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APPLICATION NUMBER:

203567Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA #:	203567
Submission Date:	December 20, 2013
Brand Name:	JUBLIA
Generic Name:	Efinaconazole solution, 10%
Dosage Form:	Solution
Dosage Strength:	10%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Dermatology and Dental Products
Applicant:	Dow Pharmaceutical Sciences, Inc.
Relevant IND(s):	077,732
Submission Type:	Resubmission
Indication:	Topical treatment of onychomycosis in adults

Background and regulatory history: Efinaconazole is a new molecular entity (NME) and belongs to triazole antifungal drug class. The applicant is seeking an indication for once daily topical treatment of onychomycosis in adults with 10% solution formulation of efinaconazole. The original NDA was submitted on July 26, 2012 and this submission received a complete response due to Chemistry Manufacturing and Control (CMC) deficiencies on May 13, 2013 (see communication in DARRTS). The Clinical Pharmacology program submitted with the original application was found acceptable, provided the applicant adequately addressed the labeling comments (see Clinical Pharmacology review dated March 07, 2013, in DARRTS).

On December 20, 2013 the applicant re-submitted their NDA to address the CMC deficiencies. The applicant has changed the container closure system. No new Clinical Pharmacology or Clinical trials were conducted. In the opinion of the medical officer Dr. Gary Chiang, the steps adopted by the applicant to address the CMC issues do not warrant any new Clinical trials. Based on this assessment, additional Clinical Pharmacology trials will not to be needed to support an indication in adults.

Pediatric assessment: With the original NDA application, the applicant [REDACTED] (b) (4) [REDACTED] With this re-submission, the applicant has requested for a waiver in pediatric subjects from 0 - 11 years old and has provided the reason of low prevalence of onychomycosis in this age group. The applicant has requested a deferral to conduct pediatric assessment in subjects aged 12 to 17 years, post approval of this NDA in adults. Along with this submission, the applicant has submitted a synopsis of the proposed protocol (DPSI-IDP-108-P3-03), a vehicle controlled safety and efficacy trial of IDP-108 topical solution in pediatric subjects with mild to moderate onychomycosis of the toenails. The applicant has not proposed any pharmacokinetic (PK) assessment in this trial.

Reviewer comments: To support an indication in pediatrics, the applicant will need to evaluate the PK of IDP-108 under maximal use conditions in the target pediatric population.

This NDA was presented to the Pediatric Review Committee (PeRC) on April 30, 2014. PeRC recommended a waiver of <2 year of age group for reason that studies are impossible or highly impractical and a deferral for ≥ 2 years of age. This recommendation is similar to what PeRC has recommended previously for tavaborole (down to 6 years of age) and terbinafine (down to 2 years of age). The PeRC recommends opening up enrollment to younger ages to see whether subjects could be enrolled. In the tavaborole and terbinafine cases, DDDP had decided to move forward with waiver for <12 years and a decision along similar lines would likely be taken by DDDP for this NDA. PeRC agreed with Clinical Pharmacology recommendation to add PK assessment under maximal use conditions in a subset of pediatric subjects.

Summary of important Clinical Pharmacology findings: No new Clinical Pharmacology trials were conducted. The original submission contained 2 PK trials, Trial DPSI-IDP-108-P1-03 was a maximal use PK trial in adult subjects with severe onychomycosis and Trial DPSI-IDP-108-P1-02 was conducted in healthy adult subjects. The original NDA also contained information about drug metabolism and drug interaction assessment. These data were reviewed with the original application (for further information, see Clinical Pharmacology review dated March 07, 2013, in DARRTS).

Labeling recommendations: The Clinical Pharmacology detailed labeling recommendations were provided in the original NDA Clinical Pharmacology review (see review dated March 07, 2013 in DARRTS). Additional labeling edits that are being proposed in this review cycle are provided below.

With the original NDA application review, it was suggested to delete Section 7 – Drug Interactions. In this cycle, to be consistent with other recent labels, the review team decided to add this section and following is the addition shown as **bold and underlined text**.

7 Drug Interactions

No formal drug-drug interaction studies have been conducted with JUBLIA. In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

Reviewer comments: Other than adding Section 7 to the label, no additional edits were made in Section 12.2 – Pharmacodynamics and Section 12.3 – Pharmacokinetics, in this review cycle.

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

Post-marketing requirements: Pharmacokinetic assessment of IDP-108 under maximal use conditions in sufficient number of subjects aged 12 to 17 years with moderate to severe onychomycosis of the toenails.

Clinical Pharmacology briefing: An official briefing was not conducted for this NDA resubmission.

