Clinical Pharmacology Review

NDA #:	207917
Submission Date:	September 17, 2014
Brand Name:	Epiduo Forte
Generic Name:	Adapalene 0.3%/ benzoyl peroxide 2.5% Gel
Dosage Form:	Gel
Dosage Strength:	Adapalene 0.3%/ benzoyl peroxide 2.5%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	Division of Clinical Pharmacology - 3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Galderma Research and Development Inc.
Relevant IND(s):	(b) (4), 067801
Submission Type:	New-submission
Indication:	Topical treatment of acne vulgaris in subjects 12 years of age and older

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1. Executive Summary

The applicant has developed a new strength of the fixed-dose combination (FDC) of adapalene and benzoyl peroxide in an aqueous gel vehicle for the topical treatment of acne vulgaris in subjects 12 years of age and older. The proposed FDC, Epiduo Forte, contains a (b) (4) of adapalene (0.3% w/w) and the (b) (4) strength of benzoyl peroxide (2.5% w/w) (b) (4) as that of the currently approved fixed-dose combination Epiduo Gel (adapalene/ benzoyl peroxide, 0.1%/2.5%) (NDA 22320, Date of approval 12/08/2008).

The Differin® (adapalene Gel, 0.3% and 0.1%; Cream, 0.1%; Lotion 0.1%) brand of acne monotherapy products are also approved in the US. The applicant of this New Drug Application (NDA) (Galderma) owns the currently approved Epiduo and Differin brands.

To support this NDA, the applicant has conducted three new clinical trials shown below, and have requested for a (b) (4)

- Dermal safety trial in healthy subjects (RD.06.SRE.18242)
- Maximal use pharmacokinetic (PK) trial in subjects with severe acne vulgaris (RD.06.SRE.18229)
- Phase 3 safety and efficacy trial in subjects with moderate to severe acne vulgaris (RD.06.SRE.18240)

The applicant has cross referenced 15 clinical trials from previously approved Differin Gel, 0.3% (NDA 21753, Date of approval 06/19/2007) and Epiduo Gel NDAs. Both Epiduo and Differin brands are owned by the same applicant as this NDA. The Clinical Pharmacology program consists of a new maximal use PK trial (RD.06.SRE.18229) conducted with the new Gel formulation. Hence PK information obtained from other products which is provided by the applicant via cross reference would not directly apply towards decision making for this NDA application.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Applicant.

1.2 Post-Marketing Requirements/ Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics: The applicant has conducted a parallel group maximal use PK trial (RD.06.SRE.18229) that assessed the relative bioavailability of adapalene following administration of adapalene 0.3%/ benzoyl peroxide 2.5% Gel (Epiduo Forte Gel) or adapalene 0.3% Gel (Differin® Gel), in subjects 12 years and older with severe acne vulgaris. The respective formulations were applied once a day to the face, shoulders, upper chest and upper back. Subjects were stratified by age groups, i.e. 12 to 17 years and 18 to 35 years to ensure sufficient numbers of subjects are enrolled in the lower age range (12 to 13 year old). PK was assessed via serial blood sampling on Days 1, 15 and 29.

The results indicated that after the first topical application, adapalene plasma concentrations were quantifiable at low levels in 50% of subjects treated with adapalene 0.3%/benzoyl peroxide 2.5% Gel (range <0.10 to 0.35 ng/mL) and 33% of subjects treated with adapalene 0.3% Gel (range <0.10 to 0.29 ng/mL). At the end of treatment period (Day 29), adapalene plasma levels were quantifiable in 62% of subjects (range

<0.10 to 0.38 ng/mL) and 47% of subjects (range <0.10 to 0.46 ng/mL) treated with adapalene 0.3%/benzoyl peroxide 2.5% Gel and adapalene 0.3% Gel, respectively.

The mean systemic exposure of adapalene (C_{max} and AUC_{0-24h}) could not be accurately calculated at each PK period due to high number of subjects with non-quantifiable systemic exposure. Based on the available systemic exposure (AUC) and trough concentrations (C_{trough}), adapalene systemic concentrations appears to be at or near steady state following administration of the first dose with little or no accumulation. The mean ± SD C_{max} and AUC_{0-24h} of adapalene following administration of the new adapalene 0.3%/benzoyl peroxide 2.5% Gel on Day 29 were quantifiable in 16/26 subjects and were 0.16 ± 0.08 ng/mL and 2.49 ± 1.21 ng.h/mL, respectively.

The applicant performed comparative statistical analysis between the two treatments by 2 methods: (1) Excluding non-quantifiable data and (2) Imputing non-quantifiable data, where lower limit of quantification (LLOQ) was used for C_{max} and the lowest value observed in the trial was used for AUC_{0-24h}. The results of comparative analysis showed that the systemic exposures of adapalene observed with adapalene 0.3%/benzoyl peroxide 2.5% Gel were similar to those observed following treatment with adapalene 0.3% Gel (Differin®).

Benzoyl peroxide has been shown to be rapidly metabolized in the skin to benzoic acid, with approximately 5% of the benzoic acid being systemically absorbed and eliminated unchanged in the urine. Topical benzoyl peroxide formulations have been marketed for more than 30 years at concentrations of up to 10% while the FDC used in this study contains only 2.5% benzoyl peroxide. Hence the applicant has not assessed the PK of benzoyl peroxide in the maximal use PK trial.

Reviewer comments: *Currently marketed Epiduo Gel contains benzoyl peroxide at the same concentration as the FDC product proposed in this application. The requirement for PK assessment of benzoyl peroxide was waived in the Epiduo Gel NDA application, due to the aforementioned reasons (see Clinical Pharmacology review in DARRTS dated 10/27/2008 by Dr. Abimbola Adebowale under NDA 022320). Based on this information, this reviewer concurs with the applicant's approach of not determining the PK of benzoyl peroxide in this NDA.*

Dose finding: The applicant has not conducted any new dose selection trials. The proposed dose and dosing regimen selection was based on the efficacy and safety results from previously conducted dose finding trials that were submitted with original NDA applications of currently approved Adapalene, 0.3% Gel (Differin®) (NDA 21753) and adapalene 0.1%/benzoyl peroxide 2.5% Gel (Epiduo®) (NDA 22320).

Drug interaction assessments: The applicant has not conducted any new drug interaction studies with this NDA. The drug interaction findings were derived from Differin® Gel, 0.3%. The results of the maximal use PK trial have demonstrated that the systemic concentrations of adapalene following administration of this new FDC product are

comparable to those observed following administration of Differin® Gel, 0.3% to subjects with acne vulgaris.

QTc interval prolongation assessment: T (b) (4) The reason for not performing a TQT trial is that the systemic exposure of adapalene following administration of this new FDC Gel formulation is comparable to those obtained following administration of Differin® Gel, 0.3% under maximal use conditions and benzoyl peroxide in concentrations ranging from 2.5% to 10% is widely available in prescription and over the counter (OTC) dosage forms. (b) (4) No QT interval prolongation signals are reported for Differin Gel, 0.3% or benzoyl peroxide.

Pediatric assessment: The applicant has studied pediatric subjects down to 12 years of age in the maximal use PK trial (RD.06.SRE.18229) and the Phase 3 efficacy and safety trial (RD.06.SRE.18240). For subjects 9 to 11 years of age, the applicant has requested for a waiver as they believe this product would not represent a meaningful therapeutic benefit over existing therapies. For subjects less than 9 years of age, the applicant has requested for a waiver as they believe that studies would be highly impractical because the number of pediatric subjects with disease in this age group is very small.

Reviewer comments: *The applicant submitted their initial Pediatric Study Plan (iPSP) on June 18, 2013 to IND 067801. The applicant had proposed to evaluate PK, safety and efficacy in pediatric subjects with acne vulgaris aged 12 to 17 years and requested for a partial waiver in subjects aged 11 years and below due to reasons mentioned above. The Agency issued an agreement to the iPSP on 12/26/2013 (see communication in DARRTS under IND 067801).*

Clinical Pharmacology Briefing: An optional intra-division level briefing was conducted on May 04, 2015 with the following in attendance: CAPT. E. Dennis Bashaw, Lei Zhang, An-Chi Lu, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 Regulatory pathway

2.1.1 What regulatory pathway has the Applicant followed?

The Differin® (adapalene 0.1% and 0.3%) brand of monotherapy products and Epiduo® brand of combination product (adapalene 0.1% and benzoyl peroxide 2.5%) is approved in the US for the treatment acne vulgaris. The applicant of this NDA owns both Differin and Epiduo brands; however, since the applicant is relying on literature for benzoyl peroxide, this NDA will follow a 505(b)(2) regulatory pathway.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry the formulation?

Drug substance and Formulation: The molecular formula of adapalene is $C_{28}H_{28}O_3$ and its molecular weight is 412.5. While the molecular formula of benzoyl peroxide is $C_{14}H_{10}O_4$ (b) (4) and its molecular weight is 242.23 (anhydrous). The chemical structure of adapalene and benzoyl peroxide are shown in Figure 1 and 2, respectively.

Figure 1: Structure of adapalene

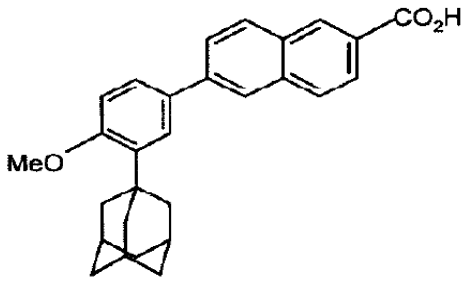
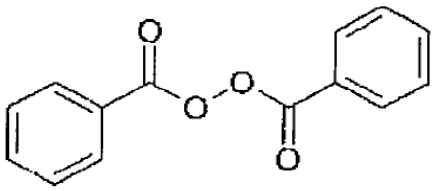


Figure 2: Structure of benzoyl peroxide



Formulation: This proposed fixed-dose combination contains a higher strength of adapalene (0.3% w/w) and the same strength of benzoyl peroxide (2.5% w/w) in the same dosage form and the (b) (4) as that of the currently approved fixed-dose combination Adapalene 0.1% / Benzoyl Peroxide 2.5% Gel (Epiduo® Gel - NDA 022320). The composition of the to-be-marketed formulation is shown in Table 1 below.

