CLINICAL PHARMACOLOGY REVIEW

Original NDA:	**22-502**
Brand Name:	Differin
Generic Name:	Adapalene
Dosage Form & Strength:	Lotion, 0.1 %
Indication:	Acne Vulgaris
Applicant:	Galderma R&D
Submission:	505(b)(1), Standard
Submission Dates:	02/27/2009
OND Division:	Dermatological and Dental Products
OCP Divisions:	Clinical Pharmacology 3
Primary Reviewer:	Seongeun Julia Cho, Ph.D.
Team Leader:	Dennis Bashaw, Pharm.D.

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1. EXECUTIVE SUMMARY

The NDA 22,502 is to seek an approval of Adapalene Lotion, 0.1% for the treatment of acne vulgaris, as a line extension of currently marketed drug products, Differin (Adapalene) Solution 0.1%, Differin (Adapalene) Gel 0.1% and 0.3 %, and Differin (Adapalene) Cream 0.1%. A fixed dose combination product (Adapalene 0.1%/benzoyl peroxide 2.5% gel) is also available. During the End of Phase 2 meeting, which was held on August 7th, 2007, the sponsor submitted a pharmacokinetic study protocol to assess the systemic exposure of adapalene and it was agreed by the agency to be acceptable. Following the meeting, the agency conveyed the following recommendations regarding the protocol; 1) to increase the number of subjects to at least 12, and 2) to record % BSA and the amount of medication applied for each patient. Subsequently, the study was conducted in accordance to these recommendations.

In this NDA, the sponsor submitted one PK study and one *in vitro* dermal penetration study along with the results of two dermal safety tests and two Phase 3 safety and efficacy studies. The sponsor also referenced 3 study reports submitted for earlier NDAs (Gel 0.3 % and Combination Adapalene, 0.1%/Benzyl Peroxide, 0.25 %), which include two in vivo PK and one skin stripping studies. In the current submission, the PK study was conducted in 14 subjects between 18 and 35 years old with severe acne vulgaris, who were treated with Adapalene Lotion, 0.1% in a dosing regimen consistent with maximum use. Results showed that all plasma concentrations from 12 of the 14 subjects studied were BLQ (< 0.1 ng/mL) and that all measurable plasma concentrations from the other two subjects were also less than 0.131 ng/mL.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology section of NDA 22-502, submitted on February 27, 2009, and found it acceptable. The sponsor's request to waive QT/QTc studies is acceptable from the clinical pharmacology standpoint, as supported by a demonstration of low systemic exposures to adapalene.

1.2 Phase IV commitment

None

1.3 Summary of clinical pharmacology findings

Plasma levels of adapalene was evaluated following applications of Adapalene Lotion, 0.1% once daily for 30 days in 14 subjects between 18 and 35 years old with acne vulgaris. The drug was applied 2 g/day on the face, back and chest, simulating a maximum use condition, covering a 1000 cm² application area (representing 5-6 % BSA). Blood samples were drawn on Day 1, 15, and 30 at pre-dose and 2, 4, 6, 8, 10, 12, and 24

hours after application, and additionally after the last application (Day 30) at 36, 48, and 72 hours post-dose.

For topical drug products, an evaluation of systemic exposure is one of safety assessment. All plasma concentrations from 12 of the 14 subjects studied were BLQ (< 0.1 ng/mL) and that even the concentrations of quantifiable samples from the other two subjects were less than 0.131 ng/mL.

Reviewer's comments:
While there is no absolute correlation between the severity of acne and the % BSA involvement, the application amount of 2 g per day in the area of 1000 cm², which corresponds to 5-6 % BSA, as recorded for each subject in this PK study, is generally consistent with maximal use conditions that were applied in phase 3 trials (severity 3-4). The average daily use of adapalene in these efficacy trials was 0.5-0.6 g.

In vitro dermal penetration was compared among several adapalene formulations by a flow through diffusion cell system employing full thickness human skin. Drugs included in the test were Adapalene Lotion, 0.1 % with 1% or 3% PPG-12/SMDI Copolymer (3 % PP-2 is in the to-be-marketed formulation), Differin® Gel, 0.1% and Differin® Cream, 0.1% . The majority of adapalene recovered in the study was contained in the epidermis (including the stratum corneum layer). Concentrations in the dermis were much lower. All receptor fluid concentrations, representing the absorbed dose, were below the limit of quantification. Adapalene Lotion, 0.1%, both 1% and 3% PP-2 formulations showed a lower total penetration than Differin Gel, 0.1% and a higher total penetration compared to Differin Cream, 0.1%.

Reviewer's comments;
Results from in vitro penetration studies are supplemental in nature and may not serve the ground for labeling of drug's potential on systemic exposure. It is based on the rationale that drug absorption in the in vitro settings cannot simulate the clinical situation because of intrinsic differences between normal and metabolically dead skin and diseased living skin (See section 2.2 in QBR for further details). Nonetheless it is acknowledged that these in vitro data are consistent with the low absorption of adapalene lotion shown in the clinical PK study.