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

/s/

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05/05/2014

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05/06/2014

Clinical Pharmacology Review

NDA #:	203567
Submission Date:	July 26, 2012
Brand Name:	Pending
Generic Name:	Efinaconazole solution, 10%
Dosage Form:	Solution
Dosage Strength:	10%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Dow Pharmaceutical Sciences, Inc.
Relevant IND(s):	077,732
Submission Type:	New-submission
Indication:	Topical treatment of onychomycosis in adults

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1. Executive Summary

Efinaconazole is a new molecular entity (NME) and belongs to triazole antifungal drug class. The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway and is seeking an indication for once daily topical treatment of onychomycosis in adults with 10% solution formulation of efinaconazole. The clinical program consists of four Phase 1 trials which include a maximal use pharmacokinetic (PK) trial in subjects with severe onychomycosis and a PK trial in healthy subjects, one Phase 2 safety and efficacy trial and two Phase 3 safety and efficacy trials in subjects with mild to moderate onychomycosis. The Sponsor has also submitted reports of two additional Phase 1 Japanese trials that were not conducted under their investigational IND 77732. The Sponsor's reason for including the non-IND trials was to provide supplemental safety data.

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor. The package integrity issues causing leakage of the product did not affect the maximal use pharmacokinetic trial as none of the products used in this trial leaked. The effect of package integrity on the safety and efficacy data produced in the Phase 3 trials is deferred to Clinical.

1.2 Post-Marketing Requirements/ Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA the Sponsor has completed 2 PK trials. Trial DPSI-IDP-108-P1-03 was a maximal use PK trial in adult subjects with severe onychomycosis and Trial DPSI-IDP-108-P1-02 was conducted in healthy adult subjects. In addition to the above, the Sponsor has also provided a summary of systemic PK results from the 2 non-IND Japanese trials, Trial KP-103-03 which evaluated concentrations in effected versus normal toenails and Trial KP-103-02 which was skin irritation and photosensitization trial in healthy subjects.

The maximal use PK trial (DPSI-IDP-108-P1-03) was conducted in 20 adult male and female subjects (18 completed) with severe onychomycosis with at least 80% of the area of both great toenails and at least 4 other toenails with onychomycosis infection. The study drug was applied once daily for 28 days to all 10 toe nails and 0.5cm of adjacent surrounding skin. Serial PK blood samples were collected at pre-dose and post dose on Day 1, Day 14 and Day 28, and a single sample was obtained any time during the 2 weeks post treatment follow up visit. PK of the parent drug (IDP-108) and 2 metabolites [H3 and H4] were assessed. Plasma concentrations of the parent drug were quantifiable in 15 out of 18 subjects on Day 1 and in all subjects on Day 14 and Day 28. The ratio of mean AUC and Mean C_{min} on Day 14 versus Day 28 was ≤ 1.18 for the parent drug (IDP-108) suggesting concentrations in-vivo were near steady state by Day 14. The mean \pm SD values of $AUC_{(0-t)}$ and C_{max} on Day 28 for the parent drug were 12.15 ± 6.91 ng*h/mL and 0.67 ± 0.37 ng/mL, respectively. The concentration profile for the parent drug at steady state on Day 28 was relatively flat over the 24 hour dosing interval.

The Sponsor has also provided information on drug metabolism and addressed the potential for drug-drug interaction. In-vivo, H3 was the major metabolite in human plasma but it is inactive. In-vitro, H4 was the major metabolite and it is active. In-vivo H4 was quantifiable only in 4 subjects and in those subjects it was present $< 25\%$ of the parent compound based on the ratio of the AUCs (Mean ratio = 0.14). All other metabolites were formed in very low levels in-vivo, and did not warrant further investigation. Multiple CYP enzymes were involved in efinaconazole metabolism with CYP2C19 and CYP3A4 identified as the primary isozymes.

Efinaconazole reversibly inhibited CYP2C8, CYP2C9, CYP2C19 and CYP3A4 and there was minimal inhibition of CYP1A2, CYP2A6, CYP2E1 and CYP2D6 activity. The major metabolite H3, had much less CYP activity. Efinaconazole was not an inducer of CYP1A2 or CYP3A4 in human hepatocytes in-vitro. The mean plasma levels of efinaconazole following administration to subjects with onychomycosis under maximal use conditions were low (< 2 nM) and the risk of CYP mediated drug-drug interaction appears to be low.

Pediatric assessment: The Sponsor

(b) (4)

. The Pediatric Review Committee (PeRC) did not agree and the Division of Dermatology and Dental Products (DDDP) is considering

(b) (4)

(b) (4)

(b) (4)

then evaluation of PK under maximal use conditions in pediatric subjects would be recommended.

