1.4)	1 (1.4)

Table A2. Summary of Medication Usage.

Statistics	Adapalene Gel 0.3% (N=56)	Adapalene Gel 0.1% (N=60)	Vehicle Gel (N=61)	Total (N=177)
Total Medication Usage (g)				
N	56	60	61	177
Mean	63.96	70.21	83.12	72.68
S.D.	44.391	42.080	56.193	48.476
Median	50.85	63.65	74.70	58.80
Min , Max	4.4 , 206.9	7.0 , 221.9	9.7 , 243.3	4.4 , 243.3
Daily Medication Usage (g/day)				
N	56	60	61	177
Mean	0.856	0.865	1.049	0.925
S.D.	0.5156	0.5167	0.7587	0.6139
Median	0.660	0.775	0.850	0.750
Min , Max	0.11 , 2.11	0.13 , 2.61	0.13 , 3.78	0.11 , 3.78

4.3 *In Vitro* Studies

Table 4.3.1. List of *In Vitro* Studies

Study Report No.	Type of Study	Test Article	Donor Species	Tissue Preparation	Parameters
LG/AF/87/1795	Liberation and cutaneous penetration in diffusion cell system	[^{3}H]-adapalene gel, 0.1% [^{3}H]-adapalene solution, 0.1%	Human Hairless Rat	Excised dermatomized human skin Full thickness skin (hairless rat)	Distribution in receptor fluid
DCa/JF/92-020	Liberation and cutaneous penetration in diffusion cell system	[^{14}C]-adapalene gel, 0.1% [^{14}C]-adapalene cream, 0.1% [^{14}C]-adapalene solution, 0.1%	Human	Dermatomized abdominal skin in diffusion cell system	Distribution in surface excess, epidermis, dermis, receptor medium
RDS.03.SRE.4700	Liberation and cutaneous penetration in diffusion cell system	adapalene gel, 0.1% benzoyl peroxide gel, 2.5%	Human	Excised human skin in diffusion cell system	Distribution in total skin and collected fractions
RDS.03.SRE.4708	Permeation and metabolism	[^{14}C]-adapalene gel, 0.1% benzoyl peroxide gel, 2.5%	Human	Reconstructed human skin	Adapalene and potential metabolites concentrations
RDS.03.SRE.4707	Permeation and metabolism	adapalene gel, 0.1% clindamycin gel, 1%	Human	Reconstituted human epidermis	Adapalene, clindamycin and potential metabolites concentrations
DC/JF/91-143	Blood and plasma protein binding	^{3}H-adapalene	Human	Erythrocytes in plasma and in protein solutions	Distribution between erythrocyte and specific protein fractions
CF/JF/92-080	Interspecies hepatic metabolism	^{3}H-adapalene	Human, Mouse, Rat, Rabbit, Dog	Cultured hepatocytes	Cellular concentration, metabolite profiles
RDS.03.SRE.4518	Metabolism *in vitro*	Adapalene	Human and Rat	Human hepatocytes	Identification of the structure of metabolites

Studies LG/AF/87/1795, DCa/JF/92-020, RDS.03.SRE.4700 (only the bioanalytical report was included), RDS.03.SRE.4707, and RDS.03.SRE.4708 studied *in vitro* permeation of adapalene in various formulations (none of which was 0.3% adapalene gel) with diffusion cells. These studies were considered exploratory in nature for formulation development and were not reviewed. Study reports LG/AF/87/1795 and DCa/JF/92-020 have been submitted previously to IND 31,997 and NDA 20380, respectively. Study summary for Studies RDS.03.SRE.4707 and RDS.03.SRE.4708 provided by the Sponsor were included in Section 4.4 for reference.

Study DC/JF/91-143 studied blood and plasma protein binding of adapalene and has been submitted to NDA 20-380 previously and reviewed.

Studies CF/JF/92-020 and RDS.03.SRE.4518 studied *in vitro* metabolism of adapalene with radiolabeled adapalene in human hepatocytes. Study CF/JF/92-020 has been submitted to NDA 20-380 previously. Study RDS.03.SRE.4518 is exploratory in nature and was not reviewed. The study summary provided by the Sponsor was included in Section 4.4 for reference.