Overall, the results from the in vivo PK study and the in vitro dermal penetration study show low levels of systemic absorption of Adapalene lotion, 0.1 % even under a maximal use condition.

2. QUESTION BASED REVIEW

2.1 General Attributes

What is regulatory background related to the current submission?

Adapalene Lotion, 0.1%, is a line extension with a new dosage form of currently marketed drug products, Differin® (Adapalene) 0.1% solution, gel and cream. Adapalene

solution and gel were approved in the United States in 1996, the cream was approved in 2000, and a fixed combination 0.1% adapalene and 2.5% benzoyl peroxide was approved in 2008. The NDA for these products are listed below.

NDA 020338 (0.1% solution)
NDA 020748 (0.1% cream)
NDA 020380 (0.1% gel)
NDA 021753 (0.3% gel)
NDA 022320 (adapalene 0.1%/benzoyl peroxide 2.5% gel)

The current NDA is 505(b)(1), seeking for an approval of Adapalene Lotion, 0.1% for the treatment of acne vulgaris, the same proposed indication as the previously approved products described above.

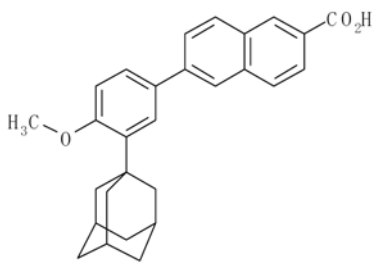
Reviewer's comments:
Systemic exposures of adapalene 0.1 % gel and 0.1 % cream have previously been studied in acne patients treated once daily to ~1000 cm2 BSA for 5 – 30 days with 2 g per day. Review of the package inserts of these products showed that the absorption of adapalene was low and most samples contained adapalene below the limit of quantitation.

What is the mechanism of action of Adapalene?

Adapalene is a naphthoic acid derivative with retinoid-like and anti-inflammatory properties. Adapalene binds to nuclear retinoid receptor, and thereby normalizes the differentiation of follicular epithelial cells and affects terminal differentiation of epidermal keratinocytes. Adapalene may also exert anti-inflammatory responses by modulating inflammatory mediators and migration of inflammatory cells and inhibiting Toll-like receptors and the expression of the transcription factor AP-1.

What are physico-chemical properties of Adapalene?

Adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid) Lotion, 0.1% is a new dosage form of adapalene 0.1% (w/w) dispersed in a fluid emulsion containing a low percentage of oil phase (< 10%).



The product is a white to off-white free flowing lotion with pH ranging from 5.0 to 6.0. Adapalene is homogeneously distributed in the lotion vehicle. The proposed formulation is shown below (Table 2.5.2.1),

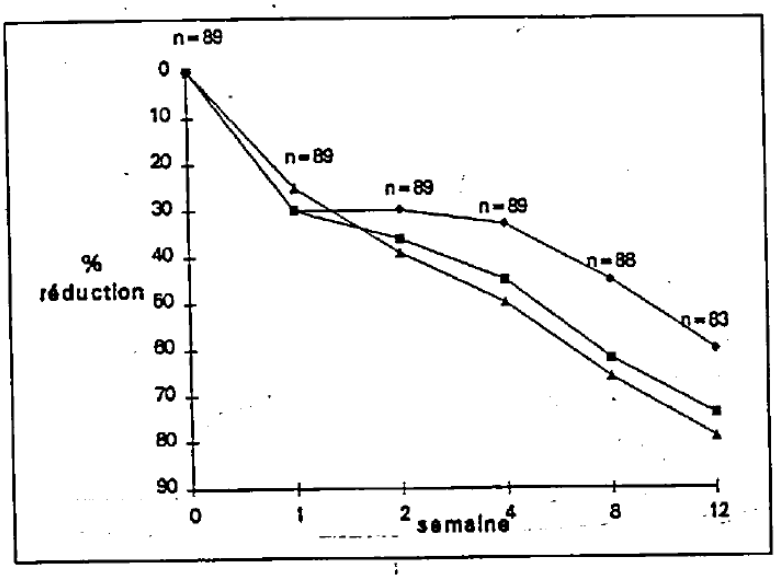
Table 2.5.2.1 Quantitative Composition of Adapalene Lotion, 0.1%

Ingredient	Grade	Function	Theoretical Weight (mg/g)	Theoretical Percentage (w/w)
Adapalene	- [1]	Active ingredient	1.0	0.1
Disodium Edetate	USP			(b) (4)
Propylparaben	NF			
Carbomer 9(b)1	NF			
Methylparaben	NF			
Poloxamer 124	NF			
Phenoxyethanol	USP			
Stearyl Alcohol	NF			
PPG-12/SMDI Copolymer [2]	-[1]			
Propylene Glycol	USP			
Polyoxyl-6 and Polyoxyl-32 Palmitostearate	-[1]			
Medium Chain Triglycerides	NF			
Sodium Hydroxide	NF			
Purified Water	USP			
Total			1000.0	100.0

2.2 General Clinical Pharmacology

What are the bases of the proposed concentration and a dosage form of Adapalene?