Clinical Pharmacology Briefing: An optional inter-division level Clinical Pharmacology briefing was conducted on February 26, 2013 with the following in attendance: Hae-Young Ahn, E. Dennis Bashaw, Gary Chiang, Bogdan Kurtyka, An-Chi Lu, Balimane Praveen, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 General Attributes of the Drug

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

Drug substance and Formulation: The chemical name of efinaconazole is (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1*H*-1,2,4-triazol-1-yl) butan-2-ol and its molecular weight is 348.39. It is represented by C₁₈H₂₂ F₂N₄O, and has the chemical structure is shown in Figure 1. Efinaconazole has 2 asymmetric centers at carbons 2 and 3 (Figure 1) and the compound has an absolute configuration of (2*R*, 3*R*).

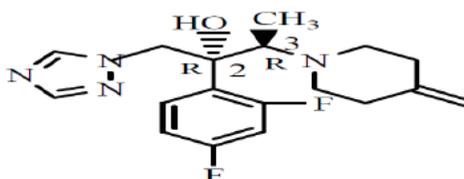


Figure 1: Structure of Efinaconazole

The drug product contains 10% w/v of active ingredient efinaconazole (IDP-108) in a solution dosage form for topical application. It is a clear, colorless to pale yellow solution with an alcohol content of approximately (b) (4) w/w. The qualitative and quantitative composition of the drug product is shown in Table 1 below.

The drug product is packaged in a 10 mL white bottle with a brush applicator and (b) (4) cap. The amount of solution in the to-be-marketed container is (b) (4) mL, and in physician sample is (b) (4) mL. The same container is used for both presentations.

Table 1: Qualitative and quantitative composition of efinaconazole solution, 10%

Ingredient	Grade	Function	Concentration (%w/w)
Efinaconazole	N/A	Active	10.0
Cyclomethicone	NF	(b) (4)	(b) (4)
Diisopropyl Adipate	Cosmetic		
C12-15 Alkyl Lactate	Cosmetic		
Butylated Hydroxytoluene	NF		
Citric Acid, Anhydrous	USP		
Edetate Disodium	USP		
Purified Water	USP		
Alcohol	USP		

Efinaconazole isomerism: Efinaconazole is the R,R stereoisomer form. Efinaconazole and the S,S; S,R, and R,S stereoisomers were quantitated in a subset of plasma samples from Trial DPSI-IDP-108-P1-02 conducted in healthy subjects by applying IDP-108 topically to back skin. According to the Sponsor, with the use of a chiral bioanalytical method, no stereo-isomers other than the R,R form were detected in plasma. Furthermore, efinaconazole did not interconvert to other stereoisomers.

2.1.2 What will be the impact of issues with the container/closure system on product quality and clinical trials?

For the two Phase 3 trials, two batches of the formulation were used:

- Batch DP1444: Manufactured on (b) (4)
- Batch DP1453F1: Manufactured on (b) (4) (Also used in maximal use PK trial DPSI-IDP-108-P1-03)

Product leakage issue: For Batch DP1444, product leaking was observed which showed up as more than 50% of the bottles being smudged and smeared, when samples arrived at Dow Pharmaceutical Sciences, Inc (Manufacturing was done by (b) (4)). Following initial investigation, the Sponsor decided to:

- (b) (4)
- (b) (4)
- (b) (4)

As per CMC reviewer’s assessment, both leaky and non-leaky bottles from batch DP1444 were used in the Phase 3 trials (for additional information see CMC review dated 02/08/2013 by Dr. Bogdan Kurtyka in DARRTS). However, it is not clear if the sponsor excluded bottles that weighed less than a certain specified limits nor is it clear what those limits were.

To address the issue of product leaking, Dr. Kurtyka’s review further states that the Sponsor implemented some improvements in the manufacturing process such as (b) (4),

(b) (4). But, it is not clear if all the improvements were implemented in the manufacture of the second clinical batch DP1453F1 (also used in the maximal use PK trial). Further, leaking was observed in 15.7% of bottles from Batch DP1453 but, as per Report 129, the leaking bottles were stored for further (b) (4) evaluations. The Sponsor has not provided any information on the (b) (4) evaluations.

Reviewer comments: From CMC review by Dr. Bogdan Kurtyka, it appears that the Sponsor used some criteria (b) (4) before relabeling and releasing Batch DP1444 to be used in the Phase 3 clinical trials, but it is not clear what were the weight limits used to reject bottle suspected of leakage. For Batch DP1453F1, none of the bottles that leaked were used in the maximal use PK trial. However, this is not clear for the Phase 3 clinical trials (although the Sponsor has reported that the leaking incidence from the Phase 3 trials is 0.2%, it is not clear that the bottles that leaked belonged to which Batch). It should be noted that the formulation contains (b) (4) alcohol, there is a potential for the strength of the product to be altered due to excessive evaporation in bottles that were leaky (in the non leaking bottle, changes in the strength due to evaporation were within the specified limits). The acceptability of the efficacy and safety data obtained from the Phase 3 trials is deferred to Clinical.

