CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020380Orig1s010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	020380/S-010
Submission Date:	September 10, 2015
Brand Name:	Differin Gel, 0.1%
Generic Name:	Adapalene
Dosage Form:	Gel
Dosage Strength:	0.1%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Galderma Labs, LP
Relevant IND(s):	116864
Submission Type:	New supplement
Indication:	Treatment of acne vulgaris

Table of Contents

1. Executive Summary

Differin (adapalene) Gel, 0.1% was approved on 05/31/1996 for the topical treatment of acne vulgaris in subjects 12 years of age and older. The purpose of this supplemental New Drug Application (sNDA) is to switch this product from prescription (Rx) to over-the-counter (OTC).

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable.

1.2 Post-Marketing Requirements/ Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this sNDA the applicant submitted a maximal use pharmacokinetic (PK) trial (RD.06.SRE.18254).

This was a multicenter, open label PK study in 24 subjects 12 years and older with moderate to severe acne vulgaris following once daily application of the drug for 29 days. Drug was applied on the entire area of the face, shoulders, upper chest and upper back. All 24 subjects completed the trial and this included 18 adolescent subjects (aged 12 to 17 years) and 6 adult subjects (aged 18 years and older). PK assessment via serial blood sampling was done on Days 1, 15 and 29 and additional trough concentrations were assessed on Days 2, 10, 16 and 22 in Adults and Days 2 and 16 in adolescent subjects.

By Day 29, systemic concentrations of adapalene were quantifiable in all 24 subjects and steady state was reached by Day 15. The mean ± SD C_{max} and AUC_{0-24} on Day 29 were 0.049 ± 0.030 ng/mL and 0.83 ± 0.49 ng.h/mL, respectively.

Clinical Pharmacology briefing: Not conducted.

Advisory Committee (AC) Meeting: An AC meeting was held on April 15, 2016 at the Hilton, 620 Perry Pkwy., Gaithersburg, MD, where maximal use PK data was presented. The committee discussed data submitted by the applicant to support OTC marketing of Differin Gel, 0.1%. There were 16 voting members and all of them voted in favor (Yes) that the safety of adapalene gel 0.1% for OTC use for the treatment of acne has been adequately demonstrated and the totality of the data support the use of this product OTC.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 Regulatory information

The applicant is requesting an Rx to OTC switch of their already approved Differin (adapalene) Gel 0.1% in subjects with acne vulgaris aged 12 years and older. The indication and age range are identical to approved Differin Gel, 0.1% as Rx.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance and Formulation: For this supplement, the applicant has made no changes to the formulation of the already marketed Differin Gel, 0.1%. Adapalene is a retinoid like product and its structure is shown in Figure 1. The composition of the formulation is shown in Table 1.

Figure 1: Structure of adapalene (Mol. wt. 412.5)

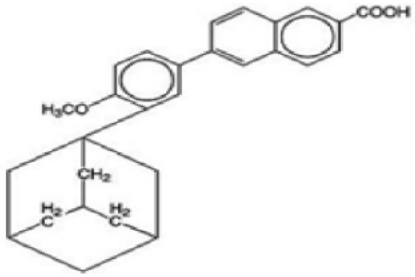


Table 1: Composition of adapalene gel, 0.1% formulation

	Formulation ID No: (b) (4)	
	% (w/w)	mg/g
Drug Substance		
Adapalene	0.1	1
Excipients		
Carbomer 940, NF	(b) (4)	
Propylene Glycol, USP		
Poloxamer 182		
Edetate Disodium, USP		
Methylparaben, NF		
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF		
Purified Water, USP		

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

Mechanism of action: The exact mechanism of action of adapalene in the treatment of acne vulgaris is unknown.

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

2.1.4 What is the proposed route of administration and dosage?

Proposed route of administration: Topical.

Proposed dosage: Apply a thin layer to the entire face and any other affected areas of the skin once daily.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies used to support dosing or claims and what are the pharmacokinetic (PK) results?

The applicant conducted a maximal use PK trial (RD.06.SRE.18254) to assess the systemic exposure of Differin Gel, 0.1% in subjects 12 years of age and older following once daily application for 4 weeks. A brief description of this trial is provided below and details are provided in Section 4 of this review.

Trial design in brief: This was a multicenter, open label PK study in 24 subjects 12 years and older with moderate to severe acne vulgaris following once daily application of the drug for 29 days on the entire area of the face, shoulders, upper chest and upper back. All 24 subjects completed the trial and this included 18 adolescent subjects (aged 12 to 17 years) and 6 adult subjects (aged 18 years and older). PK assessment via serial blood sampling was done on Days 1, 15 and 29 and additional trough concentrations were assessed on Days 2, 10, 16 and 22 in Adults and Days 2 and 16 in adolescent subjects. Details on demographic make-up, disease characteristics and PK sampling time points are provided in Section 4 of this review.

PK results: By day 29, adapalene plasma concentrations were quantifiable in all 24 subjects. Adapalene systemic concentrations appeared to be at steady state by Day 15. The mean PK profile on Day 1, Day 15 and Day 29 is shown in Figure 2 and the mean PK profile throughout the treatment period is shown in Figure 3. The summary of PK parameters is shown in Table 2.

Figure 2: Mean PK profile of adapalene on Day 1, Day 15 and Day 29

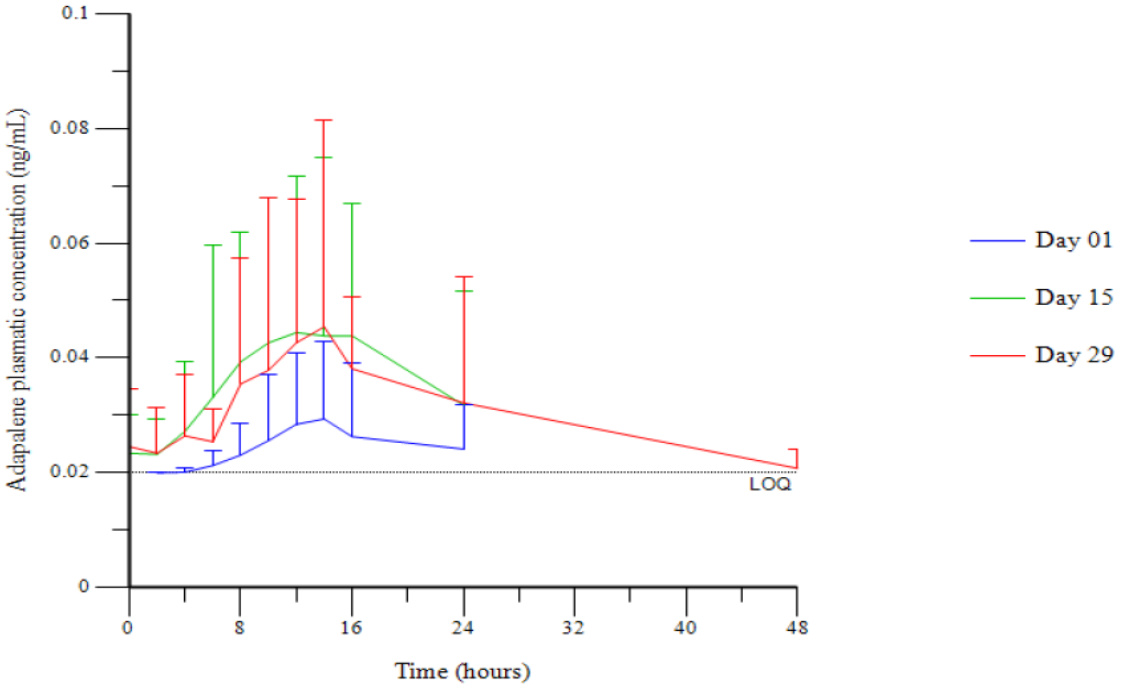
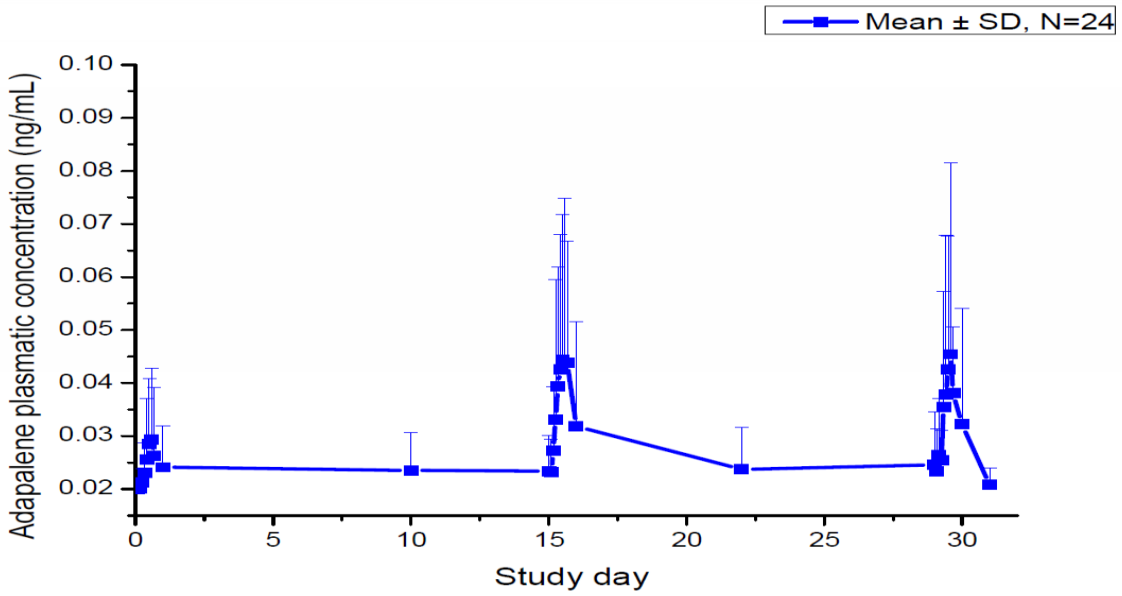