The proposed product in the current submission is Adapalene Lotion, 0.1%, and all clinical studies were conducted with this formulation. There are 5 clinical studies included in the submission; one pharmacokinetic study, 2 dermal safety studies and 2 pivotal phase 3 studies. The dosing regimen is a once daily application. The sponsor stated that the dosage and the dosing regimen were chosen based on the chemical and pharmacological properties of adapalene (high lipophilicity and high chemical stability). In support of dose selection, the sponsor referenced a literature article, in which Adapalene Gel 0.1 % was compared to Adapalene Gel 0.03 % and tretinoin 0.025 % for efficacy and safety in 89 male and female patients with acne (Alirezai et al., 1996). This literature documents that following a 12 week treatment, Adapalene Gel 0.1 % was significantly more effective than Adapalene 0.03 % Gel with regards to inflammatory and total lesion counts and the global facial acne grade, while the tolerability of adapalene gel 0.03 % and 0.1 % was shown to be similar for most of the parameters assessed.



Total lesion counts

♦ – Adapalene gel 0.03 %; Square – Adapalene gel 0.1 %; Triangle – Tretoinin 0.025 %

Reviewer's comments:
This reviewer acknowledges the study's conclusion that adapalene gel 0.1 % may be more efficacious than gel 0.03 % in reducing lesion counts and the overall acne score. However, the effectiveness (or lack thereof) of adapalene gel 0.03 % cannot be unambiguously drawn from these results as they did not include a vehicle group as a control. To note, there was no dose-ranging study conducted for Adapalene Lotion in the current submission.

What are the design features of the clinical pharmacology study and a dose-exposure relationship?

The Phase 1 clinical pharmacology study in this submission (SPR. 18108) is an open-labeled PK study to assess the systemic exposure to Adapalene Lotion, 0.1% in 14 subjects (7 male and 7 female) between 18 and 35 years old with severe acne vulgaris. Adapalene was applied once daily for 30 days by a trained nurse or study technician on the face, back and chest (simulating a maximum use condition), 2 g/day, covering a 1000 cm^2 application area (approximately 2 mg/cm^2).

Reviewer's note:
The actual ages of subjects enrolled in the study ranged from 18 to 29 years. However, it is not expected that the rate and extent of absorption of adapalene are significantly different between 18 to 29 years and 30 to 35 years.

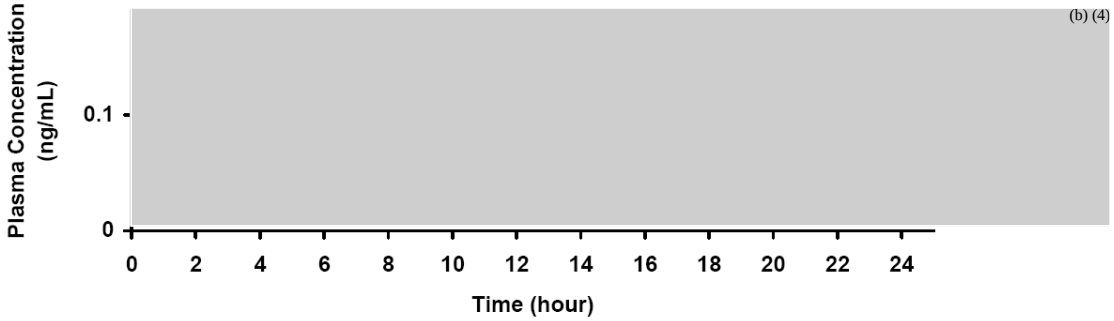
Blood samples were drawn on Day 1, 15, and 30 at pre-dose and 2, 4, 6, 8, 10, 12, and 24 hours after application, and additionally after the last application (Day 30) at 36, 48, and 72 hours post-dose. Adapalene plasma concentrations were determined by HPLC with a fluorescence detection.

All plasma concentrations from 12 of the 14 subjects studied were less than 0.1 ng/mL (the limit of quantification), and all plasma concentrations from the other two subjects were less than 0.131 ng/mL. For 12 subjects with plasma concentrations below 0.1 ng/mL, no PK parameters were calculated. Only one subject out of the other two had quantifiable adapalene concentrations for four consecutive plasma samples above the detection limit (Day 1 and Day 15), for which PK parameters (Cmax, Tmax, Cmin, Kel, t1/2, AUC0-t, AUC0-∞, and AUC0-24h) were calculated using non-compartmental methods (see the summary table 11.4.4-1). As noted before, the sponsor tested only adapalene lotion 0.1 % and did not explore any other concentrations.