Impact of leaking on the results of maximal use PK trial (DPSI-IDP-108-P1-03): The maximal use PK trial was conducted using products from Batch DP1453F1. The issue of product leakage was clarified from the Sponsor via an information request (IR) sent on December 21, 2012 (see communication in DARRTS). The Sponsor responded to this IR on January 09, 2013 and stated that “No bottles with leakage were reported during study DPSI-IDP-108-P1-03”. Furthermore, As per CMC review Dr. Bogdan Kurtyka, it seems none of the leaking bottles from Batch DP1453F1 were used in the maximal use PK trial (for additional information see CMC review dated 02/08/2013 in DARRTS). Based on this information, the product used in the maximal use PK trial is acceptable.

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

Mechanism of action: Efinaconazole is a triazole antifungal agent and it inhibits fungal lanosterol 14 α -demethylase involved in ergosterol biosynthesis. The accumulation of 14 α -methyl sterols and subsequent loss of ergosterol in the fungi cell wall may be responsible for the fungistatic and fungicidal activity of efinaconazole.

Therapeutic indication: With this application, the Sponsor is seeking an indication of topical treatment of onychomycosis (tinea unguium) in adults.

2.1.4 What is the proposed route of administration and dosage?

Proposed route of administration: Topical.

Proposed dosage: Efinaconazole solution, 10% should be topically applied once daily using the built-in flow-through brush applicator provided. When applying the drug product ensure the nail, the nail folds, nail bed, hyponychium, and as much of the

undersurface of the nail plate, are completely covered. No debridement is necessary when treating onychomycosis. A complete cure may be seen some months after mycological cure is achieved. This is related to time required for outgrowth of healthy nail.

2.2 General Clinical Pharmacology

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

Table 2 shows a list of all clinical trials provided to support this application.

Table 2: List of all clinical trials

Trial number	Objective	Treatment duration	No. of subjects
Phase 1			
DPSI-IDP-108-P1-01	Dermal Irritation	21 days	55 (healthy)
DPSI-IDP-108-P1-02	PK in Healthy subjects	28 days	10 (healthy)
DPSI-IDP-108-P1-03	Maximal use PK trial	28 days	20 (severe disease)
DPSI-IDP-108-P1-04	Contact sensitization	8 weeks	239 (healthy)
Phase 2 (The to-be-marketed formulation was not used in this trial)			
DPSI-IDP-108-P2-01 <i>Conducted in Mexico</i>	Safety and Efficacy	40 weeks	135 (mild to moderate)
Phase 3			
DPSI-IDP-108-P3-01	Safety and Efficacy	52 weeks	870 (mild to moderate)
DPSI-IDP-108-P3-02	Safety and Efficacy		781 (mild to moderate)
Non-IND Phase 1 studies (included to provide supplemental safety data)			
KP-103-02 <i>Conducted in Japan</i>	Skin irritation and Photosensitization	28 days	56 (healthy)
KP-103-03 <i>Conducted in Japan</i>	To investigate efinaconazole concentrations in effected vs. normal toenails	7 days	40 (diseased)

2.2.2 What are the design features of the clinical pharmacology and the clinical trials used to support dosing or claims?

Design features of maximal use PK trial (DPSI-IDP-108-P1-03): Topical drug bioavailability is a complex interaction of drug substance, formulation and the effect of disease itself on the barrier function of the skin. In order to adequately assess systemic safety, it is necessary to design trials to maximize the potential for drug absorption with the aim of capturing the worst case scenario. Hence, the Sponsor has conducted a maximal use PK trial in adult subjects with severe onychomycosis of toenails with at least 80% of the area of both great toenails and at least four other toenails with infection. The goal of this trial was to assess safety and systemic exposure of IDP-108 (investigational product). Study drug (IDP-108) (total volume of 0.42 mL = 42 mg dose) was applied to all 10 toe nails and 0.5 cm of adjacent skin by a trained nurse or a study technician (there was no self administration of the study drug in this trial). PK plasma samples for the determination of drug (IDP-108) and metabolite (H3 and H4) levels were

collected at baseline (pre-treatment) and serial samples up to 24 hours were obtained post treatment on Days 1, 14 and 28. Additionally a single sample was obtained at any time during the 2 week follow up period. Steady state was achieved by Day 14.