4.3 Synopses for *In Vitro* Studies

4.3.1 Study RDS.03.SPR.4707

Report :	Interim		Final	X	Page 1 of 2
Study :	Non-regulated	X	Regulated		

Group : Pharmacokinetics	**Protocol n°** : RDS.03.SPR.4707
Study period : August 2001	**Report n°** : RDS.03.SRE.4707 **Project n°** : 556
Performing laboratory : **Sponsor and test facility**	[redacted]
Title:	Permeation and metabolism of clindamycin 1%/Adapalene 0.1%gel in reconstituted human *epidermis* (RHE) in vitro

NARRATIVE SUMMARY

A cultured reconstructed human epidermis (RHE, provided by [redacted]) was used to evaluate this potential first pass cutaneous effect of Clindamycin and Adapalene alone and in a fixed combination aqueous gel formulation at 1% w/w and 0.1% w/w, respectively. The formulation was applied in the amount of 8 mg/cm², exactly weighed. Each formulation was applied onto six RHE (0.63 cm²). The RHE were incubated at 37°C (5% Co_2). At different incubation times (i.e. 1, 2, 3, 6 and 24 hours), the culture media (0.5 mL) was withdrawn from the receptor chamber and pooled two by two for sample analysis by LC-MS (Clindamycin, limit of quantification: 5 ng/mL), HPLC with fluorescence detection (Adapalene, limit of quantification: 5 ng/mL) or RIA (reference compounds).

Concerning the experimental conditions, the metabolism of testosterone (T), a steroid hormone metabolised into biologically active or inactive compounds by the skin was used as reference test. The steroid [redacted] transforms testosterone into 5-dihydrotestosterone (DHT). The testosterone absorption rate through the epidermis was constant during the first 3-6 hours and then reached a steady state. About 52% of the applied dose of testosterone were recovered in the medium. The ratio of DHT/T present in the culture media was constant over the time course of the experiment to reach 12.8% of the unmodified testosterone in the 0-24 h culture media.

These results suggest that this RHE model was suitable for testing cutaneous testosterone absorption and its biotransformation into 5-dihydrotestosterone in vitro. Furthermore, no cytotoxicity was observed (MTT assay), whatever the formulation applied.

Concerning Adapalene penetration/metabolism, no measurable concentrations of Adapalene were found in the culture medium of RHE. Similarly, no significant signals that would indicate the presence of Adapalene metabolites were seen in LC/MS. The same results were obtained after application of Adapalene formulated in association with Clindamycin (ratio 1/10) or separately.

Clindamycin was detected form 2 hours post application in some samples, the maximum flux rate being observed 24 hours post application. According to the tested formulation, the cumulative penetration represented 11.7 to 13.1% of the applied dose of Clindamycin. No significant differences were observed after application of Clindamycin formulated in association with Adapalene (ratio 10/1) or alone.

Possible Clindamycin metabolites (identified from publish data, Brodasky et al., 1997) were monitored after chromatography separation using tandem mass spectrometry. No clindamycose nor N-demethyl clindamycin were detected in any analysed samples. The method used did not permit an adequate detection of the following metabolites: clindamycin sulfoxide and N-demethyl clindamycin sulfoxide.

The results are summarized in the following table:

Product	Molecule	Lag Time (h)	Maximum flux rate (µg/cm²/h)	Total amount delivered/24 h (µg)	% dose
Testosterone	Testosterone	< 1	0.644 ± 0.08	0.674 ± 0.010	51.8
	Dihydrotestosterone	< 1	0.071 ± 0.000	0.086 ± 0.01	-
Adapalene gel	Adapalene	-	-	-	-
Clindamycin gel	Clindamycin	1 to 3	1.237	7.217 ± 0.143	13.1
	Metabolites	-	-	-	-
Clindamysin/Adapalene gel	Adapalene	-	-	-	-
	Clindamycin	3	0.930 ± 0.032	5.271 ± 0.223	11.7
	Metabolites	-	-	-	-

Distribution: **Summary:**
Report (copies):
Original:

		Signature	Date
For Galderma	F. VAN VELSEN Director Preclinical Development		17.11.2003.