Table 11.4.4-1: Summary of Pharmacokinetic Parameters for Subjects 01-001 and 01-003

	Subject 01-003			Subject 01-001		
	Day 1	Day 15	Day 30	Day 1	Day 15	Day 30
Number of concentrations ≥0.1 ng/mL	4	4	0	0	0	1
C_{max} (ng/mL)	(b) (4)					
T_{max} (hr)						
AUC_{0-t} (h*ng/mL)						
AUC_{0-24} (h*ng/mL)						

Figure 11.4.4-1: Plasma Concentration of CD0271 (Adapalene) for Subject 01-003



Reviewer's comments:
As shown in Figure 11.4.4-1 and Table 11.4.4-1, only 1 out of 14 subjects had adapalene levels above LOQ in 4 consecutive samples, and even for these samples, most were close to LOQ. Therefore, calculation of AUC based on only these four points cannot be considered reliable and should not to be included in the labeling.

The sponsor explored a dose-exposure relationship of adapalene 0.1% and 0.3% gel using skin stripping method in healthy volunteers, the results of which were submitted in the previous application (Study SRE.19027). The sponsor stated that a dose relationship was found. The study was not reviewed here, however, because skin stripping is not

considered as a validated method to evaluate dermal absorption by the Agency and we do not recommend skin penetration studies in healthy subjects due to the considerable differences in penetration barriers between intact and diseased tissues. Alternatively, dosage-exposure relationship may be deduced by a cross-study comparison of the systemic exposure of 0.3 % gel with 0.1 % gel, showing 15 out of 16 patients have detectable levels of adapalene following applications of 0.3 % gel (Study SPR.2690), compared to 3 out of 24 subjects following 0.1 % gel (NDA 22-320). The full elucidation of such a relationship, however, remains speculative at this time, given the data available to make such a comparison.

What studies were conducted to assess dermal penetration of Adapalene lotion?

In vitro dermal penetration of adapalene was evaluated by a flow through diffusion cell (Bronaugh) system using full thickness human skin, comparing Adapalene Lotion, 0.1 % with 1% or 3% PPG-12/SMDI Copolymer (3% in to-be-marketed formulation), Differin® Gel, 0.1% and Differin® Cream, 0.1% (Summary Table 2.7.2.3.1.1). The epidermis including the stratum corneum contained the major part of the adapalene recovered from the skin. Concentrations in the dermis were much lower. The amounts of drug in receptor fluid, representing the absorbed dose, were below the limit of quantification for all samples. When total penetration was compared (combination of all compartments, ie, epidermis, dermis, and absorbed), the penetration of Adapalene Lotion, 0.1% formulations showed a lower total penetration than Differin Gel, 0.1%, but a higher total penetration compared to Differin Cream, 0.1%.

Table 2.7.2.3.1.1 Disposition of Adapalene Expressed as Percent of Applied Dose, Following In Vitro Dermal Application to Human Skin

	Adapalene 0.1% Lotion (1% PP-2)	Adapalene 0.1% Lotion (3% PP-2)	Differin Gel, 0.1%	Differin Cream, 0.1%
Adapalene concentration	0.1%	0.1%	0.1%	0.1%
Total number of samples	11	11	12	12
Actual applied dose (µg)	9.37 ± 0.22	8.93 ± 0.19	9.34 ± 0.25	9.13 ± 0.15
Non absorbed dose [a]				
µg	7.07 ± 0.34	6.54 ± 0.35	6.89 ± 0.16	7.35 ± 0.25
% of the applied dose	75.45 ± 3.03	73.03 ± 3.48	74.29 ± 2.47	80.44 ± 1.95
(1) Epidermis + SC				
µg	0.10 ± 0.01	0.14 ± 0.02	0.24 ± 0.04	0.06 ± 0.01
% of the applied dose	1.12 ± 0.15	1.54 ± 0.22	2.56 ± 0.38	0.64 ± 0.11
(2) Dermis				
µg	0.002 ± 0.001	BLQ	0.018 ± 0.004	BLQ
% of the applied dose	0.03 ± 0.02		0.19 ± 0.04	
(3) Absorbed dose [b]	BLQ	BLQ	BLQ	BLQ
(1+2+3) Total penetrated				
µg	0.11 ± 0.01	0.14 ± 0.02	0.26 ± 0.04	0.06 ± 0.01
% of the applied dose	1.14 ± 0.16	1.54 ± 0.22	2.75 ± 0.39	0.34 ± 0.11
Mass balance				
µg	7.18 ± 0.34	6.68 ± 0.35 [c]	7.14 ± 0.15 [d]	7.41 ± 0.25
% of the applied dose	76.59 ± 3.03	74.59 ± 3.51 [c]	77.00 ± 2.37	81.08 ± 1.90

SC = Stratum corneum
a) Non absorbed dose = recovery in the skin surface excess and upper cell washing
b) Absorbed dose = receptor fluid (0-16 hours) + receptor rinse; c) N = 10; d) N = 11

Reviewer's comments;
While in vitro testing may be used for comparison of different formulations during early development phases, the results from these studies cannot be used to support regulatory decisions or labeling. Some of the limitations of these assays include; (1) skin used in the tests is from normal tissues with intact penetration barriers, (2) the surface is dry, which would affect drug's penetration through the outermost layer, and (3) unlike living tissues, tested materials are metabolically dead skin, which in all will alter the properties of drug absorption compared to in vivo.