Table 1: Qualitative and quantitative composition of to-be-marketed formulation of adapalene 0.3% and benzoyl peroxide 2.5% Gel

Components	Function	Percent Formula (w/w)	Quantity per g	Reference to Quality Standards
Active Compounds				
Adapalene	Active Ingredient	0.30	0.003	In-house monograph
Benzoyl Peroxide	Active Ingredient	2.50 (b) (4)	0.025 (b) (4)	USP[(b)]
Excipients				
(b) (4)				In-house monograph
Docusate Sodium	(b) (4)			USP
Edetate Disodium				USP
Glycerin				USP
Poloxamer 124				NF
Propylene Glycol				USP
Purified Water				USP

[(a)]This (b) (4) was discussed in NDA # 022320, SN0000, (b) (4)

[(b)]USP monograph with addition of specifications for particle size and modification of HPLC method for impurities

(b) (4) is a non-compendial excipient component of Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel, previously approved by FDA (NDA # 022320, SN0000, (b) (4)

2.2.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action:

Adapalene: Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

Benzoyl peroxide: Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

Therapeutic indication: Topical treatment of acne vulgaris in patients 12 years of age and older.

2.2.3 What is the proposed route of administration, dosage and dosing frequency?

Proposed route of administration: Topical.

Proposed dosage: Apply a thin layer of Epiduo Forte gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes.

Proposed dosing frequency: Once daily.

2.3 General Clinical Pharmacology

2.3.1 What were the clinical trials conducted to support this NDA?

The applicant has conducted three new clinical trials and this includes a maximal use PK trial (RD.06.SRE.18229) and one Phase 3 safety and efficacy trial (RD.06.SRE.18240). PK of Epiduo Forte gel was assessed only in the maximal use PK trial. The applicant has also cross referenced 8 clinical trials from their Differin® Gel, 0.3% NDA (NDA 21753) and 7 clinical trials from their Epiduo® Gel NDA (NDA 22320). A summary of all clinical trials submitted in this NDA is provided in Table 2 below.

Table 2: List of all clinical trials to support this NDA

Study Number	Objective(s) of the Study	Study Population	Number of Subjects	Duration of Treatment
Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel				
RD.06.SRE.18242	Dermal Tolerance (Cumulative Irritancy)	Healthy subjects	36	3 Weeks
RD.06.SRE.18229	Pharmacokinetics	Subjects with acne vulgaris	58	4 Weeks
RD.06.SRE.18240	Efficacy/Safety	Subjects with acne vulgaris	503	12 Weeks
Adapalene 0.3% Gel				
RD.03.SRE.2644	Dermal Tolerance (Cumulative Irritation and Contact Sensitization)	Healthy subjects	215	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 48 Hour Application
RD.03.SRE.2645	Dermal Tolerance (Photosensitivity)	Healthy subjects	30	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 24 Hour Application
1.CG.03.SRE.2646	Dermal Tolerance (Phototoxicity)	Healthy subjects	25	24 Hours
RD.03.SRE.2690	Pharmacokinetics	Subjects with acne vulgaris	16	10 Days
RD.06.SRE.18115	Pharmacokinetics	Subjects with acne vulgaris	51	30 Days
RD.06.SRE.18060	Efficacy/Safety	Subjects with acne vulgaris	214	12 Weeks
RD.06.SRE.18081	Efficacy/Safety	Subjects with acne vulgaris	653	12 Weeks
RD.06.SRE.18082	Long Term Safety	Subjects with acne vulgaris	551	12 Months
Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel				
RD.03.SRE.2681	Dermal Tolerance (Phototoxicity)	Healthy subjects	25	24 Hours
RD.03.SRE.2682	Dermal Tolerance (Photosensitivity)	Healthy subjects	33	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 24 Hour Application
RD.03.SRE.2683	Dermal Tolerance (Cutaneous Sensitization)	Healthy subjects	251	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 48 Hour Application
RD.06.SRE.18097	Pharmacokinetics	Subjects with acne vulgaris	24	30 Days
RD.06.SRE.18094	Efficacy/Safety	Subjects with acne vulgaris	517	12 Weeks
RD.06.SRE.18087	Efficacy/Safety	Subjects with acne vulgaris	1668	12 Weeks
RD.06.SRE.18089	Long Term Safety	Subjects with acne vulgaris	452	12 Months

2.3.2 How was the dose selected?

The applicant has not conducted any new dose selection trials. The proposed dose and dosing regimen selection was based on the efficacy and safety results from previously conducted dose finding trials that were submitted with original NDA applications of currently approved Adapalene, 0.3% Gel (Differin®) (NDA 21753) and adapalene 0.1%/benzoyl peroxide 2.5% Gel (Epiduo®) (NDA 22320).

2.3.3 What is the pharmacokinetics (PK) of adapalene under maximal use conditions?

Trial design in brief: The objective of the maximal use PK trial (RD.06.SRE.18229) was to compare the systemic exposure of adapalene following once a day application for 28 days of the new fixed-dose combination (FDC) adapalene 0.3%/ benzoyl peroxide 2.5% Gel (also known as CD0271 0.3% / CD1579 2.5% Gel) compared to Differin® Gel, 0.3% in subjects 12 years and older with severe acne vulgaris. 58 subjects with severe acne were randomized in a 1:1 ratio to the two treatment arms. Subjects were stratified according to gender (male or female) and age (18 to 35 years or 12 to 17 years) with a minimum of 8 subjects in each stratum. Sufficient quantity of study drugs were applied by the clinical staff each morning to leave a thin film on the entire face (avoiding the eyelids, lips and open wounds), upper back and upper chest to mid-chest, top of the shoulders down to shoulder blades, excluding the neck and armpits. There was no self-application by subjects in this trial. Serial plasma samples for PK analysis were collected on Days 1, 15, and 29, with additional pre-dose samples obtained on pre-specified days as per schedule shown in Tables 15 and 16 in Section 4 of this review (Further details can be found in Section 4 of this review).

PK of adapalene: After the first topical application (Day 1), adapalene plasma concentrations were quantifiable at low levels in 14 of 28 subjects (50%) in the adapalene 0.3%/ benzoyl peroxide 2.5% Gel group (C_{max} range 0.10 ng/mL to 0.35 ng/mL) and 10 of 30 subjects (33%) in the Differin 0.3% Gel group (C_{max} range 0.12 ng/mL to 0.29 ng/mL).

After 2 weeks of repeated once daily treatment, systemic adapalene levels on Day 15 were quantifiable at low levels in 12 of 26 subjects (46%) in the adapalene 0.3%/ benzoyl peroxide 2.5% Gel group (C_{max} range 0.11 ng/mL to 0.29 ng/mL) and 16 of 30 subjects (53%) in the Differin 0.3% Gel group (C_{max} range 0.10 ng/mL to 0.40 ng/mL).

After 4 weeks of repeated once daily treatment, systemic adapalene levels on Day 29 were quantifiable at low levels in 16 of 26 (62%) subjects in the adapalene 0.3%/ benzoyl peroxide 2.5% Gel group (C_{max} range 0.10 ng/mL to 0.38 ng/mL) and 14 of 30 subjects (47%) in the Differin 0.3% Gel group (C_{max} range 0.10 ng/mL to 0.46 ng/mL).

Mean adapalene plasma profiles on Day 1 (after the first dose) and after multiple doses on Day 15 and Day 29 are shown in Figure 3, 4, and 5, respectively.