Appears This Way
On Original

4.3.2 Study RDS.03.SPR.4708

Report : Interim		Final	X	Page 1 of 54
Study : Non-regulated	X	Regulated		

Group :	ADME	**Protocol:**	RDS.03.SPR.4708
Study period :	May-July 2003	**Report :**	RDS.03.SRE.4708
Project N°:	555		
Performing laboratory:	GALDERMA RESEARCH & DEVELOPMENT, 635 Route des Lucioles, B.P. 87, 06902 Sophia Antipolis CEDEX, France.		
Title:	Permeation and metabolisation of [^{14}C]-Adapalene formulated alone or in combination with benzoyl peroxide in the same formulation through Reconstructed Human Epidermis		

SUMMARY

Aim: The aim of the present study was to compare the percutaneous absorption and the metabolism of [^{14}C]-Adapalene from a formulation (#555.568/R1) containing this active ingredient at 0.1 % (w/w) or from the same formulation (#555.606/R1) containing this active ingredient at 0.1 % (w/w) in combination with benzoyl peroxide at 2.5 % (w/w).

Method: A reconstructed human epidermis model (RHE, [redacted]) was used. A finite dose (10 mg per cm²) of each formulation was applied directly onto the cornified side of six RHE (surface area: 0.63 cm²). At various incubation times (up to 24 hours), the culture medium was withdrawn from the receiver chamber for sample analysis and replaced by fresh culture medium. At the end of the 24-hour exposure period, the surface excess was removed and RHE were retained for analysis. Total radioactivity content of each sample was measured by liquid scintillation counting prior to metabolic profiling by HPLC analysis. Testosterone was used as positive control of RHE metabolisation. Additionally, the cell viability and integrity was assessed (MTT assay).

Results: No signs of cytotoxicity or tissue necrosis were observed on RHE. An extensive metabolism of testosterone (*i.e.* 100 % after a 24-hour exposure period) was observed in the RHE. These results suggest that the RHE used in this study were qualified for serving as model for *in vitro* drug metabolism.
The penetrated dose (sum of the radioactivity recovered in the 0-24 h culture medium and RHE samples) varied from 8.39 ± 1.17% to 8.30 ± 1.40% of the applied dose for the formulations #555.568/R1 ([^{14}C]-Adapalene alone) and # 555.606/R1 ([^{14}C]-Adapalene formulated in combination with benzoyl peroxide), respectively.
Whatever the formulation tested, the radioactivity was mainly distributed within the RHE. The cumulated quantities of radioactivity recovered in the culture medium varied from 0.5 to 0.3 % of the applied dose according to the tested formulation.
Regarding the adapalene metabolic profile in the RHE, whatever the tested formulation, the radioactivity was distributed over one single fraction identified as the unchanged drug (*i.e.* Adapalene). No metabolites were detected in any analyzed samples.

Conclusion: Under the experimental conditions described herein, no significant differences were observed in the penetration and metabolism of [^{14}C]-Adapalene formulated alone (# 555.568/R1) or in combination with benzoyl peroxide (#555.606/R1).

Distribution Original :	Summary:	M. Kadash, J.D. Doutremepuich,
	Report:	B. Gauthier , C. Verrier , A P. Luzy, and signatories.
		GALDERMA RESEARCH & DEVELOPMENT Archives, Sophia Antipolis site

	Name	Approval /Date
Study Director	N. Wagner	15 Sept 2003
Director of Preclinical Development:	F. van Velsen	18.09.03

4.3.3 Study RDS.03.SPR.4518

Report :	Interim		Final	X	Page 1 of 2
Study :	Non-regulated	X	Regulated		

Group : Pharmacokinetics	**Protocol n°** : RDS.03.SPR.4518
Study period : 1994	**Report n°** : RDS.03.SRE.4518 **Project n°** : 557
Performing laboratory : Sponsor and test facility	[redacted]
Title: *In vitro* metabolism studies (rat) and structural identification of two metabolites (rat and human)	