Table 2: Mean PK parameters on Day 1, Day 15 and Day 29

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)	AUC_{0-t} (ng.h/mL)
Day 1 N=24, N quantifiable (%): 15 (63%)				
Mean±SD	0.033±0.015	14.3±5.4	0.57±0.14	0.41±0.27
CV%	45%	38%	25%	66%
Min, Max	<0.020, 0.066	8, 24	0.48, 0.96	0.15, 0.96
Median	0.031	14	0.52	0.35
Day 15 N=22, N quantifiable (%): 21 (95%)				
Mean±SD	0.054±0.032	12.8±5.3	0.87±0.43	0. 77±0.51
CV%	59%	42%	50%	67%
Min, Max	<0.020, 0.144	8, 24	0.48, 1.99	0.16, 2.00
Median	0.044	12	0.73	0.62
Day 29 N=24, N quantifiable (%): 24 (100%)				
Mean±SD	0.049±0.030	11.9±4.5	0.83±0.49	0.85±0.86
CV%	62%	38%	59%	101%
Min, Max	0.025, 0.171	0, 24	0.50, 2.90	0.17, 4.46
Median	0.042	12	0.68	0.65

SD=standard deviation; CV=coefficient of variation, defined as the ratio of SD to arithmetic mean
When all concentrations of a profile were BLQ, the following imputation rules were used:
LOQ value (0.02 ng/mL) for C_{max}
The lowest calculated value (i.e., 0.4752 ng.h/mL and 0.1547 ng.h/mL) for AUC_{0-24h} and AUC_{0-t}, respectively
No imputation for the mean calculation of T_{max}

Figure 3: Mean adapalene plasma concentrations during the entire treatment period



Reviewer comments: *On Day 15, there were quantifiable concentrations in only 21 subjects. Information about the remaining 3 subjects is provided below.*

- *Subject 8076-013: Missed several PK sampling time points on Day 15 and was considered as major protocol deviation and hence excluded.*
- *Subject 8333-006: Missed several PK sampling time points on Day 15 and was considered as major protocol deviation and hence excluded.*
- *Subject 8139-009: Plasma concentrations were below the limit of quantification.*

The most exposed subject (#8139-006) was a 16 year old male subject. He received 1.89 gram of study medication on 1899 cm² BSA daily. He experienced adapalene levels above the limit of quantification starting with the first application. The highest systemic exposure was observed at day 29 with a C_{max} reaching a value of 0.171 ng/mL and an $AUC_{0\text{-}24h}$ of 2.897 ng.h/mL. The elimination half-life ($T_{1/2}$) of this subject was 15 hours. Based on this value from a single subject, adapalene is estimated to be cleared from the plasma of this subject by 4 days (approximately 5 half-lives) after the last application. Due to lack of sufficient quantifiable systemic concentrations, $T_{1/2}$ could not be reliably estimated in all subjects and hence is not reported.

2.2.2 How does the systemic concentrations of adapalene in the new maximal use PK trial (RD.06.SRE.18254) compare with other products in the market?

The comparison of systemic concentrations of adapalene in the new maximal use PK trial (RD.06.SRE.18254) submitted with this application with other products was made for qualitative purposes only. Strong inferences should not be made based on this cross-trial comparison because the study design and bioanalytical methods differed between products. The summary of available PK data is shown in Table 3 below.

Table 3: Summary of PK data for all approved adapalene containing products for the treatment of acne vulgaris (LOQ = Limit of quantification)

NDA # and approval date (age approved)	**Trade Name**	**Active ingredients**	**PK data in the label**
NDA 020380 05/31/1996 (≥ 12 years)	Differin Gel	Adapalene 0.1%	Trace amounts in the plasma (< 0.25 ng/mL) ***New maximal use PK trial***: 24/24 subjects (18 adolescents + 6 adults) had quantifiable conc. (LOQ = 0.02 ng/mL). Mean C_{max} = 0.05 ± 0.03 ng/mL and mean AUC_{0-24} = 0.83 ± 0.49 ng*h/mL
NDA 020748 05/26/2000 (≥ 12 years)	Differin Cream	Adapalene 0.1%	No quantifiable conc. (LOQ = 0.35 ng/mL)
NDA 021753 06/19/2007 (≥ 12 years)	Differin Gel	Adapalene 0.3%	15/16 adult subjects had quantifiable conc. (LOQ = 0.1 ng/mL). Mean C_{max} = 0.55 ± 0.46 ng/mL and mean AUC_{0-24} = 8.37 ± 8.46 ng*h/mL
NDA 022320 12/08/2008 (≥ 9 years)	Epiduo Gel	Adapalene 0.1%/ Benzoyl peroxide 2.5%	2/10 adult subjects had quantifiable conc. (LOQ = 0.1 ng/mL) of adapalene with maximum C_{max} = 0.21 ng/mL and AUC_{0-24} = 1.99 ng*h/mL
NDA 022502 03/17/2010 (≥ 12 years)	Differin Lotion	Adapalene 0.1%	2/14 adult subjects had quantifiable conc. (LOQ = 0.1 ng/mL), ranged from 0.102 to 0.131 ng/mL. 5/14 pediatric subjects aged 12 – 17 years had quantifiable conc. (LOQ = 0.1 ng/mL). Mean C_{max} = 0.13 ± 0.05 ng/mL and mean AUC_{0-24} = 3.07 ± 1.21 ng*h/mL
NDA 207917 07/15/2015 (≥ 12 years)	Epiduo Forte Gel	Adapalene 0.3%/ Benzoyl peroxide 2.5%	16/26 subjects aged 12 to 33 years had quantifiable conc. (LOQ = 0.1 ng/mL). Mean C_{max} = 0.16 ± 0.08 ng/mL and mean AUC_{0-24} = 2.49 ± 1.21 ng*h/mL.

Reviewer comments: *Based on the information above, one can qualitatively infer that the systemic concentrations of adapalene from the new maximal use PK trial*

(RD.06.SRE.18254) appear to be within the range of systemic concentrations of adapalene observed with other topical adapalene containing products.

2.3 Intrinsic Factors

2.3.1 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?

2.3.1.1 Effect of gender and age

The applicant explored the effect of gender and age on the PK of adapalene in trial RD.06.SRE.18254. Figure 4 and Figure 5 show the effect of sex and Figure 6 and Figure 7 show the effect of age on the C_{max} and AUC of adapalene, respectively (x axes were offset slightly to better show the error bars).