Figure 3: Mean of adapalene plasma concentrations (ng/mL) on Day 1

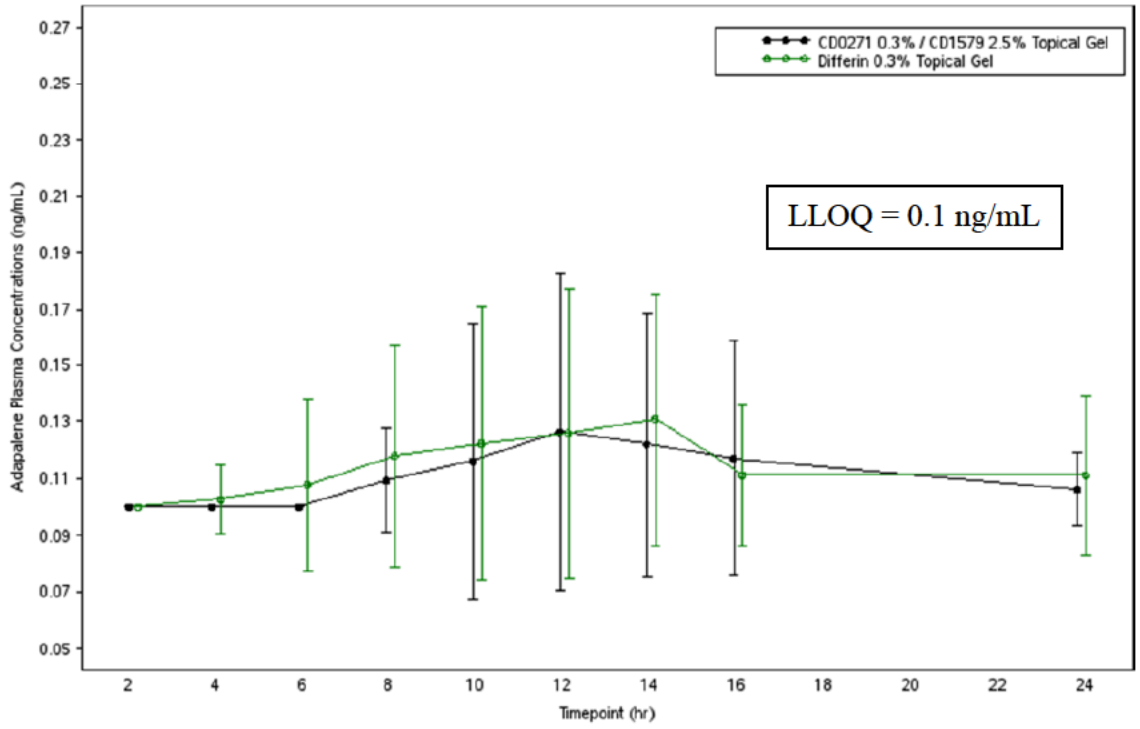


Figure 4: Mean of adapalene plasma concentrations (ng/mL) on Day 15

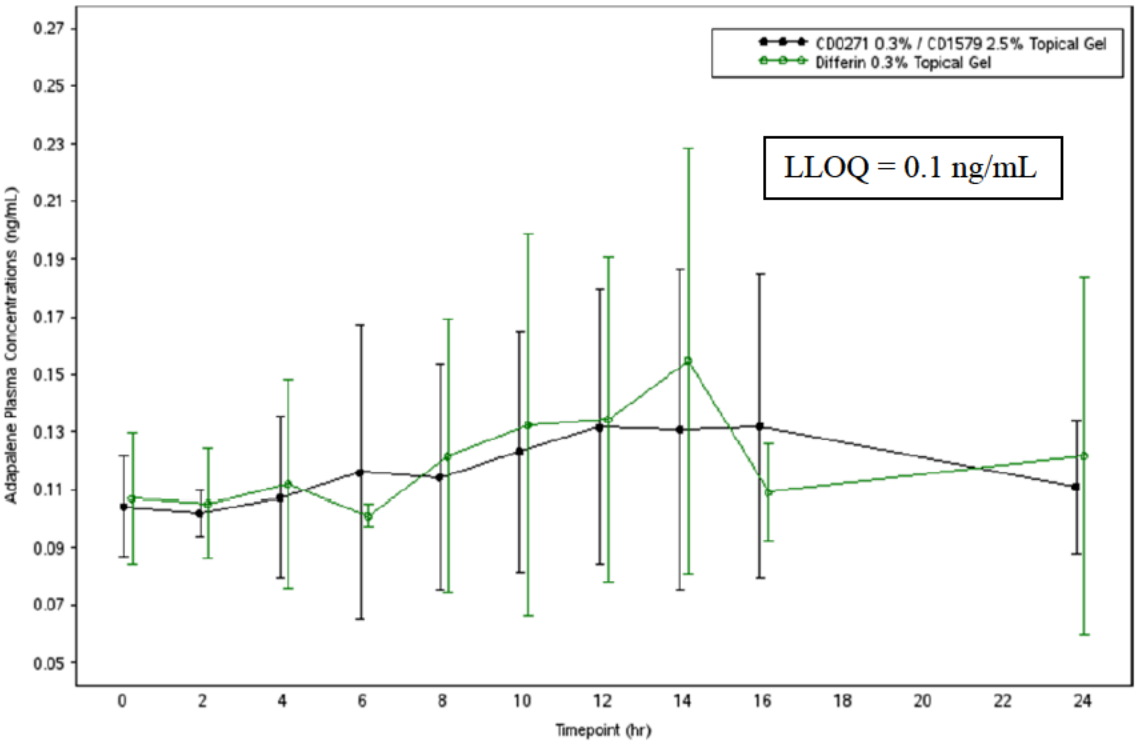
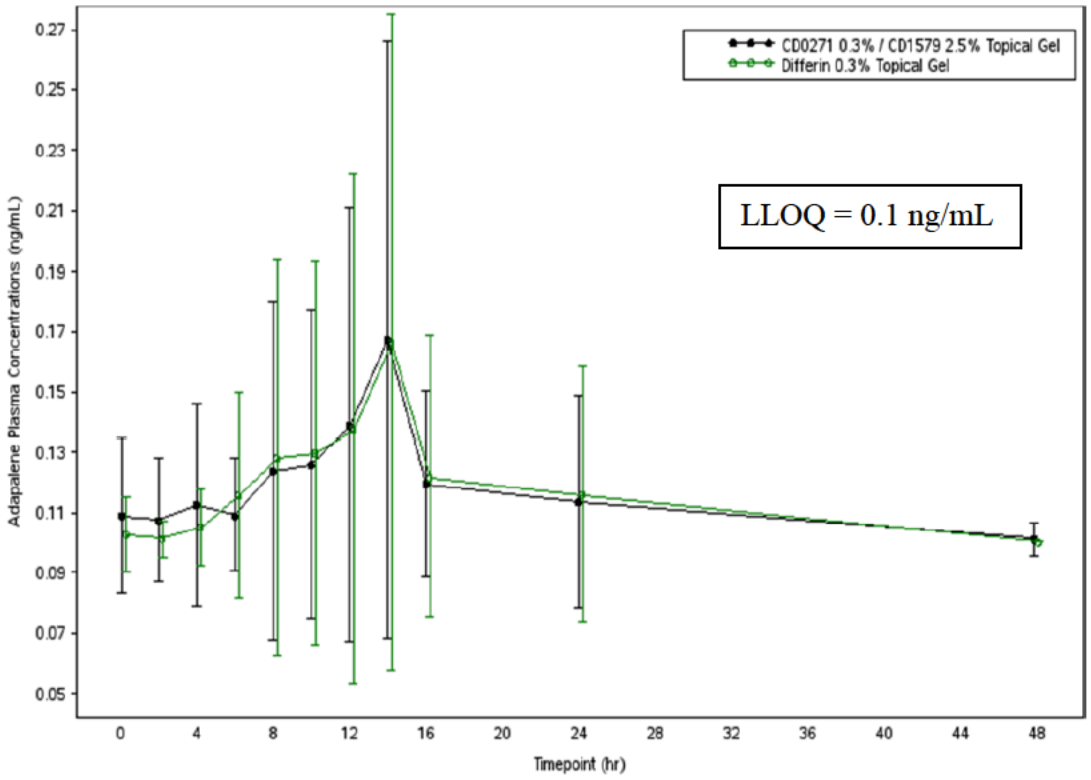


Figure 5: Mean of adapalene plasma concentrations (ng/mL) on Day 29



The mean systemic exposure to adapalene (C_{max} and $AUC_{0\text{-}24h}$) could not be accurately calculated at each PK period due to the high number of subjects with non-quantifiable systemic exposure. Overall, the mean $AUC_{0\text{-}24h}$ was 2.49±1.21 ng.h/mL at Day 29 in subjects in the adapalene 0.3%/ benzoyl peroxide 2.5%Gel group and 2.47±1.31 ng.h/mL at Day 15 in subjects in the Differin 0.3% Gel group. On Day 29, the $AUC_{0\text{-}24h}$ ranged from 1.63 to 6.41 ng.h/mL and from 1.64 to 7.40 ng.h/mL in the adapalene 0.3%/ benzoyl peroxide 2.5%Gel group and the Differin 0.3% Gel group, respectively (Table 3).

Table 3: Adapalene PK parameters

		CD0271 0.3% / CD1579 2.5% Gel (N=28)				Differin 0.3% Gel (N=30)			
		C_{max}	T_{max}	AUC_{0-24h}	AUC_{0-t}	C_{max}	T_{max}	AUC_{0-24h}	AUC_{0-t}
		(ng/mL)	(h)	(ng.h/mL)	(ng.h/mL)	(ng/mL)	(h)	(ng.h/mL)	(ng.h/mL)
Day 1	Mean ± SD	0.13±0.06	13.4±4.9	2.11±0.75	1.55±1.09	NR	NR	NR	NR
	N (n quantifiable)	28 (14)	-	-	-	30 (10)	-	-	-
	Min - Max	0.10-0.35	8.0-23.8	1.63-4.49	0.76-4.49	0.12-0.29	8.0-24.5	2.16-4.85	1.58-4.85
	CV (%)	45%	-	35%	70%	-	-	-	-
Day 15	Mean ± SD	NR	NR	NR	NR	0.15±0.08	11.5±5.6	2.47±1.31	1.90±1.61
	N (n quantifiable)	26 (12)	-	-	-	30 (16)	-	- (15)[a]	- (15)[a]
	Min - Max	0.10-0.29	0.0-14.0	1.82-5.19	1.20–5.19	0.1-0.4	0.0-23.9	1.63-6.90	0.76-6.90
	CV (%)	-	-	-	-	52%	-	53%	85%
Day 29	Mean ± SD	0.16±0.08	13.5±5.8	2.49±1.21	2.10±1.93	NR	NR	NR	NR
	N (n quantifiable)	26 (16)	-	-	-	30 (14)	-	-	-
	Min - Max	0.10-0.38	0.0-24.0	1.63-6.41	0.76-8.13	0.10-0.46	0.0-23.6	1.64-7.40	0.76-7.40
	CV (%)	53%	-	49%	91%	-	-	-	-

Note: N quantifiable is sourced from the PK Report in Appendix 16.1.12.
Note: Descriptive statistics were provided when at least 50% of subjects per visit presented quantifiable adapalene systemic levels. For descriptive statistics calculations, non-quantifiable C_{max} values were imputed by the limit of quantification (LOQ: 0.1 ng/mL); and non-quantifiable AUC were imputed to the lowest values obtained in this study (AUC_{0-t} = 0.756 ng.h/mL, AUC_{0-24h} = 1.634 ng.h/mL). However, if less than 50% of data were quantifiable, only the minimum and maximum values are presented.
[a] Subject 8076-024 at Day 15 presented one single quantifiable time-point at T_0, and so AUC calculation was not feasible.