NARRATIVE SUMMARY

^{14}C-CD271 (5 µM) was incubated with human hepatocytes in culture for 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h by [redacted]. Samples of medium formthese incubations were transported to [redacted] for extraction and metabolite isolation packed in [redacted] with each 24 h incubation period comprising a distinct batch of incubation medium. In addition, [redacted] of human hepatocyte cultures were also received from [redacted] Upon receipt, the batches of human hepatocyte media were [redacted] or liquid scintillation counting (LSC) to determine the total amount of radioactive material available for extraction and for initial metabolite profiling by high performance liquid chromatography (HPLC). Analysis of the unprocessed human hepatocyte media revealed the presence of 7 radio labeled metabolite fractions, designated A – G. The polar early eluting metabolite fractions A – C were poorly resolved but D – F were present as distinct metabolite fractions. Metabolite fraction G represented parent ^{14}C-CD271. Retention times obtained for non-radio labelled metabolite reference compounds (provided by the Study Sponsor) indicated that only O-demethyl CD271 and CD271 were chromatographically equivalent to radio labelled components (metabolite fractions F and G, respectively).

In an attempt to produce quantities of metabolites to perform preliminary extraction and structural identification studies, ^{14}C-CD271 was incubated at concentrations between 2.5 and 40 µM with precision-cut rat liver slices for 4 and 24 hours in supplemented [redacted] medium. ^{14}C-CD271 proved resistant to metabolism *in vitro* with only approximately 25% of the compound metabolised after 24 h. Although conjugated metabolites were identified in the incubation medium sufficient quantities of material could be not generated for mass spectrometry analysis.

Therefore, preliminary studies were performed on sub-samples of the human hepatocyte media which had been pooled from all incubation times. These studies were conducted to optimise metabolite deconjugation, extraction, profiling and isolation procedures. The conclusions from these preliminary studies were that the human hepatocyte media contained conjugated metabolites and that the [redacted] of these metabolites was most efficient using [redacted]. In addition, it was concluded that liquid-liquid extraction using [redacted] was a suitable procedure for the extraction of radioactivity from the media.

Thus, whole batches of human hepatocyte media (0-24, 24-48, 48-72, 72-96, 96-120 and 120-144 h) were deconjugated by incubation of the media with [redacted] at 37°C for up to 24 hours. Media batches 0-24, 48-72, 72-96 and 96-120 h were then extracted with [redacted]. Batch 24-48 h human hepatocyte medium was extracted with [redacted] The 120-144 h deconjugated human hepatocyte medium was not extracted but concentrated approximately 5-fold and transferred to the Department of Mass Spectrometry, [redacted]. In addition, [redacted] phase extraction using a [redacted] cartridge with [redacted] mass of a sub-sample of this medium was attempted but was not successful.

The [redacted] extraction procedures led to extraction efficiencies of between 29-56% for the recovery of radioactivity into the organic solvent extracts. HPLC analysis of the [redacted] media remaining following extraction indicated that the non-extracted radioactivity primarily consisted of the more polar metabolite fractions A and B.

Metabolite fractions A-E were isolated by HPLC. The extracted radioactivity was [redacted]

The remainder of each metabolite fraction was concentrated to [redacted] metabolite fractions from media batches 48-72 and 72-96 h were transferred to the Department of Mass Spectrometry at [redacted] for structural analysis. Metabolite fractions from media batches 0-24, 24-48 and 96-120 h were stored [redacted] at -20°C.

To provide further structural information of the isolated material, metabolite fractions A-G (from 48-72 and 72-96 h media batches) were dissolved in [ ] diluted to 5 nM solutions with [ ] and their fluorescence measured using an excitation wavelength of [ ]nm and an emission wavelength of [ ]nm. These data were compared against readings taken from 5nM solutions of authentic metabolite reference compounds CD 437 and CD 271 prepared in the same manner. The fluorescence of these solutions, although low, were similar with all samples which indicated that the parent structure (responsible for the fluorescence) was intact in all collected metabolite fractions.