Design features of Phase 3 clinical trials (DPSI-IDP-108-P3-01 & DPSI-IDP-108-P3-02):

The Phase 3 trials were similar in design and both the trials were multicenter, randomized, double-blind, vehicle controlled, parallel design to evaluate the safety and efficacy of once daily topical application of IDP-108 relative to vehicle in the treatment of mild to moderate onychomycosis of the toenails. In these trials, subjects were randomized (3:1) to apply either IDP-108 or vehicle once daily at bedtime to all affected toenails for 48 weeks. In both the trials, the primary efficacy endpoint consisted of a comparison between percentage of subjects in each treatment group who achieved complete cure (defined as 0% clinical involvement of the target toenail) at Week 52 (the 4 week post-treatment follow-up visit).

2.2.3 In which trials were PK assessed and what were the results?

The list of clinical trials which included PK assessment of the parent drug (IDP-108) and/or metabolites (H3 and H4) is shown below. Table 3 (a to c) provided PK summary for the first 3 trials listed below [the calculated values excluded concentrations that were below the limit of quantification (BLQ)]. For the 2 supportive trials in Japanese, the systemic concentrations of the parent drug were within the range seen for other 3 trials and a detail review was not conducted.

- DPSI-IDP-108-P1-03: Maximal use PK trial
- DPSI-IDP-108-P1-02: Healthy subject PK
- DPSI-IDP-108-P2-01: Phase 2 safety and efficacy trial*
- KP-103-02: Skin irritation and photosensitization trial (Japanese)
- KP-103-03: Assessment of concentrations in the infected and non infected nail (Japanese)

* All trials except the Phase 2 trial (DPSI-IDP-108-P2-01) used the to-be-marketed formulation. Hence results of drug exposure from the Phase 2 trial will be discussed only with the aim of assessing any systemic safety signals with respect to drug levels.

Table 3a: C_{max} and AUC (mean ± SD) in Trial DPSI-IDP-108-P1-03 (Maximal use PK trial)

Mean PK Parameters	Days 1-2	Days 14-15	Days 28-29
IDP-108			
AUC _(0-t) (ng*h/mL)	1.79±2.04 (n=15)	10.29±5.90 (n=18)	12.15±6.91 (n=18)
C _{max} (ng/mL)	0.23±0.18 (n=18)	0.62±0.30(n=18)	0.67±0.37 (n=18)
H3			
AUC _(0-t) (ng*h/mL)	1.50±1.13 (n=6)	40.03±34.02(n=18)	45.80±31.58(n=18)
C _{max} (ng/mL)	0.01±0.14 (n=18)	2.20±1.73 (n=18)	2.36±1.64 (n=18)
H4*			
AUC _(0-t) (ng*h/mL)	BLQ	1.41 ± 1.34 (n=4)	2.30 ± 0.11 (n=4)
C _{max} (ng/mL)	BLQ	0.03 ± 0.06 (n=5)	0.05 ± 0.08 (n=5)

* In most subjects H4 concentrations were BLQ

Table 3b: C_{max} and AUC (mean \pm SD) in Trial DPSI-IDP-108-P1-02 (Healthy subject PK trial)

Mean PK Parameters	Toenails		Back	
	Single dose	Multiple dose [#]	Single dose	Multiple dose [#]
IDP-108				
AUC ₍₀₋₂₄₎ (ng*h/mL)	2.64 \pm 2.85	9.48 \pm 3.86	23.56 \pm 14.30	54.45 \pm 36.99
C _{max} (ng/mL)	0.38 \pm 0.39	0.54 \pm 0.22	1.91 \pm 1.76	3.53 \pm 3.06
H3				
AUC ₍₀₋₂₄₎ (ng*h/mL)	5.65 \pm 5.30	32.52 \pm 14.70	18.86 \pm 8.37	117.22 \pm 57.96
C _{max} (ng/mL)	0.44 \pm 0.36	1.63 \pm 0.80	1.61 \pm 0.77	5.46 \pm 2.81

[#] Multiple dose - 7 daily application

Table 3c: Pre-treatment drug concentrations (mean \pm SD) in Trial DPSI-IDP-108-P2-01 (Phase 2 Safety and efficacy trial. To-be-marketed formulation not used)

Treatment	Mean pretreatment concentration (ng/mL)					
	Week 4	Week 8	Week 12	Week 24	Week 36	Follow-up 30 days [#]
Parent drug						
IDP-108, 10% semi-occlusion	0.48 \pm 0.4	1.16 \pm 2.4	0.62 \pm 0.5	0.70 \pm 0.7	0.73 \pm 0.5	0.02 \pm 0.1
IDP-108, 10%	0.68 \pm 0.8	0.74 \pm 0.7	0.63 \pm 0.5	0.70 \pm 0.5	0.75 \pm 0.7	0
IDP-108, 5%	0.40 \pm 0.2	0.50 \pm 0.6	0.57 \pm 0.8	0.89 \pm 0.8	0.41 \pm 0.4	0.12 \pm 0.3
H3 Metabolite						
IDP-108, 10% semi-occlusion	1.18 \pm 0.6	0.84 \pm 0.5	1.70 \pm 1.6	1.91 \pm 1.7	1.77 \pm 1.3	0.21 \pm 0.1
IDP-108, 10%	1.53 \pm 1.0	1.57 \pm 1.7	1.67 \pm 0.8	1.80 \pm 1.3	1.29 \pm 0.9	0.11 \pm 0.1
IDP-108, 5%	1.08 \pm 0.6	1.42 \pm 1.3	1.20 \pm 1.1	1.60 \pm 1.0	0.88 \pm 0.6	0.25 \pm 0.5