Figure 4: Mean ± SD of C_{max} (ng/mL) by sex

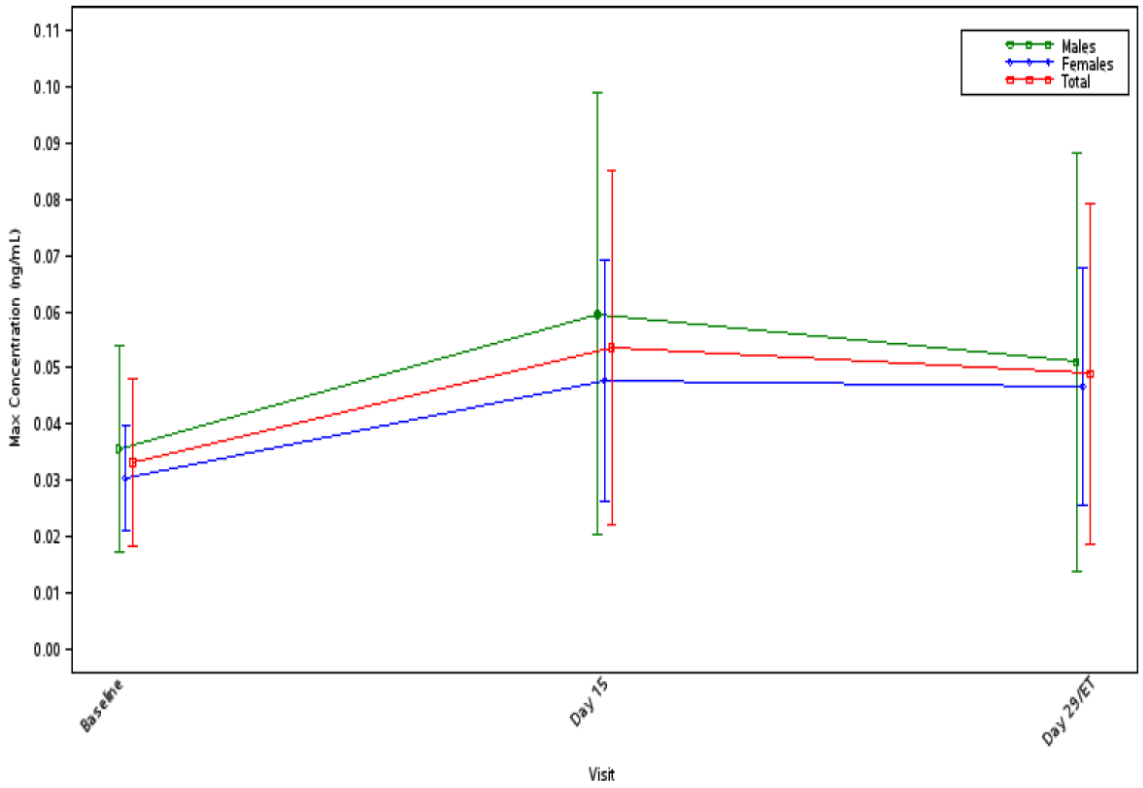


Figure 5: Mean ± SD of $AUC_{0\text{-}24h}$ (ng*h/mL) by sex

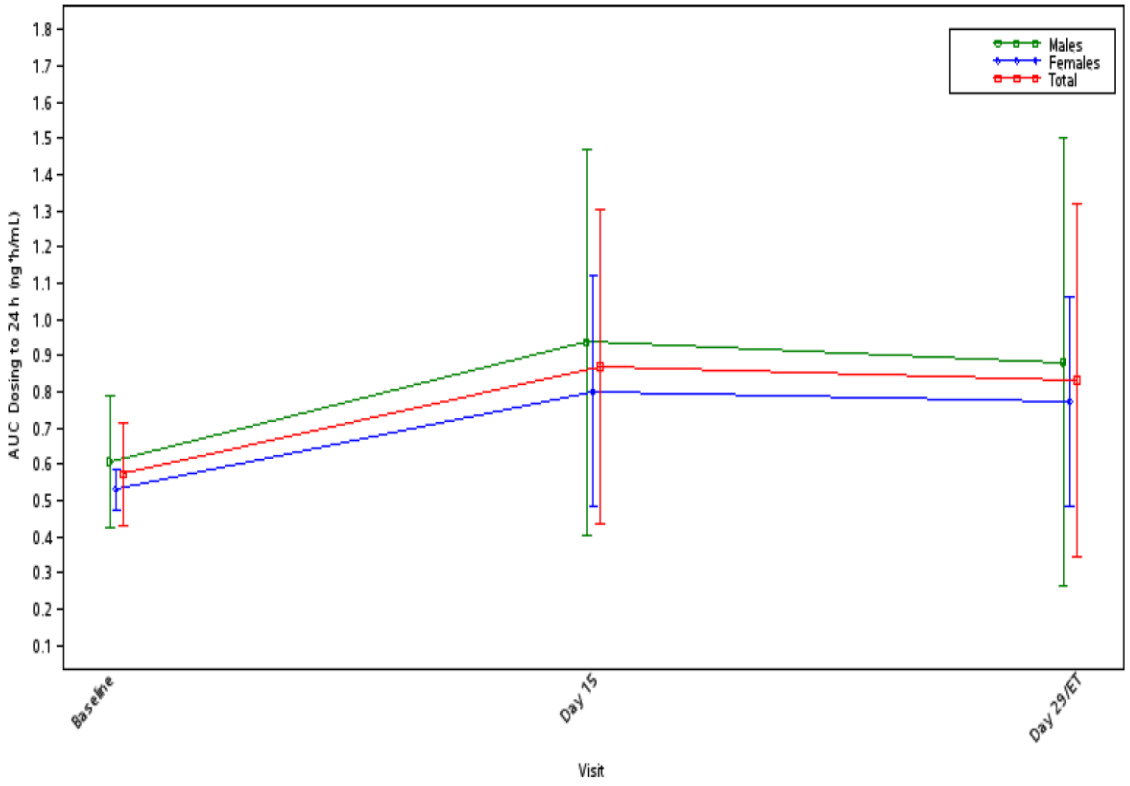


Figure 6: Mean ± SD of C_{max} (ng/mL) by age

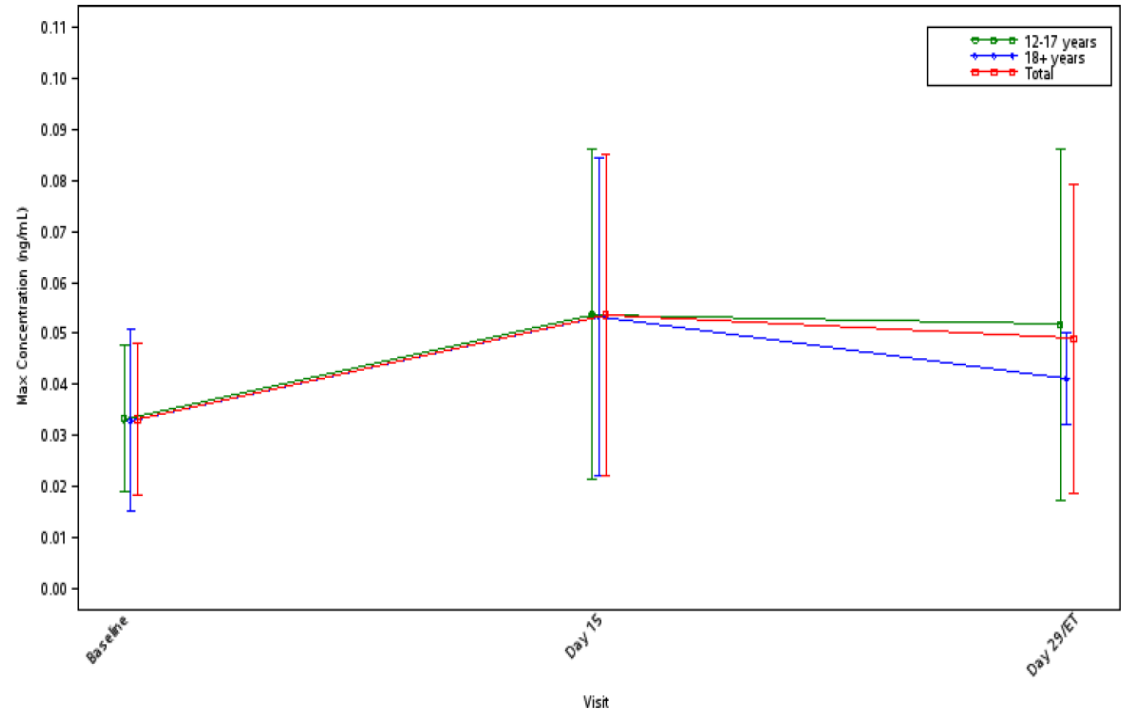
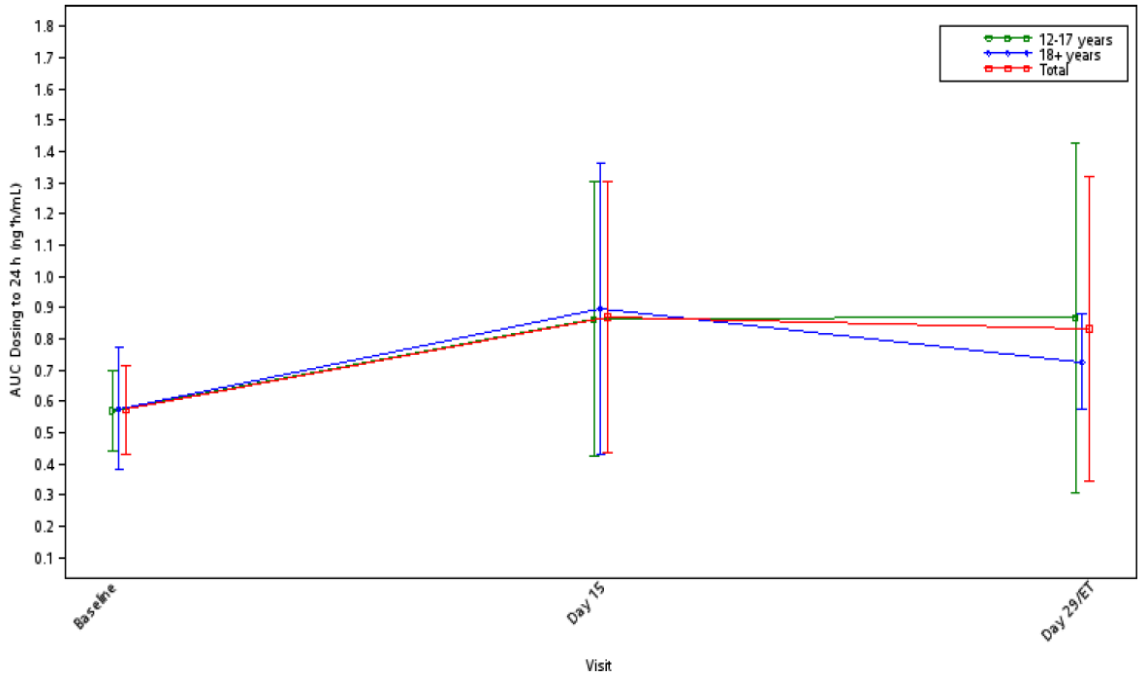