Metabolite fractions B and E (from all extracted media batches) were dissolved in [ ] and transferred to the Department of Chemistry, [ ] for analysis. The information provided by [ ] analysis of these two metabolite fractions was limited. It was determined however, that both metabolite fractions B and E appeared to be mixtures of two or more components and that metabolite fraction E contained less amounts of aromatic material than metabolite fraction B.

The only structural data obtained form Mass Spectrometry investigations throughout this study was for metabolite fractions E. This metabolite fraction consisted of a monohydroxylated metabolite of CD 271 although the precise position of [ ] could not be unequivocally determined. There was also some evidence for the presence of a second metabolite within this fraction consisting of a methylated and hydroxylated derivative of CD 271.

Distribution: **Summary:**
Report (copies):
Original:

		Signature	Date
For Galderma	F. VAN VELSEN Director Preclinical Development		/ 20.10.2003

4.4 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-753	**Brand Name**	Differin®
OCPB Division (I, II, III)	DPE III (HFD-880)	**Generic Name**	Adapalene
Medical Division	DDDDP (HFD-540)	**Drug Class**	Anti-acne agent
OCPB Reviewer	Lei Zhang, Ph.D.	**Indication(s)**	Treatment of acne vulgaris
OCPB Team Leader	Dennis Bashaw, Pharm. D.	**Dosage Form**	Gel, 0.3% (3 mg/g)
		Dosing Regimen	Once daily at nighttime
Date of Submission	3/31/04	**Route of Administration**	Topical to skin

Estimated Due Date of OCPB Review	12/30/04	Sponsor	Galderma Laboratories
PDUFA Due Date	2/1/05	Priority Classification	New Dosage Form (3-S)
Division Due Date	1/15/05		IND 61,085

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				**Study Report DC/JF/91-143 (in NDA 20-380 (0.1% Gel) Vol. 1.44)**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2	1	**Study Report RD.03.SRE.2649* Study Report RD.03.SRE.2690* * used to-be-marketed formulation**
Dose proportionality -				
fasting / non-fasting single dose:	X	1		**Study Report RDT.07.SRE.27001.P7T1 (Irritation and phototoxicity patch-test study. Single application. 0.1% gel, 0.03% gel and vehicle were also studied.)**
fasting / non-fasting multiple dose:	X	1	1	**Study Report RD.06.SRE.18060* * used to-be-marketed formulation (Phase 2 safety and efficacy study, 0.1% gel and vehicle were also studied.)**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	1		**Study Report CF/JF/92-080 (in NDA 20-380, Vol. 1.44) (rat and human hepatocytes) Study Report RDS.03.SRE.4518 (metabolite structural identification in rat and human)**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Skin Stripping Study	X	1		**Study Report RD.03.SRE.19027 (Skin stripping study in healthy subjects, single application. 0.1% gel with different formulations were also studied.)**
Permeation and metabolism study	X	3		**Study Report LG/AF/87/1795 (in IND 31,997)** **Study Report DCa/JF/92-020 (in NDA 20-380, Vol 1.44)** **Study Report RDS.03.SRE.4700** **Study Report RDS.03.SRE.4708** **Study Report RDS.03.SRE.4707**
Literature References	X			
Total Number of Studies		9	2	

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?		• **Please provide raw and summary PK data in SAS format for study RD.03.SRE.2690.** • **Please provide electronic copies of study reports for Study RD.03.SRE.2690 and Study RD.06.SRE.18060.**
QBR questions (key issues to be considered)		• **Was formulation used in pivotal PK studies the same as the intend-to-be-marketed drug formulation?** • **What are the systemic exposures (and PK profiles) of adapalene in patients under the maximal usage conditions?**
Other comments or information not included above		
Primary reviewer Signature and Date	**Lei Zhang, 5/2004**	
Secondary reviewer Signature and Date	**Dennis Bashaw, 5/2004**	

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/s/

Lei Zhang
1/18/05 02:26:37 PM
BIOPHARMACEUTICS

Raman Baweja
1/18/05 03:26:28 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

NDA	21-753
Submission Dates	3/31/2004, 6/25/2004, 7/13/2004
Drug Product	Adapalene, 0.3% gel
Applicant	Galderma Laboratories
Indication	Treatment of acne vulgaris