Based on the systemic bioavailability data following Adapalene lotion, 0.1 %, is there an exposure-safety concern that needs to be further addressed, including a long term safety study?

Results from one clinical pharmacology study in the submission demonstrate that drug plasma concentrations at all time points tested (1-72 hrs) in 12 of the 14 subjects studied following Adapalene Lotion 0.1% were BLQ (< 0.1 ng/mL) and that all plasma concentrations from the rest two subjects were also less than 0.131 ng/mL. The sponsor referred to the systemic exposure of Adapalene Gel 0.3 %, a presently marketed product, the PK and safety data of which were reviewed and used to support the approval of NDA 21-753. As a brief summary of the previous PK study, Adapalene gel 0.3 % (2 g) was applied for 10 days once daily at the same body surfaces and % area (face, chest and back, 5-6 % BSA) as in the current submission, and the plasma levels of adapalene was determined on day 10 at 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 hours after the last application. Adapalene was detectable in 15 out of 16 patients with Cmax on Day10 0.553 ± 0.466 ng/ml and AUC(0-24) 8.37 ± 8.46 ng*h/ml. As a note, none of plasma samples in the current submission following lotion contained more than 0.131 ng/ml adapalene.

The sponsor seeks for a waiver for long term safety study, based on the facts that Adapalene gel, 0.3 %, which potentially leads to higher systemic exposure than Adapalene Lotion 0.1 %, has been studied in a long-term study (IND 076057, Section 2.7.7.2.2.1.2 A Long Term Safety and Efficacy Study of Adapalene Gel, 0.3% in Subjects with Acne Vulgaris (Study RD.06.SPR.18082)).

Reviewer's comments;
A comparison of plasma exposure of Adapalene Lotion 0.1 % with the previously reported Adapalene Gel 0.3 % is a cross-study comparison. As such it is not an as rigorous analysis as a two-arm parallel study and we recognize that it may not be the most ideal in evaluating potential exposure-related safety of Adapalene Lotion 0.1%. However, both studies were conducted using the same dosage (2 g, 5-6 % BSA) and the same detection method. Under these conditions, it was shown that the frequency and concentrations of adapalene detected in plasma following Adapalene lotion 0.1 % were notably lower than those of Adapalene gel 0.3 %, and it is consistent with what is expected from the dose-response. This PK comparison provides supportive evidence for the safety of the currently proposed formulation.

In this submission, the sponsor also referred to two studies from the previous application (NDA 22-320, Protocol #s SRE.2685 and SRE.18097) to provide exposure information of Adapalene, 0.1% Gel. The purpose of these previous studies was to compare systemic exposure of Adapalene gel 0.1% with a combination product, Adapalene, 0.1%/Benzoyl Peroxide, 0.25% Gel. For the purpose of a review of the current application, only the results of Adapalene, 0.1% Gel are considered. Subjects were dosed 2 grams of Adapalene 0.1 % Gel for 10 and 30 days in Study SRE.2685 and Study SRE.18097, respectively, to the face, chest, and back of subjects at ~ 5-6 % BSA. In Study SRE.2685, blood samples were drawn on Day 10 at pre-dose and at 2, 4, 6, 8, 10, 12, 16 and 24 hours after the last dose, while in Study SRE.18097 blood samples were collected on Days 1, 10, 21, and 30 at pre-dose and 2, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours following the last application (Day 30). In Study SRE.2685, the assay LOQ was 0.25 ng/ml and all plasma levels of Adapalene were BQL. In Study SRE.18097, the assay LOQ was 0.1 ng/ml (same as in the current submission) and Adapalene plasma levels were measured in 3 out of 12 subjects with C_{max} between 0.1 and 0.2 ng/ml (see table below).

Table 2.7.2.2.3.1 Pharmacokinetic Parameters in Study SRE.18097 - Subject and Days when Adapalene Levels could be Quantified

Treatment	Subject ID number	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng. h/mL)
Adapalene 0.1% Gel	1	10	0.1611	12	2.6481
	1	21	0.1261	6	1.2623
	15	30	0.1392	24	NA
	21	30	0.1101	6	NA

NA: Not applicable. No quantifiable concentration or less than 3 consecutive quantifiable concentrations.