[#] 30 days after the last dose

Reviewer comments: Trial DPSI-IDP-108-P2-01 was conducted using a different formulation which was not the to-be-marketed formulation. The Sponsor obtained only a single pretreatment sample at each noted visit. The baseline value (pre-treatment concentration on Day 1) is not included in Table 3c because there was no drug and metabolite concentration in the sample. The purpose of including this data is to provide additional support for systemic safety because the maximum mean parent drug concentration (week 8 under semi-occlusion) is approximately 1.73 fold higher than those observed under maximal use conditions (Day 28).

Based on the available PK data (Table 3a, 3b and 3c), highest drug exposure for IDP-108 and metabolite H3 was seen in the healthy subject PK trial (DPSI-IDP-108-P1-02) following multiple applications to the back. The results showed that the mean C_{max} and AUC for IDP-108 on Day 10 following multiple administrations to the back were approximately 5.3 fold and 4.5 fold respectively, higher than the C_{max} and AUC on Day 28 in the maximal use PK trial (DPSI-IDP-108-P1-03).

Reviewer comments: Refer to section 4 for further details on the trial designs and PK results. The Phase 2 Safety and Efficacy trial DPSI-IDP-108-P2-01 is not described in detail in this review because it did not use the to-be-marketed formulation.

2.2.4 What information is known about drug metabolism?

Efinaconazole is metabolized via oxidation (H4 and H5) and cleavage (H1, H2 and H3) and most metabolites are further glucuronidated (H2, H3, H4 and H5). Following metabolite chemical structures were determined with LC-MS/MS:

- (H1): 2,3-hydroxyl 2-difluorinated phenyl triazole
- (H2): 2-hydroxyl 2-difluorinated phenyl triazole
- (H3): piperidine diol
- (H4): monohydroxylated piperidine
- (H5): 2-carbonyl 2-difluorinated phenyl triazole
- Carboxylated piperidine
- 2R,3R amine

In-vivo, H3 was the major metabolite in human plasma and it is inactive. This was the only metabolite that was higher or equal to efinaconazole levels. In-vitro, H4 was the major metabolite and it is active. In-vivo H4 was quantifiable only in 4 subjects and in those subjects it was present < 25% of the parent compound based on the ratio of the AUCs (Mean ratio = 0.14). All other metabolites had some activity but were formed in very low levels, in-vivo. This did not warrant further investigation. The maximal use PK trial evaluated both the parent drug and H3 and H4 metabolite levels.

2.2.5 What is the systemic safety margin of the drug exposure under maximal use conditions based on animal toxicity data?

The mean exposure (AUC) for the max use PK trial (DPSI-IDP-108-P1-03) for the parent drug (IDP-108) was 12.15 ng*h/mL (Range: 1.46 – 25.25). Based on the highest observed exposure (25.25 ng*h/mL), the safety margin based on animal toxicity data is 17 fold. Please see Pharmacology-Toxicology review by Dr. Linda Pellicore in DARRTS for further details.

2.2.6 What is the safety profile of efinaconazole?

According to the Sponsor, overall, no safety signals or trends were observed based on a review of adverse events (AEs) reported among subjects (both healthy volunteers and subjects with onychomycosis) who were exposed to IDP-108 (with efinaconazole concentrations of 1%, 5% and 10%) when applied to the toenails and via patches to skin on the back for up to 28 days.

There were no deaths in the Phase 1 or 2 trials. However, 2 subjects, one in each of the Phase 3 trials, died and the events were assessed by the investigators as not related to the study drug. Specifically, in Phase 3 trial DPSI-IDP-108-P3-01, one subject committed suicide after being lost to follow-up and in the second Phase 3 trial DPSI-IDP-108-P3-02

one subject died due to lung squamous cell carcinoma. Both the deaths were determined by as unrelated to the study drug (IDP-108) the investigator.