Addendum to CPB Review

The "Recommendation" (Section 1.1) of the review is modified as follows for clarification:

1.1 · Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, the Sponsor has evaluated systemic exposure of adapalene in patients following application of 2 g of adapalene 0.3%, gel per day to the diseased skin that covered a skin area of about 1000 cm^2 (~5-6% BSA) for 10 days. The dose (2 g/day) was at the high end considering that mean daily dose used in the three 12 week Phase 2 and 3 studies was approximately 0.6 to 0.9 g/day. The application is acceptable from a Clinical Pharmacology and Biopharmaceutics standpoint. Recommendations for consideration for the final labeling were included in Section 3.

Comment to the Medical Officer:

It is noted that the patients in the PK study RD.03.SRE.2690 were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible (based on the amount of drug applied, the drug may have only been applied to 5-6% BSA of the diseased skin). The dose (2 g/day) was, however, at the high end considering that mean daily application in the three 12 week Phase 2 and 3 studies (RD.06.SRE.18060, RD.06.SRE.18081 and RD.03.SRE.2673) was approximately 0.6 to 0.9 g/day. If there is no systemic safety concern from the current clinical trials (where mean daily dose of 0.6 to 0.9 g were used) for this product, labeling needs to reflect the amount of drug applied in the clinical trials. If a larger than 2 g dose is expected to be used in patients (for patients with >6% BSA), additional PK studies that enroll patients with larger body surface areas may be necessary to link adverse events to adapalene exposure.

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

Concurrence:

Raman K Baweja, Ph.D.
Clinical Pharmacology Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

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/s/

Lei Zhang
1/19/05 12:38:28 PM
BIOPHARMACEUTICS

Raman Baweja
1/19/05 01:12:47 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

PRODUCT (Generic Name):	Adapalene 0.3% Gel
PRODUCT (Proposed Brand Name):	Differin Gel (0.3%)
DOSAGE FORM:	Topical Gel
NDA:	21-753 (Amendment to NA letter)
PROPOSED INDICATIONS:	Acne vulgaris
SUBMISSION DATE:	December 18, 2006
SPONSOR:	Galderma Laboratories, LP
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Sue Chih Lee, Ph.D.
OCP DIVISION:	DCP III
OND DIVISION:	HFD 540

EXECUTIVE SUMMARY

Adapalene is a naphthoic acid derivative with retinoid activity that is used as an anti-acne agent. The original NDA for adapalene gel (0.3%) was submitted on March 31, 2004 and received the Agency's "Not Approvable" letter dated February 1, 2005.

Adapalene gel (0.3%), is the fourth drug product of adapalene developed by the Sponsor and represents a higher strength dosage form of an approved product. NDAs for adapalene 0.1% solution (NDA 20-338) and adapalene 0.1% gel (NDA 20-380) were approved on May 31, 1996. Adapalene 0.1% cream (NDA 20-748) was approved on May 26, 2000. All these dosage forms of adapalene are indicated for once daily application at nighttime in the topical treatment of acne vulgaris. In the original submission for this NDA, the sponsor evaluated systemic exposure of adapalene in patients following application of 2 g of adapalene 0.3%, gel per day to the diseased skin that covered a skin area of about 1000 cm2 (~5-6% BSA) for 10 days. The dose (2 g/day) was at the high end considering that mean daily dose used in the three 12 week Phase 2 and 3 studies was approximately 0.6 to 0.9 g/day. The application was acceptable from a Clinical Pharmacology standpoint.

However, the submission (NDA21-753) received the Agency's "Not Approvable" letter dated February 1, 2005 stating the following deficiencies:

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapalene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.

2. The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%.

To address these deficiencies, the sponsor was asked to provide:

1. Adequate evidence that the higher concentration of adapalene gel offers benefit over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study).

2. A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study.

The subject of this application is the sponsor's response to the NA letter. The sponsor submitted amendment to the unapproved NDA addressing deficiencies cited by the Agency. As no deficiency in the area of clinical pharmacology was cited in the "NA' letter, the sponsor did not submit any new information that requires clinical pharmacology review. However, the sponsor submitted revised package insert. Pharmacokinetic information in this new label has been reviewed and comments have been communicated to the sponsor.