Based on this cross-study comparison, the sponsor seeks for a waiver for conducting a QT/QTc study with Adapalene Lotion, because (1) Adapalene Lotion 0.1 % is the same or a lower strength of adapalene compared to marketed products, (2) leads to similar or lower systemic exposure compared to marketed products, and (3) according to the sponsor's claim, there is no signal of cardiotoxicity observed from Pharmacovigilance Database, clinical and preclinical studies, and the literature of marketed products.

Reviewer's comments:
Again, while recognizing that a cross-study analysis comparing two formulations (Lotion vs. Gel) or dose strengths (0.1 % vs. 0.3 %) does not provide an absolute determination of PK properties of the proposed product, it is this reviewer's opinion that the information provided in this NDA supports the applicant's conclusion that the systemic exposure following Adapalene Lotion 0.1 % is low. Therefore, waiver requests for long-term safety and QT/QTc studies deem to be reasonable from the clinical pharmacology standpoint.

Were the correct moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters?

In the previous application (Adapalene 0.1% Gel), pharmacological assessment of adapalene could not be conducted because the plasma levels of adapalene from all 78 subjects were below the limit of quantification (LOQ = 0.25 ng/mL; Study RD.06.SRE.18060; 6-16 hours post drug application at Weeks 2, 8 and 12). For the current application, the sponsor applied a newer bioassay method that had a limit of quantification of 0.1 ng/mL. All measurements of drug plasma concentrations were made using HPLC with a fluorescence detection (RD.06.SPR.18108). See Section 2.5 for a summary of the validation of the analytical method.

2.3 Intrinsic factors

Are there differences in the exposure based on gender, age, or ethnic background following the application of Adapalene Lotion?

No study was performed to explore the effects of intrinsic factors on drug exposure. However, the phase 3 efficacy studies have found that female subjects, older subjects (18 – 64 years of age vs. 12-17 years), and non-Caucasian subjects were more likely to have Investigator Global Assessment (IGA) successes and greater lesion count reductions than were the opposing subjects within the same subset categorizations. Since the efficacy trials did not have a PK arm sub-group, and the number of subjects in PK study 18108 that had measurable plasma levels of the drugs was very small, it is not possible to assess a potential relationship between the efficacy and the systemic exposure.

The demographics of subjects who participated in the PK study are 50% (7 subjects) female vs. 50% (7 subjects) male, and 79% (11 subjects) White, 14% (2 subjects) Hispanic, and 7% (1 subject) White/Asian (note: subjects selected all that applied). No subjects were below 18 years of age.

Listing 16.2.4.1: Demographic Information
(Page 1 of 1)

Site-Subject	Initials	Date of Screening	Date of Birth	Age	Gender	Screening Height (in)	Screening Weight (lb)	Skin Type	Ethnicity	Race	Inst. to use mois.?	Cont. to meet crit.?	Explain
01-001	[redacted]	05/17/2007	[redacted]	18	Female	63.2	146.0	III	Not Hispanic/Latino	White	No	Yes	
01-002		05/17/2007		29	Female	65.0	200.0	I	Not Hispanic/Latino	White	Yes	Yes	
01-003		05/23/2007		25	Female	64.0	140.0	III	Not Hispanic/Latino	White	No	Yes	
01-004		05/24/2007		19	Male	66.5	117.8	III	Hispanic/Latino	White	No	Yes	
01-005		05/22/2007		19	Male	61.0	210.2	IV	Not Hispanic/Latino	White	No	Yes	
01-006		05/22/2007		18	Male	70.0	163.6	IV	Not Hispanic/Latino	White, Asian	No	Yes	
01-007		05/18/2007		27	Male	73.0	245.0	III	Not Hispanic/Latino	White	No	Yes	
01-008		05/29/2007		18	Female	64.0	142.6	II	Not Hispanic/Latino	White	No	Yes	
01-009		05/30/2007		26	Female	71.0	152.0	II	Not Hispanic/Latino	White	No	Yes	
01-010		06/05/2007		21	Male	61.0	255.0	IV	Hispanic/Latino	White	No	Yes	
01-011		06/12/2007		29	Female	62.5	200.6	III	Hispanic/Latino	Other: Hispanic	No	Yes	
01-012		06/13/2007		19	Male	57.0	175.8	IV	Hispanic/Latino	Other: Hispanic	No	Yes	
01-013		06/12/2007		23	Female	62.0	129.8	II	Not Hispanic/Latino	White	No	Yes	
01-014		06/29/2007		19	Male	70.5	149.6	ND	Not Hispanic/Latino	White	No	Yes	

Table 11-24: Subgroup Analysis of the Primary Endpoints for the Subgroup Gender
(RD.06.SPR.18113 and RD.06.SPR.18114 Combined)
(Intent-to-Treat Subjects)
(Page 1 of 2)

Gender	Males		Females	
Week 12 Dichotomized IGA[a]	Adapalene Lotion, 0.1% (N=485)	Lotion Vehicle (N=511)	Adapalene Lotion, 0.1% (N=583)	Lotion Vehicle (N=562)
Success	107 (22.1%)	79 (15.5%)	162 (27.8%)	102 (18.1%)
Failure	378 (77.9%)	432 (84.5%)	421 (72.2%)	460 (81.9%)