Figure 7: Mean ± SD of AUC_{0-24h} (ng*h/mL) by age



Even though the C_{max} and AUC in males appear to be numerically slightly higher than females (by about 10%), statistical analysis showed that ratios of AUC_{0-24h}, C_{max}, and C_{trough} between genders, and the same ratios between age groups, were not significantly different for any parameter as shown in Table 4.

Table 4: Inferential statistics: estimates of gender effect and age group effect on PK parameters

Parameter (Ratio between covariates	Ratio (90% CI)	p-value
Ratio between genders (male vs female) [a]		
AUC_{0-24h}	1.10 (0.90, 1.34)	0.439
C_{max}	1.10 (0.84, 1.44)	0.566
C_{trough}	0.95 (0.82, 1.10)	0.549
Ratio between age groups (12 to17 years vs. 18 and older) [b]		
AUC_{0-24h}	1.01 (0.80, 1.29)	0.919
C_{max}	1.04 (0.76, 1.43)	0.833
C_{trough}	1.05 (0.89, 1.25)	0.622

CI=confidence interval

For imputation, the following substitutions for missing results were made: the smallest calculated AUC value for the AUCs; otherwise LOQ was substituted for BLQ. For the calculations related to C_{max}, concentrations below the limit of quantification (BLQ) were replaced by the LOQ value (i.e., 0.02 ng/mL). In case of missing data (no sample collection, data excluded from analysis), no imputation was done and the data was excluded from analysis. Data were transformed into natural logarithms prior to analysis and the estimates and CI's were back-transformed into original scales by taking the antilog and presented in the summary table

a) Based the following model: parameter = subject + study visit + gender + random errors

b) Based the following model: parameter = subject + study visit + age group + random errors

2.3.1.2 Pediatric assessment

Differin Gel, 0.1% is currently approved as a prescription (Rx) medication for the treatment of acne vulgaris in subjects 12 years of age and older. The applicant has conducted a maximal use PK trial in subjects 12 years of age and older and is seeking an approval for Rx to OTC switch in this age range.

2.3.1.3 Renal and hepatic impairment

The applicant has not conducted any new trials to assess the effect of renal and hepatic impairment on PK of adapalene following topical application of Differin Gel, 0.1%.

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

The applicant has not conducted any new clinical trials in pregnant and/or lactating women.

2.4 Extrinsic Factors

2.4.1 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.

2.4.2 Drug-drug interactions

The applicant has not conducted any new drug interaction studies.

2.5 General Biopharmaceutics

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

The maximal use PK trial was conducted using the marketed formulation of Differin Gel, 0.1%.

2.6 Analytical Section

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

The active moieties were identified and measured using high performance liquid chromatography and Turbo ion spray- Tandem Mass Spectrometry (HPLC with TIS - MS/MS detection).

2.6.2 Which metabolites have been selected for analysis?

No metabolites have been selected for analysis.

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

Total concentration was measured.

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

The range of standard curve for adapalene was 0.02 ng/mL to 1 ng/mL. This range was adequate as plasma concentrations were quantifiable in all 24 subjects and none of the plasma concentrations for adapalene exceeded the upper limit of the concentration range.

2.6.5 What are the accuracy and precision at LLOQ?

Mean Inter-Batch Results (n=30)
Accuracy (% Bias) = - 1.8%
Precision (CV%) = 9.1%

Mean Intra-Batch Results (n=6)
Accuracy (% Bias) = 5.2%
Precision (CV%) = 7.4%

Reviewer comments: *The accuracy and precision for the quality control samples were within ± 15%.*

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Parameter	*Adapalene*
Freeze/Thaw cycle stability	4 cycles at approximately - 20ºC
Room temperature stability	At least 24 hours
Auto-sampler stability	At least 90 hours at approximately 10 ºC
Long term stability	162 days 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.*

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

Incurred Samples Reanalysis (ISR) was performed for around 10% of the study samples. ISR acceptance criteria was individual bias should be within ±20% of the mean values for at least 2/3 (~ 67%) of the repeats. The results indicated that 72% of the samples reanalyzed were within the ISR predefined acceptance criteria.

3. Detailed Labeling Recommendations

There are no specific recommended changes in the label from Clinical Pharmacology perspective.

4. INDIVIDUAL STUDY REVIEW

Maximal use PK trial (RD.06.SRE.18254)

Title: A PK study to determine the systemic exposure of Differin® Gel, 0.1% following once daily topical application for 4 weeks under maximal use conditions in adolescent and adult subjects with moderate to severe acne vulgaris.

Trial objectives: To assess the systemic exposure to adapalene in subjects 12 years of age and older with moderate to severe acne vulgaris, when Differin Gel 0.1% was applied under maximal use conditions once daily for 29 days on the face, shoulders, upper chest, and upper back.

Study design: This was a multicenter, open-label study in male and female subjects 12 years of age and older with moderate to severe acne vulgaris. Specifically, subjects 12 to 15 years of age were required to have moderate or severe acne while subjects 16 years of age and older were required to have severe acne based on Investigator's Global Assessment (IGA) scale as shown in Table 5 below. Already marketed Differin Gel, 0.1% was applied as a thin layer once daily in the morning by the clinical staff to the face, shoulders, upper chest, and upper back for 29 days.

Table 5: Investigator's Global Assessment Scale

0	Clear	Clear skin with no inflammatory or noninflammatory 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.

Approximately 41 subjects were screened in order to enroll 24 eligible subjects. The goal was to obtain a minimum of 16 evaluable adolescent subjects.

- Group 1: 18 adolescent subjects (age 12 to 17)
- Group 2: 6 adult subjects (age 18 and older)

Enrollment was to be stratified based on age and gender in order to obtain:

- Stratum 1: at least 8 male adolescent subjects
- Stratum 2: at least 8 female adolescent subjects
- Stratum 3: 3 male adult subjects
- Stratum 4: 3 female adult subjects

All 24 enrolled subjects completed the trial and Figure 8 shows schematic representation of the number of subjects enrolled under each Stratum. Summary of demographics is shown in Table 6 and age and sex distribution is shown in Figure 9.