In the two Phase 3 trials combined, 1640 subjects reported 2763 AEs. According to the Sponsor most of the events occurred in a relatively few number of subjects (less than 1% of the subjects in each treatment group). In general, similar percentages of subjects in each treatment group experienced similar types of AEs. The most commonly reported treatment-related AEs (experienced by 1% or more of the subjects in either study drug group regardless of seriousness or severity) included application site dermatitis and application site vesicles. The Sponsor also claims that none of the 65 SAEs were treatment-related and most occurred in only one subject. Overall, 33 subjects, all but one of whom was in the IDP-108 group, discontinued either the study drug or the trial because of an AE. Most of the events were associated with application site reactions, and many of these were assessed as treatment-related. Finally the Sponsor concluded that no safety signals or unexpected trends associated with the use of IDP-108 were observed in the Phase 3 trials.

Reviewer comments: *For further information on drug safety, please see Clinical review by the medical officer Dr. Gary Chiang.*

2.2.7 Has the potential for QT prolongation adequately addressed?

In response to the Sponsor's request for TQT assessment waiver, the Division of Dermatology and Dental Products (DDDP) granted the waiver request on 04/14/2010 (see communication in DARRTS under IND 077732).

Summary of DDDP review of TQT waiver request: The waiver request was reviewed by the medical office Dr. Brenda Vaughan (see review in DARRTS dated 03/18/2010 under IND 077732). According to Dr. Vaughan, CDER's DCRP QT Interdisciplinary Review Team was consulted who took into consideration the PK results from Study DPSI-IDP-108-P1-02, that was conducted in 10 healthy subjects by applying the drug to healthy nails or back. Additionally, no potential for IDP-108 to delay cardiac repolarization (based on hERG inhibition, tissue distribution, cardiovascular safety pharmacology and ECG analysis in chronic studies) were identified. Although results from Study DPSI-IDP-108-P1-02 were considered inconclusive, the QT Interdisciplinary Review Team recommended a waiver of TQT study based on the fact that the bioavailability of IDP-108 and H3 metabolite were low. The team however recommended that periodic ECGs should be collected in all Phase 3 trials.

Reviewer comments: *The molecular weight of IDP-108 is 348.39. Therefore 1 nM concentration will be 348.39 ng/L or 0.34839 ng/mL. The mean C_{max} of IDP-108 in the maximal use PK trial (DPSI-IDP-108-P1-03) was 0.67 ng/mL, which is above the sub-nanomolar range (as per DDDP current practice, TQT assessment waivers have been granted when the systemic concentrations under maximal use conditions are in the sub-nanomolar range and no hERG inhibition is observed).*

From the PK trial in healthy subjects (DPSI-IDP-108-P1-02) the mean C_{max} of IDP-108 following multiple applications to the back was 3.53 ng/mL, which is ~ 5.27 fold higher than the mean C_{max} under maximal use conditions.

Considering the fact that no hERG inhibition was observed and further the Sponsor has indicated no significant ECG changes were observed in the Phase 3 trials, QT prolongation does not appear to be a safety concern. Furthermore, the waiver request was granted (in 2010) based on systemic concentrations (from trial DPSI-IDP-108-P1-02) which were ~ 5.27 fold higher than the mean C_{max} under maximal use conditions. Therefore, the new PK data from the maximal use PK trial do not warrant further reevaluation of the waiver.

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

Based on the data from the maximal use PK trial (DPSI-IDP-108-P1-03), there was high variability in the PK data and it appears that there is no effect of gender on the PK parameters of the parent drug as shown in Table 4 below.

Table 4: PK parameters (mean ± SD) of the parent drug separated by gender

PK Parameters	Male (n=12)	Female (n=6)
AUC _(0-T) (ng*h/mL)	11.55 ± 5.59	13.34 ± 9.54
C_{max} (ng/mL)	0.61 ± 0.28	0.79 ± 0.51

2.3.1.2 Pediatric subjects

(b) (4)
At the Pediatric Review Committee (PeRC) meeting held on January 23, 2013, PeRC did not agree (b) (4) and the Division of Dermatology and Dental Products (DDDP) is considering (b) (4) . In case DDDP (b) (4), then evaluation of PK under maximal use conditions in pediatric subjects would be recommended.

2.3.1.3 Renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of IDP-108. This study is not justified given the low level of absorption and the topical indication.

Reviewer comments: See Reviewer comments under Section 2.3.4.

2.3.1.4 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of IDP-108. This study is not justified given the low level of absorption and the topical indication.

Reviewer comments: *From all the PK assessments, the highest systemic concentrations (C_{max}) for IDP-108 were observed in a trial in healthy subjects (DPSI-IDP-108-P1-02), where the mean value of C_{max} following multiple applications to the back was 3.53 ng/mL. This was approximately ~ 5.27 fold higher than the mean C_{max} under maximal use conditions which was 0.67 ng/mL (DPSI-IDP-108-P1-03). Based on the summary of safety provided by the Sponsor, there appears to be no systemic safety concerns across all clinical trials. Furthermore, the maximum drug exposure under maximal use conditions had 17 fold margin of safety based on animal toxicity data. Considering all this information, assessment of drug exposure in renal and hepatic impaired subjects does not appear warranted.*

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

The Sponsor has not conducted any studies in pregnant and lactating women. The nature of the disease (onychomycosis) is not life threatening and does not warrant requiring such assessment.