The subject with highest systemic exposure to adapalene (AUC_{0-24h}) in the CD0271 0.3% / CD1579 2.5% Gel group was a 14-year-old male subject who received a daily dose of 2.48 g (Subject 8139-026: at Day 29 had C_{max} 0.35 ng/mL and AUC_{0-24h} 6.41 ng.h/mL). The most exposed subject to adapalene (AUC_{0-24h}) in the Differin 0.3% Gel group was a 17-year-old female subject who received a daily dose of 2.18 g (Subject 8139-020: at Day 29, C_{max} 0.46 ng/mL, AUC_{0-24h} 7.40 ng.h/mL). The prime purpose of PK assessment was to calculate the relative bioavailability (BA) of adapalene following administration of the two formulations and the results are shown in Section 2.3.4.

Assessment of steady state: The mean systemic exposure of adapalene (C_{max} and AUC_{0-24h}) could not be accurately calculated at each PK period due to high number of subjects with non-quantifiable systemic exposure. Based on the available systemic exposure (AUC_{0-24h}) (see Table 5 and 7) and the range of trough concentrations (C_{trough}) (Table 4), adapalene systemic concentrations appears to be at or near steady state following administration of the first dose with little or no accumulation for both the treatment groups.

Table 4: Summary of residual concentrations C_{trough} (ng/mL)

Residual concentration C_{trough} (ng/mL)	Descriptive statistics	CD0271 0.3% / CD1579 2.5% Gel (N=28)	Differin 0.3% Gel (N=30)
Day 2	N (N quantifiable) Min - Max	28 (8) 0.10-0.15	30 (7) 0.10-0.23
Day 10[a]	N (N quantifiable) Min - Max	14 (2) 0.13-0.21	15 (1) 0.16-0.16
Day 15	N (N quantifiable) Min - Max	26 (2) 0.12-0.19	30 (5) 0.10-0.19
Day 16	N (N quantifiable) Min - Max	26 (6) 0.12-0.17	30 (8) 0.10-0.39
Day 22[a]	N (N quantifiable) Min - Max	14 (1) 0.10-0.10	15 (2) 0.11-0.25
Day 29	N (N quantifiable) Min - Max	26 (4) 0.11-0.20	30 (2) 0.11-0.17

[a]According to the protocol, adolescent subjects (12-17 years old) were not sampled at Days 10 and 22
Note: N quantifiable is sourced from the PK Report in Appendix 16.1.12.

Reviewer comments: *Due to high number of non-quantifiable subjects the mean values of trough concentrations (C_{trough}) were not calculated. However, based on the range of trough concentrations provided in the Table 4 above along with the ratios of values of AUC_{0-24h} (Tables 5 and 7) (calculation of ratios between treatment days is not shown), it is reasonable to assume adapalene concentrations to be at or near steady state following administration of the first dose for both the treatment arms.*

PK of benzoyl peroxide: Only plasma concentrations of adapalene were quantified. Benzoyl peroxide concentrations were not quantified because benzoyl peroxide has been shown to be metabolized in the skin to benzoic acid, with approximately 5% of the benzoic acid being systemically absorbed and eliminated unchanged in the urine. Topical benzoyl peroxide formulations have been marketed for more than 30 years at a concentration of up to 10% while Epiduo Forte Gel contains only 2.5% benzoyl peroxide.

Reviewer comments: *Currently marketed Epiduo Gel contains benzoyl peroxide at the same concentration as Epiduo Forte Gel product proposed in this application. The requirement for PK assessment of benzoyl peroxide was waived in the Epiduo Gel NDA application, due to the aforementioned reasons (see Clinical Pharmacology review in DARRTS dated 10/27/2008 by Dr. Abimbola Adebowale under NDA 022320). Based on this information, this reviewer concurs with the applicant's approach of not determining the PK of benzoyl peroxide in this NDA.*

2.3.4 What were the results of relative bioavailability (BA) between the two treatments?

Due to high number of non-quantifiable data the applicant performed treatment comparison to assess relative BA of adapalene in two ways as shown below:

- Treatment comparison when excluding non-quantifiable data
- Treatment comparison when imputing non-quantifiable data

The results of the treatment comparison using the above two approaches showed that the systemic exposure of adapalene following administration of Epiduo Forte Gel are not higher than those produced following administration of Differin, 0.3% Gel. Details are provided below.

Treatment comparison when excluding non-quantifiable data: The summary of descriptive statistics and inferential statistical analysis is shown in Table 5 and 6.

Table 5: Summary of descriptive statistics of PK parameters when excluding non-quantifiable data

Visit Parameter	CD0271 0.3%/CD1579 2.5% Topical Gel (N=28)	Differin 0.3% Topical Gel (N=30)
Baseline/Day 1		
AUC0-24h (ng*h/mL)		
n	14	10
Mean	2.592	3.196
SD	0.8137	0.8221
CV%	31%	26%
Geometric Mean	2.487	3.104
Median	2.514	3.158
Min, Max	1.63, 4.49	2.16, 4.85
Cmax (ng/mL)		
n	14	10
Mean	0.160	0.195
SD	0.0726	0.0605
CV%	45%	31%
Geometric Mean	0.149	0.187
Median	0.143	0.173
Min, Max	0.10, 0.35	0.12, 0.29
Day 15		
AUC0-24h (ng*h/mL)		
n	12	15
Mean	3.055	3.306
SD	1.0035	1.4323
CV%	33%	43%
Geometric Mean	2.910	3.075
Median	3.043	2.780
Min, Max	1.82, 5.19	1.88, 6.90
Cmax (ng/mL)		
n	12	15
Mean	0.186	0.199
SD	0.0581	0.0866
CV%	31%	44%
Geometric Mean	0.178	0.184
Median	0.186	0.181
Min, Max	0.11, 0.29	0.10, 0.40

Visit Parameter	CD0271 0.3%/CD1579 2.5% Topical Gel (N=28)	Differin 0.3% Topical Gel (N=30)
Day 29		
AUC0-24h (ng*h/mL)		
n	16	14
Mean	3.027	3.378
SD	1.2895	1.6424
CV%	43%	49%
Geometric Mean	2.822	3.072
Median	2.359	2.671
Min, Max	1.79, 6.41	1.64, 7.40
Cmax (ng/mL)		
n	16	14
Mean	0.190	0.204
SD	0.0901	0.1015
CV%	47%	50%
Geometric Mean	0.172	0.185
Median	0.166	0.171
Min, Max	0.10, 0.38	0.10, 0.46

Note: Subjects with either missing/not calculated AUC or Cmax below 0.1 ng/mL are excluded from this table.
CV% = 100*(SD/Arithmetic Mean).

Table 6: Inferential statistical analysis of Pharmacokinetics parameters when excluding non-quantifiable data (Treatment comparison)

		Least Square Means [1]					
Visit Parameter	N	CD0271 0.3%/CD1579 2.5% Topical Gel	Differin 0.3% Topical Gel	Ratio [2]	%CV [3]	90% CI [4]	P-Value [5]
Baseline/Day 1							
AUC0-24h (ng*h/mL)	24	2.487	3.104	0.801	28.3	(0.658, 0.976)	0.067
Cmax (ng/mL)	24	0.149	0.187	0.797	36.1	(0.621, 1.022)	0.132
Day 15							
AUC0-24h (ng*h/mL)	27	2.910	3.075	0.946	36.7	(0.748, 1.197)	0.692
Cmax (ng/mL)	27	0.178	0.184	0.967	38.2	(0.757, 1.235)	0.817
Day 29							
AUC0-24h (ng*h/mL)	30	2.822	3.072	0.918	42.0	(0.715, 1.180)	0.569
Cmax (ng/mL)	30	0.172	0.185	0.931	47.0	(0.705, 1.230)	0.665

*: Subjects with either missing/not calculated AUC or Cmax below 0.1 ng/mL are excluded from this table.
[1] Anti-log transformation of least-squares geometric means of log transformed data.
[2] Ratio calculated as Anti-log transformation of the estimate from the one-way analysis of variance model (Anova) with treatment as fixed effect.
[3] Estimated intra-subject coefficient of variation, %CV=100*SQRT(eMSE-1), where MSE is the mean square error term from the ANOVA.
[4] The 90% confidence interval on the ratio.
[5] P-value from the analysis of variance model (ANOVA) with treatment as fixed effect.

Treatment comparison when imputing non-quantifiable data: To conduct this analysis, non-quantifiable data were imputed, C_{max} to the L.O.Q. (0.1 ng/mL) and $AUC_{0\text{-}24h}$ to the lowest value observed in the study (1.634 ng.h/mL). Summary of descriptive statistics and inferential statistical analysis when non-quantifiable data are imputed are shown in Table 7 and Table 8, respectively.