Figure 8: Schematic representation of study disposition

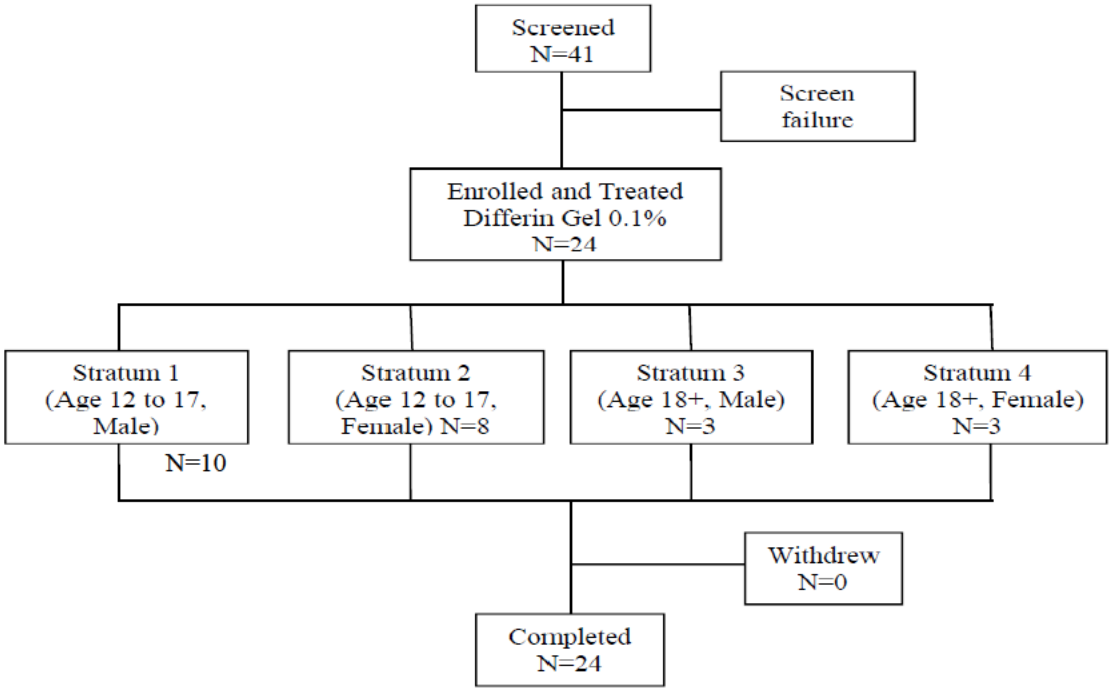
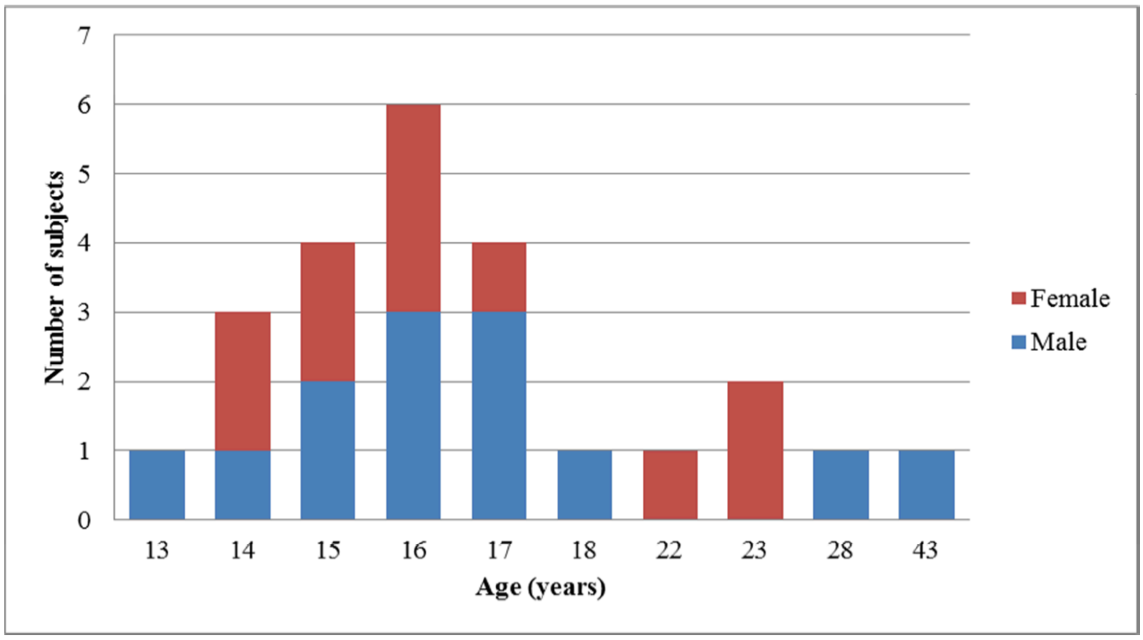


Table 6: Summary of demographics and disease characteristics

	Males (N=13)	Females (N=11)	12 to 17 years (N=18)	18+ years (N=6)	Total (N=24)
Age					
Mean	18.8	17.4	15.5	26.2	18.2
Median (min, max)	16.0 (13, 43)	16.0 (14, 23)	16.0 (13, 17)	23.0 (18, 43)	16.0 (13, 43)
Gender					
Male	13 (100.0%)	NA	10 (55.6%)	3 (50.0%)	13 (54.2%)
Female	NA	11 (100.0%)	8 (44.4%)	3 (50.0%)	11 (45.8%)
Race					
White	13 (100.0%)	11 (100.0%)	18 (100.0%)	6 (100.0%)	24 (100.0%)
Ethnicity					
Hispanic or Latino	8 (61.5%)	8 (72.7%)	14 (77.8%)	2 (33.3%)	16 (66.7%)
Not Hispanic or Latino	5 (38.5%)	3 (27.3%)	4 (22.2%)	4 (66.7%)	8 (33.3%)
IGA Score at Baseline					
3=Moderate	0	3 (27.3)	3 (16.7)	0	3 (12.5)
4=Severe	13 (100.0%)	8 (72.7)	15 (83.3)	6 (100.0)	21 (87.5)
IGA Score at Baseline for 12 to 15 Years					
3=Moderate	0	3 (27.3%)	NA	NA	3 (12.5%)
4=Severe	4 (30.8%)	1 (9.1%)	NA	NA	5 (20.8%)
IGA Score at Baseline for 16+ Years					
3=Moderate	0	0	NA	NA	0
4=Severe	9 (69.2%)	7 (63.6%)	NA	NA	16 (66.7%)

NA=not applicable

Figure 9: Age and sex distribution



PK sampling schedule: The PK sampling schedule for adults is shown in Table 7 and for adolescents is shown in Table 8.

Table *7: PK sampling schedule for adult subjects*

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 (Predose)	Predose	Predose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after Day 15 dose (Predose)	Predose	Predose, 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_{0-24h}	C_{trough}	C_{trough}	C_{trough}, C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24h} R1	C_{trough}	C_{trough}	C_{trough}, C_{max}, t_{max}, AUC_{0-24h}, AUC_{0-t}, AUC_{0-inf}, R2, R3, Kel, $t_{1/2}$		

a) Sampling times = from time of the application start.

Table 8: PK sampling schedule for adolescent subjects (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 (Predose)	Pre-dose, 2, 4, 8, 10, 12, and 14 hours after the morning dose	24 hours after Day 15 dose (Predose)	Predose, 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_{0-24h}	C_{trough}	C_{trough}, C_{max}, t_{max}, AUC_{0-t} , AUC_{0-24h} R1	C_{trough}	C_{trough}, C_{max}, t_{max}, AUC_{0-24h}, AUC_{0-t}, AUC_{0-inf}, R2, R3, Kel, $t_{1/2}$		

a) Sampling times = from time of the application start.

Note: According to the adapalene PK profile, C_{max} occurs around 10 to 12 hours. An additional time point after this T_{max} and before 24 hours would secure the calculation of the total AUC. Although 16 hours is optimal for PK, 14 hours was the best compromise for adolescent subjects (Day 1, 15, and Day 29) as no overnight clinic stay would be required.

Protocol deviations: The PK sampling times up to 16 hours allowed a ±10 minute sampling time window and the ones obtained at 24 and 48 hours, allowed a ±30 minute sampling time window. The applicant has noted 14 deviations in 14 subjects related to PK blood draw errors due to either PK sampling time outside the window or missing PK samples. Additional 49 deviations in 16 subjects were noted related to dose application (noncompliance) mostly due to either application not in the required body surface area (study medication was not applied to the upper chest region of the shoulders), or dose applied outside window (i.e. application time was more than 30 minutes late). These deviations are being classified as minor by the applicant.

Other minor deviations included the use of prohibited medication by one subject (i.e. topical Neosporin ointment was applied twice daily for 4 days for treating lacerations at the nose and administrative errors which included extended centrifugation time of blood samples (affected one blood sample in 2 subjects) or the fact that the blood samples were placed in the centrifuge after 20 min (affected only one blood sample in 2 subjects).

Out of 24 subjects, the applicant has noted 3 major protocol deviations in 2 (8.3%) subjects (Table 8). Both these subjects were males and aged 18 years and older. Both subjects had PK blood draw errors and missed multiple PK samples on Day 15 and in addition one of these 2 subjects was also non-compliant due to missed dose on Day 14 (the day before PK sampling) (details in Table 9). Both subjects were excluded from the determination of PK parameters on Day 15.

Table 9: Summary of major protocol deviations

	Males (N=13)	Females (N=11)	12 - 17 years (N=18)	18+ years (N=6)	Total (N=24)
Number of Subjects with Major Protocol Deviation(s)	2 (15.4)	0	0	2 (33.3)	2 (8.3)
Administrative Errors	0	0	0	0	0
Entrance Criteria Deviation	0	0	0	0	0
Prohibited Medication	0	0	0	0	0
Non-Compliance	1 (7.7)	0	0	1 (16.7)	1 (4.2)
PK Blood Draw Error	2 (15.4)	0	0	2 (33.3)	2 (8.3)

Note: Percentages for the number of subjects with major protocol deviation(s) are based on number of subjects in the Safety Population in each treatment group.

Reviewer comments: *The applicant's classifications of protocol deviations appear reasonable.*

Identity of the investigational product: Details about the investigational product used in this trial is shown in Table 10 below.