Recommendation:

The revised label has been reviewed and comments have been communicated to the sponsor. No additional action is necessary for the clinical pharmacology aspect of this amendment.

The following section described the amended portion of the label encompassing revised PK information:

Pharmacokinetics: Absorption of adapalene from DIFFERIN Gel, 0.3% through human skin is low. In a pharmacokietics study, 16 acne patients were treated once daily for 10 days with 2 grams of DIFFERI Gel, 0.3% applied to the face, chest and back, corresponding to approximately 2 mg/cm^2. Fifteen patients had quantifiable (LOQ = 0.1 ng/mL) adapalene levels resulting in a mean Cmax of 0.553 ± 0.466 ng/mL on Day 10 of treatment. The mean $AUC_{0\text{-}24hr}$ was 8.37± 8.46 ng.h/mL as determined in 15 of the 16 patients on Day 10. The terminal apparent half-life, determined in 15 of 16 patients, ranged from 7 to 51 hours, with a mean of 17.2±10.2 hours. Adapalene was rapidly cleared from plasma andwas not detected 72 hours after the last application for all but

one subject. Exposure of potential circulating metabolites of adapalene was not measured. Excretion of adapalene appears to be primarily by the biliary route.

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Division of Clinical Pharmacology III

Team Leader: Sue Chih Lee, Ph.D._____

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/s/

Tapash Ghosh
5/1/2007 10:25:20 AM
BIOPHARMACEUTICS

Sue Chih Lee
5/1/2007 02:52:26 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

PRODUCT (Generic Name):	Adapalene 0.3% Gel
PRODUCT (Proposed Brand Name):	Differin Gel (0.3%)
DOSAGE FORM:	Topical Gel
NDA:	21-753 (Amendment to NA letter)
PROPOSED INDICATIONS:	Acne vulgaris
SUBMISSION DATE:	December 18, 2006
SPONSOR:	Galderma Laboratories, LP
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Sue Chih Lee, Ph.D.
OCP DIVISION:	DCP III
OND DIVISION:	HFD 540

EXECUTIVE SUMMARY

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However, the submission (NDA21-753) received the Agency's "Not Approvable" letter dated February 1, 2005 stating the following deficiencies:

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapalene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.

2. The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%.

To address these deficiencies, the sponsor was asked to provide:

1. Adequate evidence that the higher concentration of adapalene gel offers benefit over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study).

2. A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study.

The subject of this application is the sponsor's response to the NA letter. The sponsor submitted amendment to the unapproved NDA addressing deficiencies cited by the Agency. As no deficiency in the area of clinical pharmacology was cited in the "NA' letter, the sponsor did not submit any new information that requires clinical pharmacology review. However, the sponsor submitted revised package insert. Pharmacokinetic information in this new label has been reviewed and comments have been communicated to the sponsor.

Recommendation:

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The following section described the amended portion of the label encompassing revised PK information:

Pharmacokinetics: In a pharmacokietics study, 16 acne patients were treated once daily for 10 days with 2 grams of DIFFERIN Gel, 0.3% applied to the face, chest and back[ ] [ ] corresponding to approximately 2 mg/cm^2. Fifteen patients had quantifiable (limit of quantitation: 0.1 ng/mL) adapalene levels resulting in a mean Cmax of 0.553 ± 0.466 ng/mL on Day 10 of treatment. The mean $AUC_{0\text{-}24hr}$ was 8.37± 8.46 ng.h/mL as determined in 15 of the 16 patients on Day 10. The terminal apparent half-life, determined in 15 of 16 patients, ranged from 7 to 51 hours, with a mean of 17.2±10.2 hours. [ ]

[ ] Exposure of potential circulating metabolites of adapalene was not measured. Excretion of adapalene appears to be primarily by the biliary route.

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Division of Clinical Pharmacology III

Team Leader: Sue Chih Lee, Ph.D._____

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/s/

Tapash Ghosh
6/15/2007 02:11:33 PM
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Sue Chih Lee
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