Table 7: Summary of descriptive statistics of Pharmacokinetics parameters when imputing non-quantifiable data

Visit Parameter	CD0271 0.3%/CD1579 2.5% Topical Gel (N=28)	Differin 0.3% Topical Gel (N=30)
Baseline/Day 1		
AUC0-24h (ng*h/mL)		
n	28	30
Mean	2.113	2.155
SD	0.7460	0.8778
CV%	35%	41%
Geometric Mean	2.016	2.024
Median	1.634	1.634
Min, Max	1.63, 4.49	1.63, 4.85
Cmax (ng/mL)		
n	28	30
Mean	0.130	0.132
SD	0.0590	0.0568
CV%	45%	43%
Geometric Mean	0.122	0.123
Median	0.100	0.100
Min, Max	0.10, 0.35	0.10, 0.29

Visit Parameter	CD0271 0.3%/CD1579 2.5% Topical Gel (N=28)	Differin 0.3% Topical Gel (N=30)
Day 15		
AUC0-24h (ng*h/mL)		
n	26	30
Mean	2.290	2.470
SD	0.9822	1.3090
CV%	43%	53%
Geometric Mean	2.133	2.242
Median	1.634	1.757
Min, Max	1.63, 5.19	1.63, 6.90
Cmax (ng/mL)		
n	26	30
Mean	0.140	0.150
SD	0.0582	0.0783
CV%	42%	52%
Geometric Mean	0.130	0.136
Median	0.100	0.102
Min, Max	0.10, 0.29	0.10, 0.40
Day 29		
AUC0-24h (ng*h/mL)		
n	26	30
Mean	2.491	2.448
SD	1.2145	1.4114
CV%	49%	58%
Geometric Mean	2.287	2.194
Median	2.081	1.634
Min, Max	1.63, 6.41	1.63, 7.40
Cmax (ng/mL)		
n	26	30
Mean	0.155	0.149
SD	0.0828	0.0862
CV%	53%	58%
Geometric Mean	0.140	0.133
Median	0.106	0.100
Min, Max	0.10, 0.38	0.10, 0.46

Note: For subjects with Cmax below BLQ, or AUC missing, their values are imputed by the following: Cmax = 0.1 ng/mL and AUC0-24h = 1.634 (ng*h/mL).
CV% = 100*(SD/Arithmetic Mean).

Table 8: Inferential statistical analysis of Pharmacokinetics parameters when imputing non-quantifiable data (Treatment comparison)

		Least Square Means [1]					
Visit Parameter	N	CD0271 0.3%/ CD1579 2.5% Topical Gel	Differin 0.3% Topical Gel	Ratio [2]	%CV [3]	90% CI [4]	P-Value [5]
Baseline/Day 1							
AUC0-24h (ng*h/mL)	58	2.016	2.024	0.996	32.6	(0.866, 1.146)	0.963
Cmax (ng/mL)	58	0.122	0.123	0.991	34.9	(0.854, 1.150)	0.919
Day 15							
AUC0-24h (ng*h/mL)	56	2.133	2.242	0.951	40.8	(0.798, 1.134)	0.637
Cmax (ng/mL)	56	0.130	0.136	0.961	40.8	(0.806, 1.145)	0.704
Day 29							
AUC0-24h (ng*h/mL)	56	2.287	2.194	1.042	43.5	(0.865, 1.256)	0.711
Cmax (ng/mL)	56	0.140	0.133	1.049	45.7	(0.863, 1.275)	0.685

**: For subjects with Cmax below BLQ, or AUC missing, their values are imputed by the following: C_{max} = 0.1 ng/mL and $AUC_{0\text{-}24h}$ = 1.634 (ng*h/mL).

[1] Anti-log transformation of least-squares geometric means of log transformed data.

[2] Ratio calculated as Anti-log transformation of the estimate from the one-way analysis of variance model (Anova) with treatment as fixed effect.

[3] Estimated intra-subject coefficient of variation, %CV=100*SQRT(eMSE-1), where MSE is the mean square error term from the ANOVA.

[4] The 90% confidence interval on the ratio.

[5] P-value from the analysis of variance model (ANOVA) with treatment as fixed effect.

The applicant concluded that overall, treatment comparison using statistical analyses when excluding or imputing non-quantifiable data have shown the similarity of systemic exposure of adapalene following administration of Epiduo Forte Gel and Differin 0.3% Gel.

Reviewer comments: *This reviewer concurs with the applicant's observation. It is noted that the 90% confidence interval (CI) sometimes deviated from the standard bioequivalence (BE) criteria of 80-125%; however, the data suggests that systemic exposures of adapalene following administration of Epiduo Forte Gel were not higher than those produced following administration of Differin 0.3% Gel.*

2.3.5 Did the applicant assess drug metabolism?

The applicant has not conducted any new drug metabolism studies. New studies to assess drug metabolism are not needed at this time because both adapalene and benzoyl peroxide are already marketed products and are available as monads and as a combination product.

2.3.6 What information is submitted to assess or waive TQT trial?

(b) (4). The reason for not performing a TQT trial is that the systemic exposure of adapalene following

administration of this new FDC Gel formulation is comparable to those obtained following administration of Differin® Gel, 0.3% under maximal use conditions and benzoyl peroxide in concentrations ranging from 2.5% to 10% is widely available in prescription and over the counter (OTC) dosage forms. (b) (4) No QT interval prolongation signals are reported for Differin Gel, 0.3% or benzoyl peroxide.

2.3.7 What is the summary of safety?

According to the applicant, in the three new trials conducted, which includes dermal safety trial (RD.06.SRE.18242), maximal use PK trial (RD.06.SRE.18229) and Phase 3 trial (RD.06.SRE.18240), there were no deaths reported. There was only one severe adverse event (SAE) of generalized anxiety disorder reported. Few subjects discontinued due to treatment emergent adverse events (TEAEs) and these events were local and considered to be mild to moderate in severity and included skin irritation, eczema, atopic dermatitis, and skin burning sensation.

Reviewer comments: *For additional details, see Clinical review for overall analysis of safety data.*

2.3.8 What is the summary of efficacy?

Treatment response was defined as the percent of subjects who were rated 'Clear' and 'Almost Clear' at Week 12 with at least a two-grade improvement based on the Investigator's Global Assessment (IGA), and mean absolute change from baseline at Week 12 in both inflammatory and non-inflammatory lesion counts. An IGA score of 'Clear' corresponded to clear skin with no inflammatory or non-inflammatory lesions. An IGA score of 'Almost Clear' corresponded to a few scattered comedones and a few small papules. According to the applicant, superiority of Epiduo Forte Gel over vehicle gel was demonstrated in the overall study population (IGA 3 moderate and IGA 4 severe) at week 12 for IGA success rate (see Table 9).

Table 9: Clinical efficacy of Epiduo Forte Gel at Week 12

	Epiduo Forte gel (N = 217)	**Vehicle gel (N = 69)**
IGA: Two Grade Improvement and Clear or Almost Clear	33.7%	11.0%
Inflammatory Lesions: Mean Absolute (Percent) Change	27.04 (68.70%)	14.40 (39.23%)
Non-inflammatory Lesions: Mean Absolute (Percent) Change	40.18 (68.34%)	18.47 (37.38%)

Reviewer comments: *For additional details see Clinical and Biostatics reviews.*

2.4 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1 Effect of age

Effect of age: The applicant could not perform any statistical analysis to assess the effect of age on PK due to high number of non-quantifiable data. Based on the range of exposure between adolescent (12 to 17 years old) and adult subjects (18 to 35 years old) with quantifiable data, there appears to be no effect of age on PK of adapalene, however, no definitive conclusions can be made (Table 10).

Table 10: Systemic exposure parameters by age

Time point	PK parameter	Descriptive statistics	Adolescent subjects (<18 years)		Adult subjects (≥18 years)	
			CD0271 0.3% / CD1579 2.5% Gel (N=13)	Differin 0.3% Gel (N=15)	CD0271 0.3% / CD1579 2.5% Gel (N=15)	Differin 0.3% Gel (N=15)
Day 1		N quantifiable	8	7	6	3
	AUC_{0-24h} (ng.h/mL)	Mean ± SD Min - Max	2.13±0.72 1.63-3.94	2.37-4.85	1.88-4.49	2.16-3.32
	C_{max} (ng/mL)	Mean ± SD Min, Max	0.13±0.05 0.10-0.27	0.12-0.29	0.10-0.35	0.14-0.23
Day 15		N quantifiable	5	10	7	6
	AUC_{0-24h} (ng.h/mL)	Mean ± SD Min, Max	1.94-3.89	2.96±1.68 1.63-6.90	2.43±1.13 1.63-5.19	2.16-2.91
	C_{max} (ng/mL)	Mean ± SD Min, Max	0.12-0.27	0.18±0.10 0.10-0.40	0.14±0.06 0.10-0.29	0.10-0.19
Day 29		N quantifiable	6	9	10	5
	AUC_{0-24h} (ng.h/mL)	Mean ± SD Min, Max	2.70±1.63 1.63-6.41	2.82±1.75 1.63-7.40	2.31±0.72 1.63-3.80	1.64-4.23
	C_{max} (ng/mL)	Mean ± SD Min - Max	0.18±0.11 0.10-0.38	0.17±0.11 0.10-0.46	0.14±0.05 0.10-0.23	0.15-0.25

Note: N quantifiable is sourced from the PK Report in Appendix 16.1.12.
Note: Descriptive statistics were provided when at least 50% of subjects per visit presented quantifiable adapalene systemic levels. For descriptive statistics calculations, non-quantifiable C_{max} values were imputed by the limit of quantification (LOQ: 0.1 ng/mL); and non-quantifiable AUC were imputed to the lowest values obtained in this study (AUC_{0-t} = 0.756 ng.h/mL, AUC_{0-24h} = 1.634 ng.h/mL). However, if less than 50% of data were quantifiable, only the minimum and maximum values are presented.

2.4.2 Effect of gender

Effect of gender:
The applicant could not perform any statistical analysis to assess the effect of gender on PK due to high number of non-quantifiable data. Based on the range of exposure in male versus female subjects with with quantifiable data, that there appears to be no effect of gender on PK of adapalene, however, no definitive conclusions can be made (Table 11).