Table 10: Description of the investigational product

	Investigational Product
Trade Name or Equivalent	Differin Gel 0.1%
Name of Drug Substance	Adapalene
Internal Code	CD0271
Pharmaceutical form	Gel
Strength/Concentration	0.1%
Formula number	(b) (4)
Packaging (type and size)	45 g tube
Storage conditions	Store at controlled room temperature 68°-77°F (20°-25°C), excursions permitted between 59° and 86°F (15°-30°C). Protect from freezing.

Treatment compliance: Summary of treatment compliance and actual study drug exposure is shown in Table 11 and 12, respectively.

Table 11: Summary of treatment compliance

Compliance [a] with Study Treatment (%)	Males (N=13)	Females (N=11)	12 to 17 years (N=18)	18+ years N=6)	Total (N=24)
Mean	99.47	100.00	99.81	99.43	99.71
SD	1.296	0.000	0.813	1.408	0.974
Median	100.00	100.00	100.00	100.00	100.00
Min - Max	96.6 – 100.0	100.0 – 100.0	96.6 – 100.0	96.6 – 100.0	96.6 – 100.00

SD=standard deviation

a) Compliance (%) in days = Actual study drug exposure in days /expected study drug exposure in days, where expected study drug exposure is defined as treatment duration in days

Table 12: Summary of actual study drug exposure (days)

Study drug exposure [a] (days)	Males (N=13)	Females (N=11)	12-17 years (N=18)	18+ years (N=6)	Total (N=24)
Mean	28.8	29.0	28.9	28.8	28.9
SD	0.38	0.00	0.24	0.41	0.28
Median	29.0	29.0	29.0	29.0	29.0
Min - Max	28 - 29	29 - 29	28 - 29	28 - 29	28 - 29

SD= standard deviation

a) Actual study drug exposure = Treatment duration (days) minus number of days with no application

Quantity of product used: Mean daily medication usage was 1.95 g/day (range 1.21 g to 2.92 g). According to the applicant, the overall mean average daily medication (1.95 g/day) that was applied by the subjects at home (except of PK sampling days) was nearly identical to the Baseline dose which was applied in the clinic by trained clinical staff. This indicates that the actual amount applied at subsequent visits was similar as at initial visit.

The mean average daily medication usage was slightly higher in males (1.97 g/day) than in females (1.92 g/day) and the mean average daily doses applied in adolescent subjects (1.85 g/day) were lower than those applied in adult subjects (2.24 g/day). In particular, only 3 subjects had daily doses >2.5 g. The amounts applied per cm^2 of treated body surface area (BSA) ranged from 0.6 mg/cm^2 to 1.6 mg/cm^2 and the mean value was 1.1 mg/cm^2 (see summary in Table 13).

Table 13: Mean amounts of Differin 0.1% Gel applied per cm² of treated BSA

	Males (N=13)	Females (N=11)	12-17 years (N = 18)	18+ years (N = 6)	Total (N = 24)
Mean ± SD (mg/cm²)	1.0 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	1.1 ± 0.2
Min, Max (mg/cm²)	0.6, 1.4	1.0, 1.6	0.6, 1.4	0.8, 1.6	0.6, 1.6
Median (mg/cm²)	1.0	1.2	1.0	1.1	1.1

Body surface area (BSA) treated: The mean BSA treated was 1864.7 cm^2 (range from 1387.4 to 2893.9 cm^2). The mean BSA was and was higher in males (2092.3 cm^2) than in females (1595.9 cm^2). The mean total treated surface area was also higher in adult subjects (2022.5 cm^2) than in adolescent subjects (1812.2 cm^2). There were 9 subjects that applied the study drug on >2000 cm^2 surface area (Subjects 8076-004, 8076-009, 8076-013, 8076-017, 8076-018, 8139-005, 8139-008, 8333-006, and 8333-008).

The mean percentage of treated surface area was 9.2% overall, and was higher in males (9.7%) than in females (8.7%). The mean percentage of treated surface area was lower in adolescent subjects (8.7%) than in adult subjects (9.4%). Table 14 provides a summary of daily medication usage and treated surface area.

Table 14: Summary of daily medication usage and treated surface area

	Males (N=13)	Females (N=11)	12-17 years (N=18)	18+ years (N=6)	Total (N=24)
Daily Medication Usage (g/day) determined at Baseline					
Mean	1.974	1.923	1.856	2.235	1.950
SD	0.5338	0.2488	0.3845	0.4224	0.4198
Median	1.890	1.910	1.895	2.145	1.905
Min - Max	1.21 – 2.92	1.38 – 2.26	1.21 – 2.81	1.83 – 2.92	1.21 – 2.92
Daily Average Medication Usage (g/day) [a]					
Mean	1.974	1.920	1.854	2.235	1.949
SD	0.5338	0.2558	0.3869	0.4224	0.4217
Median	1.890	1.910	1.895	2.145	1.905
Min - Max	1.21 – 2.92	1.35 – 2.26	1.21 – 2.81	1.83 – 2.92	1.21 – 2.92
Total Treated Surface Area (cm^2) [b]					
Mean	2092.262	1595.855	1812.172	2022.450	1864.742
SD	443.1489	243.5190	384.2249	584.6664	438.2693
Median	2109.400	1495.900	1778.800	1905.100	1778.800
Min - Max	1395.40 – 2893.90	1387.40 – 2196.70	1387.40 – 2787.30	1416.70 – 2893.90	1387.40 – 2893.90
Percentage of Treated Surface Area (%) [c]					
Mean	9.665	8.717	9.399	8.725	9.231
SD	1.5238	1.3865	1.6032	1.1576	1.5100
Median	9.510	8.590	9.490	8.600	9.420
Min - Max	6.92 – 13.05	6.80 – 11.27	6.92 – 13.05	6.80 – 10.21	6.80 – 13.05

SD=standard deviation

a) Daily average medication usage = total medication usage (g) throughout the study divided by actual study drug exposure (days)

b) The total treated surface area (cm^2) is calculated as the actual treated surface area of the upper back and upper chest, including shoulder, and the estimated facial surface area (2% of total body surface area)

c) The percentage of treated surface area is calculated as the total treated surface area divided by total body surface area × 100

PK results: By day 29, adapalene plasma concentrations were quantifiable in all 24 subjects. The summary of PK parameters is shown in Table 2 and the mean PK profile on

Day 1, Day 15 and Day 29 is shown in Figure 2 and the mean PK profile throughout the treatment period is shown in Figure 3, under Section 2.2.1 of this review.

Summary of systemic exposure of subjects at steady state in subjects applying the highest amount of study drug (> 2.5g) to the highest surface area (>2000 cm^2) is shown in Table 15 below.

Table 15: Systemic exposure to adapalene at steady state in subjects applying the highest amount of drug product (>2.5 g) to the highest surface areas (>2000 cm^2)

Subject No / Day		Age (years)	Daily dose weight (g)	Total treated surface area (cm^2)	Percentage pf body surface area (%)	C_{max}[a] (ng/mL)	AUC_{0-24h}[b] (ng.h/mL)
8076-009	Day 15 Day 29	15	2.81	2081.2	9.35	0.063 0.064	0.77 0.68
8076-013	Day 15 Day 29	18	2.51	2207.6	10.21	NR 0.049	NR 0.98
8076-017	Day 15 Day 29	43	2.92	2893.9	9.58	0.026 0.033	0.52 0.67

NR: Not reportable – the parameter could not be calculated

a) C_{max}: overall mean±SD, (median), min-max values obtained at Day 15 in this study: 0.054±0.032, (0.044), <0.02-0.144 ng/mL; at Day 29: 0.049±0.030, (0.042), 0.025-0.171 ng/mL

b) AUC_{0-24h}: overall mean±SD, (median), min-max values obtained at Day 15 in this study: 0.87±0.43, (0.73), 0.48-1.99 ng.h/mL; at Day 29: 0.83±0.49, (0.68), 0.50-2.90 ng.h/mL

Reviewer comment: *It is noted that the subject (#8139-006) with highest systemic exposure (C_{max} reaching a value of 0.171 ng/mL and an AUC_{0-24h} of 2.897 ng.h/mL) used 1.89 gram of study medication on 1899 cm² BSA daily. This subject is not among those that used highest amount of drug on the largest body surface area (as shown in Table 15).*

Individual subject PK profiles on Day 1, Day 15 and Day 29 are shown in Figures 10, 11, and 12 respectively.