Table 11-26: Subgroup Analysis of the Primary Endpoints for the Subgroup Race
(RD.06.SPR.18113 and RD.06.SPR.18114 Combined)
(Intent-to-Treat Subjects)
(Page 1 of 2)

Race	Caucasian		Non-Caucasian	
Week 12 Dichotomized IGA[a]	Adapalene Lotion, 0.1% (N=697)	Lotion Vehicle (N=707)	Adapalene Lotion, 0.1% (N=371)	Lotion Vehicle (N=366)
Success	184 (26.4%)	115 (16.3%)	85 (22.9%)	66 (18.0%)
Failure	513 (73.6%)	592 (83.7%)	286 (77.1%)	300 (82.0%)

Table 11-25: Subgroup Analysis of the Primary Endpoints for the Subgroup Age
(RD.06.SPR.18113 and RD.06.SPR.18114 Combined)
(Intent-to-Treat Subjects)
(Page 1 of 3)

Age	Age (< 18 years)		Age 18-64	
Week 12 Dichotomized IGA[a]	Adapalene Lotion, 0.1% (N=665)	Lotion Vehicle (N=679)	Adapalene Lotion, 0.1% (N=403)	Lotion Vehicle (N=394)
Success	149 (22.4%)	114 (16.8%)	120 (29.8%)	67 (17.0%)
Failure	516 (77.6%)	565 (83.2%)	283 (70.2%)	327 (83.0%)

Reviewer's note:
Subjects included in the PK study were 18-35 years old, so no information is available regarding the systemic exposure of the drug in 12-17 years old. However, it is reasonable to expect that the absorption of the drug may not substantially be affected by the age and should be comparable between these age groups.

2.4 Extrinsic factors

What extrinsic factors affect Adapalene exposure?

The effects of extrinsic factors on the exposure of Adapalene Lotion were not evaluated in this NDA. Extrinsic factors that are known to affect pharmacokinetic properties of Adapalene in previous dosage forms should also be applicable to Adapalene Lotion, 0.1%.

2.5 Analytical section

Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. Adapalene was measured in plasma using HPLC with a fluorescence detection method.

Was the validation of the analytical method used to determine drug concentrations in this NDA acceptable?

Yes.

Bioanalytical method:

- Active Compound: Adapalene (CD271)
- Internal Standard: (b) (4)
- Sample preparation: Enzymatic hydrolysis followed by liquid-liquid extraction
- Calibration sample concentrations: 0.1, 0.25, 0.5, 2, 5 and 10 ng/ml
- LOQ concentration: 0.10 ng/mL
- Acceptance criteria for calibration samples: Individual bias of the back-calculated values +/- 20 % at the LOQ and +/- 15 % at the other concentrations for at least 2/3 of the values and with at least 6 calibration levels within the acceptance criteria.
- Acceptance criteria for LOQ: Adapalene – individual interference +/- 20 % of signal at the limit of quantification (LOQ). Internal standard – individual interference +/- 5 % of signal at working concentration
- Results for calibration curves and LOQ: Pre-defined acceptance criteria were met for all analytical runs

- Quality Control Samples – QC samples were freshly prepared on each day of analysis with blank human plasma spiked with known amounts of Adapalene and analyzed in three replicates. QC samples concentration: 0.2, 1 and 8 ng/ml
- Acceptance criteria: Individual bias within ±15% for at least 2/3 of the value
- Results from QC samples: Pre-defined acceptance criteria were met

3. DETAILED LABELING RECOMMENDATIONS

Sections related to Clinical Pharmacology only are listed below.

(b) (4)

4. APPENDIX

4.1 OCBP Filing Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA/BLA Number	22,502	Brand Name	Differin

OCP Division (I, II, III, IV, V)	III	Generic Name	Adapalene
Medical Division	Derm	Drug Class	Naphthoic acid derivative
OCP Reviewer	Julia Cho	Indication(s)	Acne Vulgaris
OCP Team Leader	Dennis Bashaw	Dosage Form	Lotion 0.1 %
Pharmacometrics Reviewer		Dosing Regimen	Applied once daily
Date of Submission	03/02/09	Route of Administration	Topical
Estimated Due Date of OCP Review	11/02/09	Sponsor	Galderma Lab
Medical Division Due Date	11/02/09	Priority Classification	Standard
PDUFA Due Date	01/02/09		