Table 11: Summary of systemic exposure parameters by gender

Time point	PK parameter	Descriptive statistics	Male		Female	
			CD0271 0.3% / CD1579 2.5% Gel (N=17)	Differin 0.3% Gel (N=17)	CD0271 0.3% / CD1579 2.5% Gel (N=11)	Differin 0.3% Gel (N=13)
Day 1		N quantifiable	9	5	5	5
	AUC_{0-24h} (ng.h/mL)	Mean±SD Min, Max	2.07±0.65 1.63-3.94	NR 2.16-3.58	NR 1.81-4.49	NR 2.99-4.85
	C_{max} (ng/mL)	Mean±SD Min, Max	0.13±0.05 0.10-0.27	NR 0.12-0.25	NR 0.10-0.35	NR 0.16-0.29
Day 15		N quantifiable	5	7	7	8
	AUC_{0-24h} (ng.h/mL)	Mean±SD Min, Max	NR 1.94-3.89	NR 2.08-6.90	2.68±1.17 1.63-5.19	2.73±1.31 1.63-5.79
	C_{max} (ng/mL)	Mean±SD Min, Max	NR 0.12–0.27	NR 0.10-0.40	0.16±0.07 0.10-0.29	0.15±0.08 0.10-0.35
Day 29		N quantifiable	10	8	6	7
	AUC_{0-24h} (ng.h/mL)	Mean±SD Min, Max	2.56±1.37 1.63-6.41	NR 1.64-5.00	2.35±0.91 1.63-3.99	2.89±1.80 1.63-7.40
	C_{max} (ng/mL)	Mean ± SD Min, Max	0.16±0.09 0.10-0.38	NR 0.11-0.32	0.15±0.07 0.10-0.30	0.17±0.11 0.10-0.46

Note: N quantifiable is sourced from the PK Report in Appendix 16.1.12.
Note: Descriptive statistics were provided when at least 50% of subjects per visit presented quantifiable adapalene systemic levels. For descriptive statistics calculations, non-quantifiable C_{max} values were imputed by the limit of quantification (LOQ: 0.1 ng/mL); and non-quantifiable AUC were imputed to the lowest values obtained in this study (AUC_{0-t} = 0.756 ng.h/mL, AUC_{0-24h} = 1.634 ng.h/mL). However, if less than 50% of data were quantifiable, only the minimum and maximum values are presented.

2.4.3 Pediatric subjects

The applicant has studied pediatric subjects down to 12 years of age in the maximal use PK trial (RD.06.SRE.18229) and the Phase 3 efficacy and safety trial (RD.06.SRE.18240). For subjects 9 to 11 years of age, the applicant has requested for a waiver as they believe this product would not represent a meaningful therapeutic benefit over existing therapies. For subjects less than 9 years of age, the applicant has requested for a waiver as they believe that studies would be highly impractical because the number of pediatric subjects with disease in this age group is very small.

Reviewer comments: *The applicant submitted their initial Pediatric Study Plan (iPSP) on June 18, 2013 to IND 067801. The applicant had proposed to evaluate PK, safety and efficacy in pediatric subjects with acne vulgaris aged 12 to 17 years and requested for a partial waiver in subjects aged 11 years and below due to reasons mentioned above. The Agency issued an agreement to the iPSP on 12/26/2013 (see communication in DARRTS under IND 067801).*

2.4.4 Renal and hepatic impairment

The PK of adapalene 0.3%/ benzoyl peroxide 2.5% Gel in subjects with renal or hepatic impairment was not evaluated by the Applicant. Systemic exposure of adapalene following application of adapalene 0.3%/ benzoyl peroxide 2.5% Gel was similar to those obtained following administration of currently marketed adapalene 0.3% Gel (Differin®).

2.4.5 What pregnancy and lactation use information is there in the application?

The applicant has not conducted any trials in pregnant and lactating women.

2.5 Extrinsic Factors

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated in vivo.

2.5.2 Drug interactions

The applicant has not conducted any new drug interaction studies with this NDA. The drug interaction findings were derived from Differin® Gel, 0.3%. The results of the maximal use PK trial have demonstrated that the systemic concentrations of adapalene following administration of this new FDC product are comparable to those observed following administration of Differin® Gel, 0.3% to subjects with acne vulgaris.

2.6 General Biopharmaceutics

2.6.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable because BCS classification does not apply to topical products.

2.6.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation (0534.0201) was used in the maximal use PK trial and the Phase 3 trial and there was no manufacturing site change. Hence relative bioavailability assessment to bridge between clinical and to-be-marketed formulation is not needed.

2.6.3 What data support or do not support a waiver of in vivo BE data?

The to-be-marketed formulation (0534.0201) was used in the maximal use PK trial and the Phase 3 trial.

2.6.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.7 Analytical Section

2.7.1 How are the active moieties identified, and measured in the clinical trials?

The active moiety was identified and measured using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS)

2.7.2 Which metabolites have been selected for analysis?

None of the metabolites were selected for analysis.

2.7.3 For all moieties measured, is free, bound, or total measured?

Total concentrations were measured for adapalene. Benzoyl peroxide could not be measured due to its rapid conversion to benzoic acid.

2.7.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve was 0.1 ng/mL to 10 ng/mL. The Upper Limit of Quantification (10 ng/mL) was adequate as none of the plasma concentrations in the clinical trials exceed this limit. However, the sensitivity of the assay [Lower Limit of Quantification (0.1 ng/mL)] could have been better due to several subjects with non-quantifiable concentrations. However, the available data would suffice towards regulatory decision on this NDA application.

2.7.5 What are the accuracy and precision at LLOQ?

Between-run mean accuracy = 2.6% (n=80)
Between-run mean precision = 7.6% (n=80)
Within-run mean accuracy = -0.3% (n=6)
Within-run mean precision = 8.6% (n=6)

2.7.6 What is the plasma sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, auto - sampler, etc.)?

Parameter	***Adapalene***
Freeze/Thaw cycle stability	3 cycles at - 20ºC
Room temperature stability	At least 24 hours
Auto-sampler stability	At least 110 hours at + 10 ºC
Long term stability	At least 2 years at - 20 ºC

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for the maximal use PK trial.*

2.7.7 What are the results of incurred sample reanalysis (ISR)?

ISR were performed for approximately 10% of the study samples. The ISR acceptance criteria was defined as individual bias within ±20% of the mean values for at least 2/3 (~ 67%) of the repeats. 125 samples were reanalyzed and 89 samples (~ 71%) passed the acceptance criteria.

3. <u>Detailed Labeling Recommendations</u>

The following changes are recommended in Sponsor's proposed labeling. The **<u>bold and underlined</u>** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

7. DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with EPIDUO FORTE gel.

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

8.4 Pediatric Use

Safety and effectiveness of EPIDUO FORTE gel in pediatric patients under the age of 12 have not been established.

8.5 Geriatric Use

Clinical studies of EPIDUO FORTE gel did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adapalene

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

Benzoyl peroxide

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

12.2 Pharmacodynamics

Pharmacodynamics of EPIDUO FORTE gel is unknown.

12.3 Pharmacokinetics

A pharmacokinetic study was conducted in **<u>26</u>** -adult and adolescent subjects (12 to 33 years of age) with severe acne vulgaris who were treated with once-daily applications during a 4-week period with, on average, 2.3 grams/day (range: 1.6-3.1 grams/day) of EPIDUO FORTE gel applied as a thin layer to the face,

shoulders, upper chest and upper back. After a 4-week treatment, 16 subjects (62%) had quantifiable adapalene plasma concentrations above the limit of quantification (b) (4) of 0.1 ng/mL), with a mean C_{max} of 0.16 ± 0.08 ng/mL and a mean AUC_{0-24hr} of 2.49 ± 1.21 ng.h/mL. The most exposed subject had adapalene C_{max} and AUC_{0-24hr} of 0.35 ng/mL and 6.41 ng.h/mL, respectively. Excretion of adapalene appears to be primarily by the biliary route.

Benzoyl peroxide is absorbed by the skin where it is converted to benzoic acid and eliminated in the urine.

4. INDIVIDUAL STUDY REVIEW

Trial Number: RD.06.SRE.18229 (Maximal use PK trial)

Title: A pharmacokinetic study to determine the systemic exposure to CD0271 (adapalene) during dermal application of either a fixed-dose combination (FDC) of CD0271 0.3%/ CD1579 2.5% Gel (adapalene 0.3%/ benzoyl peroxide 2.5% Gel) or Differin 0.3% Gel for 4 weeks in adolescent and adult subjects with acne vulgaris

Bio-analytical Facility: Galderma [redacted] (b) (4)

Trial Objectives: The primary objective of this trial was to assess and compare the systemic exposure to adapalene following administration of FDC CD0271 0.3% / CD1579 2.5% Gel and Differin 0.3% Gel after repeated once-daily topical applications in subjects with severe acne vulgaris.

Study Drugs: The description of the study drugs is provided in Table 12 below.

Table 12: Description and usage of study drugs

	Investigational product	Comparator Product
Trade Name or Equivalent	Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel	Differin 0.3% Gel
Name of Drug Substance (INN)	adapalene / benzoyl peroxide	adapalene
Internal Code	CD0271 / CD1579	CD0271
Pharmaceutical Form	Gel	Gel
Strength / Concentration	CD0271 0.3% / CD1579 2.5%	CD0271 0.3%
Formula number	[redacted] (b) (4)	
Packaging (type and size)	45 g bottle with pump	30 g tube
Storage Conditions	Store below 25°C; do not freeze or refrigerate	Store at 25°C; excursions permitted to 15° – 30°C (59° – 86°F) Protect from freezing
Dosage (total daily dose)	A thin film applied on face, shoulders, upper chest and upper back. The total amount of product applied will be recorded.	A thin film applied on face, shoulders, upper chest and upper back. The total amount of product applied will be recorded.
Route	Topical	Topical
Dose Regimen	once daily in the morning	once daily in the morning
Duration of administration	4 weeks	4 weeks
Location of Treated Area	Face, shoulders, upper chest and upper back	Face, shoulders, upper chest and upper back

Formulation: Gel.