Figure 10: CD0271 individual plasma concentrations versus time at Day 1

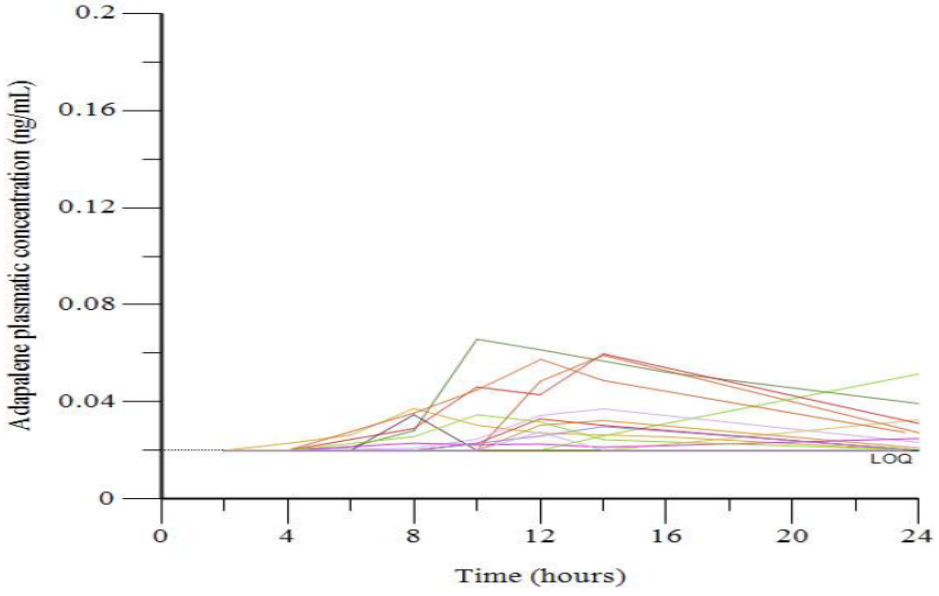


Figure 11: CD0271 individual plasma concentrations versus time at Day 15

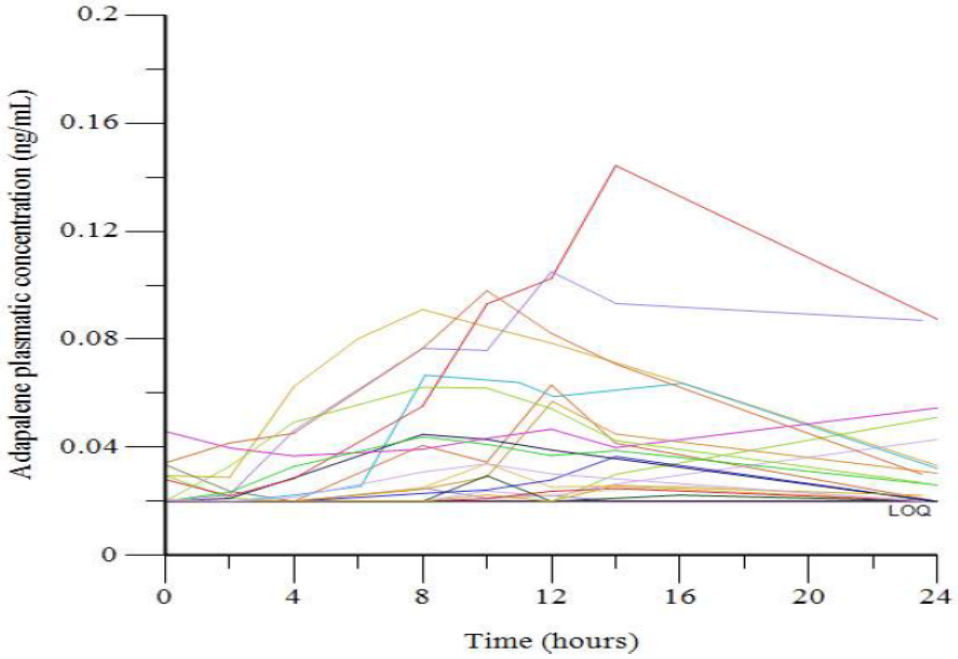
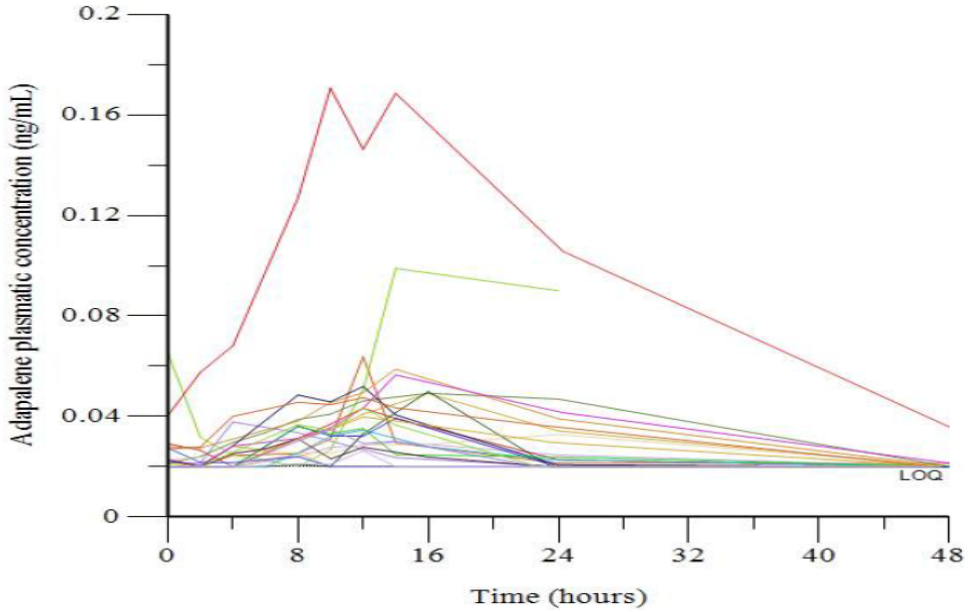


Figure 12: CD0271 individual plasma concentrations versus time at Day 29



Assessment of steady state: Based on accumulation ratio calculations, the systemic concentrations of adapalene appear to be at steady state by Day 15.

The mean accumulation ratios are shown in Table 16. The data suggests that the systemic exposure increased between Day 1 and Day 15 and Day 1 and Day 29 based on the mean values of R1 (AUC_{0-24} Day 15/AUC_{0-24} Day 1) and R2 (AUC_{0-24} Day 29/AUC_{0-24} Day1), respectively. Based on the mean value of R3 (AUC_{0-24} Day 29/AUC_{0-29} Day15) of 1.0 ±

0.4, it suggests that there was no apparent increase in systemic exposure between Day 15 and Day 29. This suggests that adapalene systemic concentrations were at steady state by Day 15.

Table 16: Summary of accumulation ratios for AUC_{0-24h}

	R1	R2	R3
N (n) [a]	24 (13)	24 (15)	24 (21)
Mean±SD	1.7±0.7	1.4±0.7	1.0±0.4
CV (%)	43%	45%	38%
Min, Max	0.9, 3.3	0.9, 3.4	0.3, 2.1
Median	1.4	1.2	0.9

SD=standard deviation
CV=coefficient of variation, defined as the ratio of SD to arithmetic mean
R1=AUC_{0-24h} Day 15 / AUC_{0-24h} Day 1
R2=AUC_{0-24h} Day 29 / AUC_{0-24h} Day 1
R3=AUC_{0-24h} Day 29 / AUC_{0-24h} Day 15
a) N= total number of subjects, n =number of subjects with evaluable AUC_{0-24h}

Influence of different parameters on the systemic exposure: For each subject the AUC_{0-t} were plotted versus the amounts applied (Figure 13), the body weight (Figure 14), and the treated Body Surface Area (Figure 15).