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			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				Please submit bioanalytical method validation report RDS.03.VRE.34016 (or identify its location if submitted)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1	1	SPR18108
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
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:				In vitro penetration study using human skin is noted.
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Pivotal trials were done with a to-be-marketed product.
2	Has the applicant provided metabolism and drug-drug interaction information?		x		Systemic exposure (at maximal conditions) appears low and most plasma conc are below LOQ, 0.1 ng/ml.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		x		Bioanalytical method validation report RDS.03.VRE.34016 not found. Place submit or identify its location if already submitted
5	Has a rationale for dose selection been	x			Sponsor referred to the dose ranging

	submitted?				results of a previous approved formulation. No dose ranging study was conducted using the proposed formulation
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		x		Incorrect references and/or hyperlinks were found (eg., page 8, section 2.7.2, RDS.03.SRE.4789). Please confirm the entire document for accuracy.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	Since most plasma concentrations were below the detection limit, data were presented only in a tabular format
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			Quantifiable concentrations were observed only for two subjects out of 14, for which Cmax, Tmax, AUC0-t, and AUC0-24h were calculated.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	Refer to a comment #5 above
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		A waiver from pediatric study in children below the age of 12 is being requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		Refer to notes #2 and #5 above
	General				
18	Are the clinical pharmacology and			x	Refer to notes #2 and #5 above

	biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

We could not locate the bioanalytical method validation report RDS.03.VRE.34016. Place identify the sections where it is located, or submit the report if omitted.
Incorrect references and/or hyperlinks were found. For example, the study in section 2.7.2 on page 8, RDS.03.SRE.4789 is incorrectly referenced. Please confirm the entire document for the accuracy of references and appropriate hyperlinks.
The application states that "lower systemic exposure is seen with Adapalene Lotion, 0.1% than that observed with Adapalene 0.3% Gel (…NDA 021753)…". Please provide appropriate information support this comparison, including a complete report on PK studies of Adapalene 0.3% Gel.
The application states that "systemic exposure to Adapalene from Adapalene Lotion, 0.1% and Epiduo Gel with the same adapalene 0.1% concentration are not different from one another". Please submit the complete PK study report on Epiduo Gel with individual data and identify the appropriate section

Seongeun Julia Cho
Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw
Team Leader/Supervisor Date

4.2 Proposed labeling

10 Page of Draft Labeling as been withheld in full after this page as B4 (CCI/TS)

Attachment – List of clinical studies

Table 2.5.1.4.1 Summary of Adapalene Lotion, 0.1% Clinical Studies

Study No./Description	Treatment Dose/Duration	No. Subjects/ Patient Population
RD.06.SPR.18108 A pharmacokinetic study to determine the systemic exposure to Adapalene during dermal application of Adapalene Lotion 0.1% for 30 days in subjects with acne vulgaris	Adapalene Lotion, 0.1%; 2 g once daily/30 days	14 acne vulgaris subjects (7 males and 7 females) 18-35 years old
RD 06. SPR 18110 A Single Center Evaluation of the Cumulative Irritation of Adapalene Lotion, 0.1% and Adapalene Vehicle Lotion Following Repeated Topical Application to Healthy Subjects	Adapalene Lotion, 0.1%, White Petrolatum, Adapalene Vehicle Lotion, and 0.2% SLS; 0.2 mL, 0.2 g for 5 days/wk for 15 applications over 21 days	50 healthy M&F subjects aged 18 to 65 years, of which 44 completed the study.
RD 06. SPR 18111 A Single Center Evaluation of the Contact Sensitization of Adapalene Lotion (0.1%) and Placebo for Adapalene Lotion (0.1%) Following Repeated Topical Applications to Healthy Subjects	Induction phase: White Petrolatum, Placebo for Adapalene Lotion, 0.1% and Adapalene Lotion, 0.1% (0.2 mL, 0.2 g); occlusive patches on left side of back 3 days/wk for 3 consecutive weeks for a total of nine applications. Challenge phase: 7-18 days after last induction application, occlusive patches of the Placebo for Adapalene Lotion, 0.1% and Adapalene Lotion, 0.1% were applied to the right side of backs for ~48 hrs.	203 evaluable healthy M&F subjects, 18-65 years of age
RD.06.SPR.18113 A Multi-center, Randomized, Double-Blind, parallel-group study to demonstrate the Efficacy and Safety of Adapalene Lotion, 0.1% compared with vehicle lotion in subjects with Acne Vulgaris	Application of Adapalene Lotion, 0.1% or Lotion vehicle once daily to face and trunk as applicable for 12 weeks.	1075 M&F subjects 12-50 years old with acne vulgaris (533 adapalene Lotion, 0.1%; 542 Lotion vehicle)
RD.06.SPR.18114 A Multi-center, Randomized, Double-Blind, parallel-group study to demonstrate the Efficacy and Safety of Adapalene Lotion, 0.1% compared with vehicle lotion in subjects with Acne Vulgaris	Application of Adapalene Lotion, 0.1% or Lotion vehicle once daily to face and trunk as applicable for 12 weeks.	1066 M&F subjects 12-64 years old with acne vulgaris (535 adapalene Lotion, 0.1%; 533 Lotion vehicle)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEONGEUN CHO
09/25/2009

EDWARD D BASHAW
10/01/2009