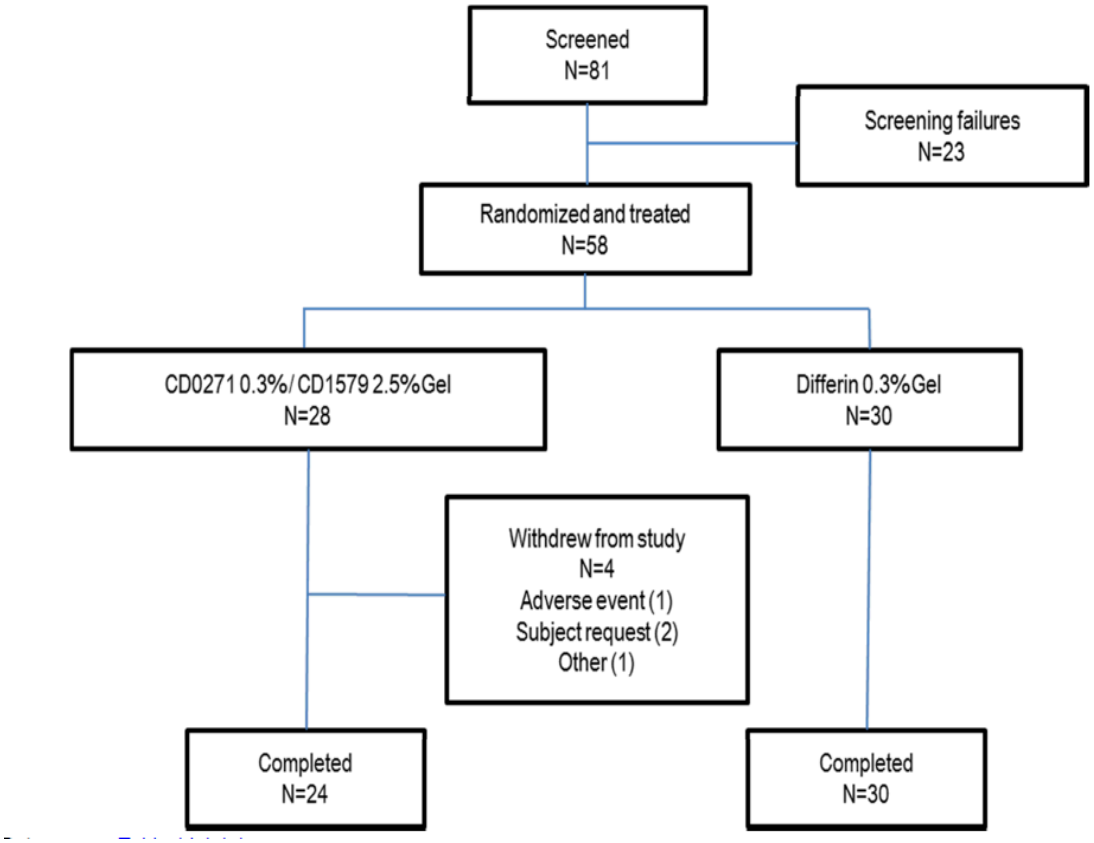
Number of subjects: 58 subjects with severe acne based on Investigator's Global Assessment (IGA) scale score (IGA = 4) (Table 13) were randomized as shown in Figure 6 and subjects were stratified according to gender (male or female) and age (18 to 35

years or 12 to 17 years) with a minimum of 8 subjects in each stratum. There were 4 subjects and 5 subjects within the lowest age range of 12-13 years in adapalene 0.3%/ benzoyl peroxide 2.5% Gel and Differin® Gel, 0.3%, groups respectively (Gender and age distribution is shown in Figure 7 and 8).

Table 13: Investigator's Global Assessment (IGA) scale score

0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

Figure 6: Schematic representation of the Clinical trial



Four subjects withdrew early form the trial and all subjects belonged to CD0271 0.3%/ CD 1579 2.5% Gel arm. Details are provided in Table 14 below.

Table 14: Reasons for subject discontinuation from the trial

Subject No.	Reason for withdrawal	Availability of PK data
Subject 8076-018	Subject was discontinued early at Day 10 due to erythema	Only Day 1
Subject 8333-001	Subject was discontinued early at Day 3 because this subject missed dose on Day 3 and all subsequent visits	Only Day 1
Subject 8139-019	Subject missed the 48 h PK sample on Day 31 due to scheduling conflict	No impact on PK data
Subject 8333-012	Subject missed the 48 h PK sample on Day 31 due to scheduling conflict	No impact on PK data

Reviewer comments: *As shown in Figure 6, there were 28 subjects in the FDC Gel arm at the start of the trial and 24 completed. However PK data are available from 26 subjects following the last drug application.*

Figure 7: Gender and age distribution of subjects in FDC Gel group

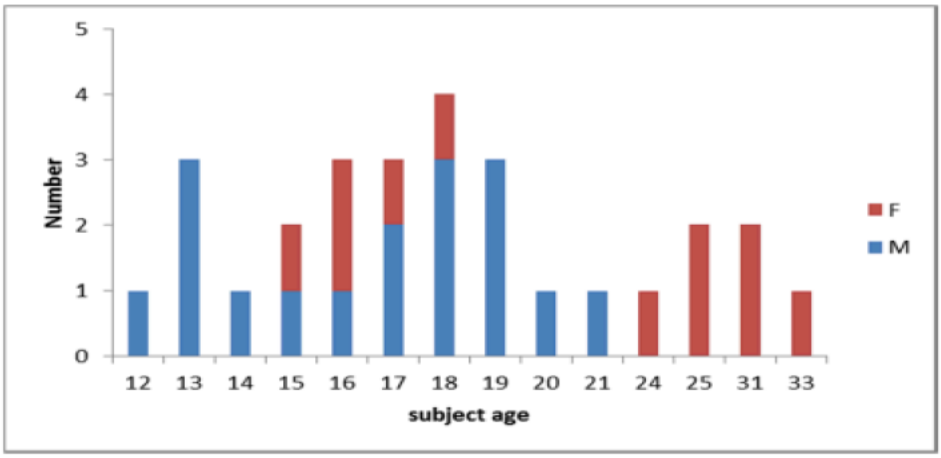
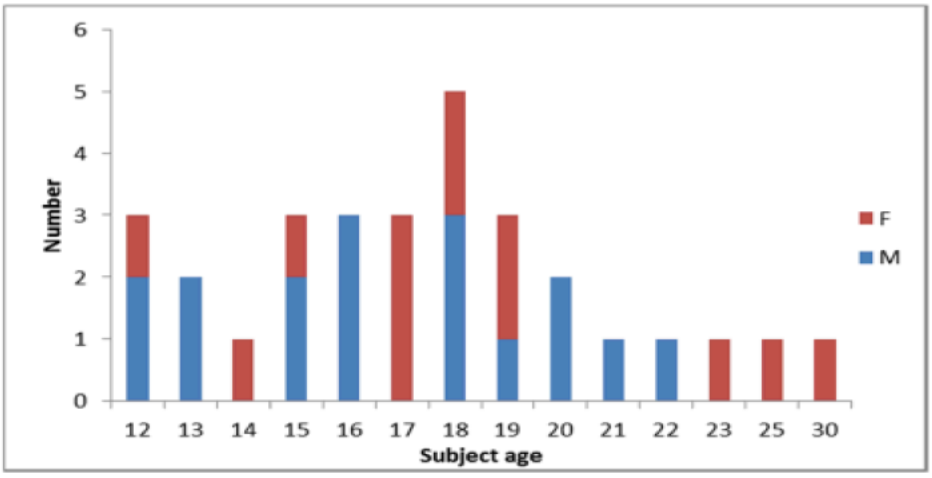


Figure 8: Gender and age distribution of subjects in Differin Gel group



Amount of formulation used: Sufficient quantity of study drugs were applied by the clinical staff each morning to leave a thin film on the entire face (avoiding the eyelids, lips and open wounds), upper back and upper chest to mid-chest, top of the shoulders down to shoulder blades, excluding the neck and armpits. The dose was weighed in a container on a scale prior to each application and was recorded. There was no self-application by subjects in this trial. The weight of the daily dose applied ranged from 1.60 g to 3.05 g in the CD0271 0.3% / CD1579 2.5% Gel group and from 1.39 g to 3.22 g in the Differin 0.3% Gel group.

Reviewer comments: *In the Phase 3 trial (RD.06.SRE.18240), in subjects who applied the study drug on the face and trunk, the mean daily drug usage was 0.917 g (range 0.06 – 3.34 g; median = 0.74 g) of CD0271 0.3%/ CD1579 2.5% Gel, while in subjects who applied to the face only the mean daily usage was 0.821 g (range 0.06 – 3.34 g; median = 0.62 g). Considering this information, the amount of formulation used in the maximal use PK trial appears to be within the upper range.*

PK sampling times: Plasma for PK analysis was collected on Days 1, 2, 10, 15, 16, 22, 29, 30, and 31 in adults and on Days 1, 2, 15, 16, 29, 30 and 31 in adolescent subjects. PK sampling times for adults is shown in Table 15 and for adolescent (12 to 17 years) is shown in Table 16.