Figure 13: Individual AUC_{0-t} per Day of treatment versus the amounts applied

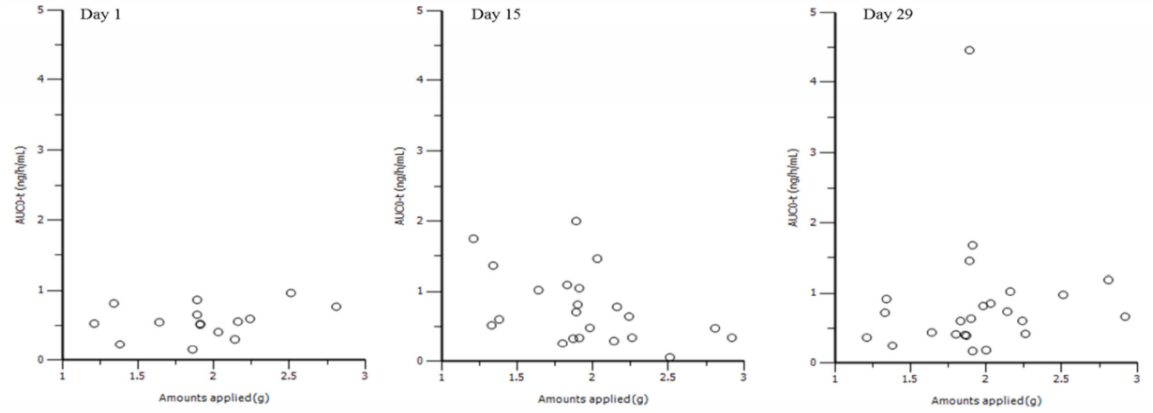


Figure 14: Individual AUC_{0-t} per Day of treatment versus the body weight

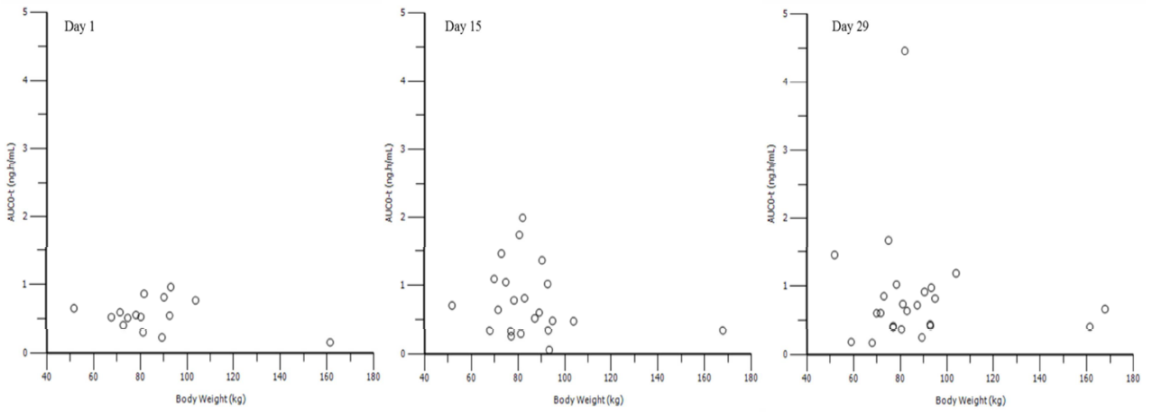
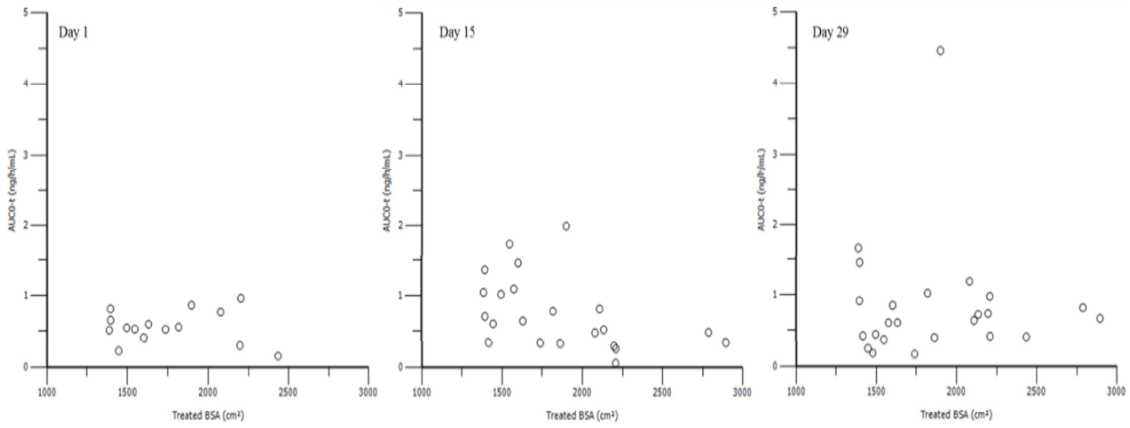


Figure 15: Individual AUC_{0-t} per Day of treatment versus the total treated body surface area



Reviewer comments: *Among the covariates (shown in Figures 13, 14 and 15), although it seems that there was no effect of the amount of formulation applied, body weight and body surface area on the exposure (AUC), this could be due to the fact that people with larger body weight applied more drug to larger BSA. Due to this, strong inferences cannot be made based on the data.*

Influence of disease severity on systemic exposure to adapalene: A summary of IGA and main PK parameters (C_{max}, T_{max}, AUC_{0-24h}, and AUC_{0-t}) across study visits (Baseline/Day 1, Day 15, and Day 29/End of Treatment) is presented in Table 17.

Table 17: Summary of Investigator's Global Assessment (IGA) and PK parameters (Mean ± SD, [Median]) across study visits

Visit	N (%)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng.h/mL)	AUC_{0-t} (ng.h/mL)
Baseline/Day 1					
0=Clear	0	0.033±0.015 (0.031)	14.3±5.4 (14)	0.57±0.14 (0.52)	0.41±0.27 (0.35)
1=Almost Clear	0				
2=Mild	0				
3= Moderate	3 (12.5%)				
4=Severe	21 (87.5%)				
Total	24 (100.0%)				
Day 15					
0=Clear	0	0.054±0.032 (0.044)	12.8±5.3 (12)	0.87±0.43 (0.73)	0.77±0.51 (0.62)
1=Almost Clear	0				
2=Mild	1 (4.2%)				
3= Moderate	5 (20.8%)				
4=Severe	18 (75.0%)				
Total	24 (100.0%)				
Day 29/ET					
0=Clear	0	0.049±0.030 (0.042)	11.9±4.5 (12)	0.83±0.49 (0.68)	0.85±0.86 (0.65)
1=Almost Clear	0				
2=Mild	7 (29.2%)				
3= Moderate	10 (41.7%)				
4=Severe	7 (29.2%)				
Total	24 (100.0%)				

Reviewer comments: *By steady state (Day 15) 75% of the subjects had severe disease compared to 87.5% of the subjects with severe disease at Baseline.*

Brief summary of adverse events (AEs): There were a total of 17 treatment emergent AEs (TEAEs) reported by 8 of the 24 subjects (33.3%) enrolled in this study. According to the applicant, 10 of the AEs reported in 5 subjects were of mild severity and 7 events reported in 5 subjects were considered to be of moderate severity. None of the subjects reported to have severe AEs. Of the total 17 TEAEs, 10 were considered as non-related to study drug by the investigator. None of the TEAEs resulted in discontinuation from the study. The most frequent TEAE were local and this included skin irritation, pruritus and skin erosion. Table 18 provides a summary of TEAEs by system organ class.

Table 18: Summary of treatment-emergent adverse events by system organ class

	Males (N=13)			Females (N=11)			12 to 17 years (N=18)			18+ years (N=6)			Total (N=24)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Any Treatment-Emergent Adverse Events	4	(30.8)	9	4	(36.4)	8	5	(27.8)	10	3	(50.0)	7	8	(33.3)	17
Skin and subcutaneous tissue disorders	2	(15.4)	4	2	(18.2)	3	3	(16.7)	4	1	(16.7)	3	4	(16.7)	7
Skin irritation	1	(7.7)	1	2	(18.2)	2	2	(11.1)	2	1	(16.7)	1	3	(12.5)	3
Pruritus	1	(7.7)	2	1	(9.1)	1	1	(5.6)	1	1	(16.7)	2	2	(8.3)	3
Skin erosion	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1
Nervous system disorders	1	(7.7)	1	1	(9.1)	2	1	(5.6)	1	1	(16.7)	2	2	(8.3)	3
Headache	1	(7.7)	1	1	(9.1)	2	1	(5.6)	1	1	(16.7)	2	2	(8.3)	3
Immune system disorders	1	(7.7)	1	1	(9.1)	1	1	(5.6)	1	1	(16.7)	1	2	(8.3)	2
Seasonal allergy	1	(7.7)	1	1	(9.1)	1	1	(5.6)	1	1	(16.7)	1	2	(8.3)	2
Infections and infestations	1	(7.7)	1	1	(9.1)	1	1	(5.6)	1	1	(16.7)	1	2	(8.3)	2
Body tinea	0		0	1	(9.1)	1	0		0	1	(16.7)	1	1	(4.2)	1
Pharyngitis streptococcal	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1
Gastrointestinal disorders	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1
Abdominal pain	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1
General disorders and administration site conditions	0		0	1	(9.1)	1	1	(5.6)	1	0		0	1	(4.2)	1
Feeling hot	0		0	1	(9.1)	1	1	(5.6)	1	0		0	1	(4.2)	1
Injury, poisoning and procedural complications	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1
Laceration	1	(7.7)	1	0		0	1	(5.6)	1	0		0	1	(4.2)	1

n=subject count; %=percent subjects; E=event count

Adverse events are coded using MedDRA version 16.0. If a subject had multiple occurrences of an AE, the subject was presented only once in the respective subject count. Events were counted each time in the event (E) column. Treatment-emergent AEs are defined as AEs that started after the first dose of study treatment. Percentages are based on the number of subjects in the Safety Population in each treatment group

Reviewer comments: *See Clinical review for further drug safety information.*

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/s/

CHINMAY SHUKLA
05/18/2016

DOANH C TRAN
05/18/2016