Table 15: PK sampling times in adults

PK Sampling Day	Day 1	Day 2	Day 10	Day 15	Day 16	Day 22	Day 29 / Early Termination	Day 30	Day 31
Plasma samples time points[a]	2, 4, 6, 8, 10, 12, and 16 hours after the initial dose	24 hours after initial dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after Day 15 dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after last dose on Day 29	48 hours after last dose on Day 29
Systemic PK parameters	C_{max}, T_{max}, AUC_{0-t} , AUC_{0-24hr}	C_{trough}	C_{trough}	C_{trough} , C_{max}, T_{max}, AUC_{0-t} , AUC_{0-24hr}	C_{trough}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24hr}, AUC_{0-t}, AUC_{0-inf}, Kel, $T_{1/2}$		

a Sampling times = from time of the application start

Table 16: PK sampling times in adolescents (12 to 17 years old)

PK Sampling Day	Day 1	Day 2	Day 15	Day 16	Day 29 / Early Termination	Day 30	Day 31
Plasma samples time points[a]	2, 4, 8, 10, 12, and 14 hours after the initial dose	24 hours after initial dose (Pre-dose)	Pre-dose, 2, 4, 8, 10, 12, and 14 hours after the morning dose	24 hours after Day 15 dose (Pre-dose)	Pre-dose, 2, 4, 8, 10, 12, and 14 hours after the morning dose	24 hours after last dose on Day 29	48 hours after last dose on Day 29
Systemic PK parameters	C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24hr}	C_{trough}	C_{trough} , C_{max}, T_{max}, AUC_{0-t} , AUC_{0-24hr}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24hr}, AUC_{0-t}, AUC_{0-inf}, Kel, $T_{1/2}$		

a Sampling times = from time of the application start

Reviewer comments: *The purpose of the maximal use PK trial is to assess systemic exposure of the drug under maximal use conditions and the trial conducted by the applicant (RD.06.SRE.18229) appears to be adequately designed.*

Demographics: Demographic characters of subjects shown in Table 17 suggest that the population studied appears to be fairly representative of American population.

Table 17: Demographic characteristics

Demographic characteristics		CD0271 0.3% / CD1579 2.5% Gel (N=28)	Differin 0.3% Gel (N=30)	Total (N=58)
Age (years)	n	28	30	58
	Mean	19.0	17.6	18.3
	SD	5.59	4.01	4.84
	Median	18.0	17.5	18.0
	Min, Max	12, 33	12, 30	12, 33
Age group	<18 years	13 (46.4)	15 (50.0)	28 (48.3)
	≥18 years	15 (53.6)	15 (50.0)	30 (51.7)
Gender	Male	17 (60.7)	17 (56.7)	34 (58.6)
	Female	11 (39.3)	13 (43.3)	24 (41.4)
Race	White	21 (75.0)	23 (76.7)	44 (75.9)
	Black or African American	7 (25.0)	6 (20.0)	13 (22.4)
	Asian	0	0	0
	American Indian or Alaskan Native	0	1 (3.3)	1 (1.7)
	Other	0	0	0
Ethnicity	Hispanic or Latino	7 (25.0)	10 (33.3)	17 (29.3)
	Not Hispanic or Latino	21 (75.0)	20 (66.7)	41 (70.7)

Note: Percentages are based on the number of enrolled subjects in the Safety Population with available data in each treatment group.

PK results and relative BA assessment: Results are described in Section 2.3.3 and 2.3.4 and will not be repeated in this section. Included here are individual subject PK profiles of adapalene following administration of new FDC Gel on Days 1, 15 and 29 are shown in Figures 9, 10, and 11, respectively.

Figure 9: Individual subject PK profile on Day 1 following administration of new FDC Gel (LLOQ = 0.1 ng/mL)

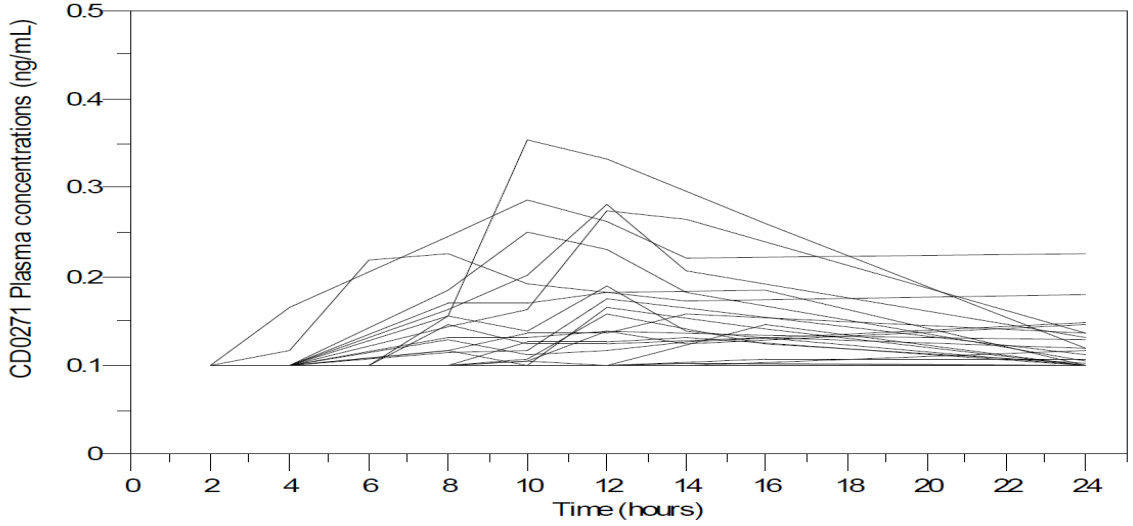


Figure 10: Individual subject PK profile on Day 15 following administration of new FDC Gel (LLOQ = 0.1 ng/mL)

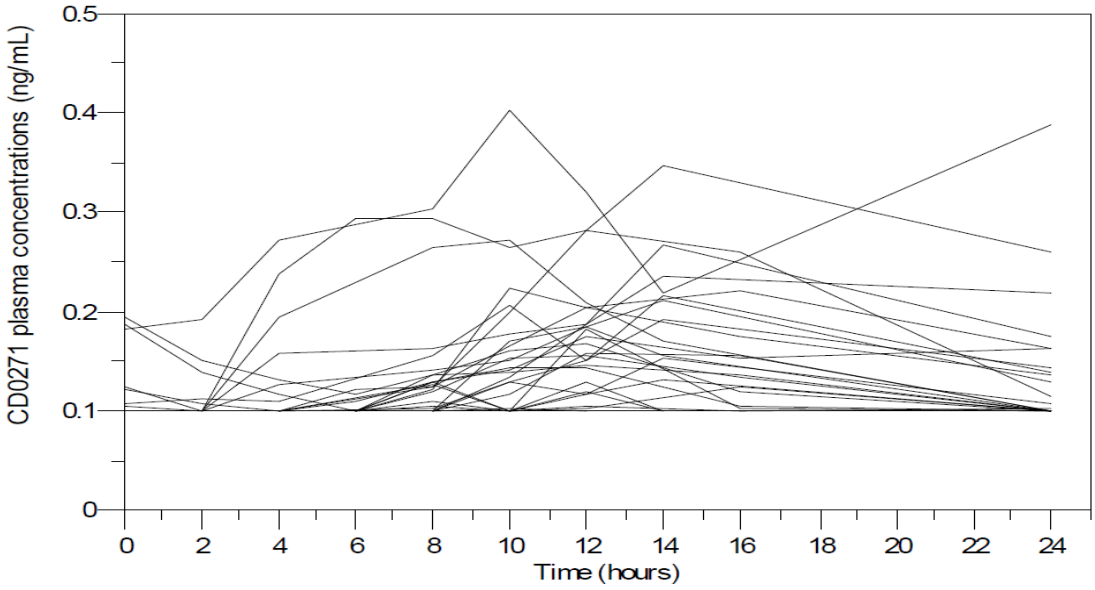
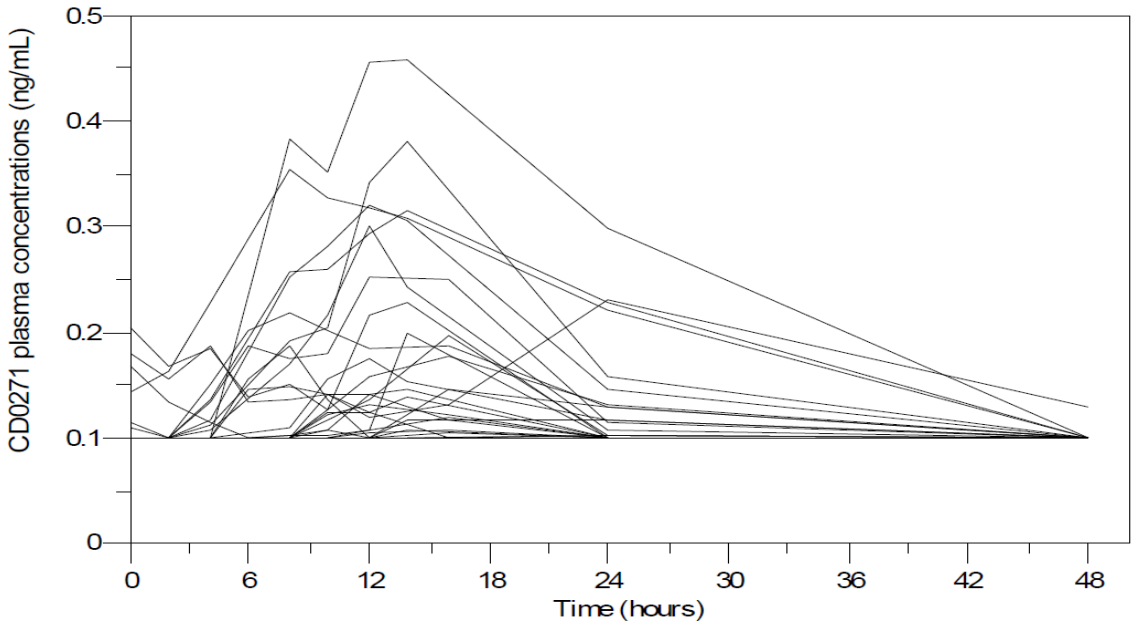


Figure 11: Individual subject PK profile on Day 29 following administration of new FDC Gel (LLOQ = 0.1 ng/mL)



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/s/

CHINMAY SHUKLA
05/05/2015

DOANH C TRAN
05/05/2015