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 explored.

2.4.2 Drug-drug interactions

The Sponsor evaluated metabolic drug-drug interaction potential of efinaconazole in-vitro by identifying the CYP enzymes involved in efinaconazole metabolism and by assessing its capacity for induction and inhibition of CYP activity. The potential for H3 to inhibit CYP enzymes was also tested.

Multiple CYP enzymes were involved in efinaconazole metabolism with CYP2C19 and CYP3A4 identified as the primary isozymes associated with oxidative metabolism. CYP2C19 appeared to be the main CYP enzyme mediating H4 formation from efinaconazole.

Efinaconazole reversibly inhibited CYP2C8, CYP2C9, CYP2C19 and CYP3A4 and there was minimal inhibition of CYP1A2, CYP2E1, CYP2D6 and CYP2A6 activity. The major metabolite H3, had much less CYP activity and competitively inhibited CYP2B6. Efinaconazole non-competitively inhibited CYP2B6

In the maximal use PK trial (DPSI-IDP-108-P1-03) the highest steady state C_{max} on Day 28 was 1.47 ng/mL for parent (mean C_{max} = 0.67 ng/mL) and 7.45 ng/mL for H3 (mean C_{max} = 2.4 ng/mL). These concentrations were low with the R value ($1 + [I]/K_i$) below 1.1 (based on in-vitro efinaconazole CYP inhibition data for the most sensitive isoform was CYP2C9 with K_i of 0.26 μ M or 91 ng/mL and the R value was 1.007). Hence, the potential for drug interactions due to CYP inhibition is unlikely. Therefore, further in-vivo evaluations were not undertaken.

Efinaconazole was not an inducer of CYP1A2 or CYP3A4 in human hepatocytes in vitro at concentrations as high as 350 ng/mL. The mean steady state plasma levels in onychomycosis patients under maximal use conditions on day 28 was 0.67 ng/mL, efinaconazole is not expected to induce CYP1A2 and CYP3A4 in vivo. The Sponsor did not evaluate the induction potential on CYP2B6.

2.5 General Biopharmaceutics

2.5.1 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

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

The proposed-to-be-marketed formulation is used in the maximal use PK trial and two pivotal Phase 3 clinical trials. Hence relative bioavailability assessment is not needed.

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

A waiver of in-vivo BE is not necessary as the proposed to-be-marketed formulation was used in the two pivotal Phase 3 trials.

2.5.3 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.

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?

The active moiety (IDP-108) and metabolites H3 and H4 were identified using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS).

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites H3 and H4 were selected for analysis. H3 was the major metabolite in-vivo (with exposure equal to or sometimes greater than the parent compound), and H4 was the major metabolite in-vitro [in-vivo H4 is present < 25% of the parent compound based on the ratio of the AUCs (Ratio = 0.14)]. H3 is an inactive metabolite and H4 has some activity. All other metabolites had some activity but were produced at very low levels and were not investigated further.

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

Total concentrations of IDP-108 and H3 and H4 metabolites was measured.

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

- Range for parent compound IDP-108: 0.1 to 100 ng/mL
- Range for metabolite H3: 0.1 to 100 ng/mL
- Range for metabolite H4: 0.1 to 100 ng/mL

This range was adequate as none of the plasma concentrations for IDP-108, H3 and H4 in the clinical trials exceeded the upper limit of 100 ng/mL.

Reviewer comments: The same CRO was used for Trial DPSI-IDP-108-P1-03 (maximal use PK trial), Trial DPSI-IDP-108-P1-02 (Healthy subject PK trial) and Trial DPSI-IDP-108-P2-01 (Phase 2 Safety and Efficacy trial). The name of the CRO was (b) (4)

2.6.5 What are the accuracy and precision at LLOQ?

LLOQ = 0.1 ng/mL. The mean values of intrarun (n=6) and inter-run (n=3) precision [reported as coefficient of variation (CV)] and accuracy [reported as Bias] is shown in the Table 5 below.

Table 5: Mean accuracy and precision

Analyte	Intrarun				Inter-run	
	CV		Bias		CV	Bias
	From	To	From	To		
IDP-108	5.2%	8.2%	-9.1%	1.0%	7.6%	-3.3%
H3	8.2%	11.1%	-9.8%	7.0%	12.1%	0.0%
H4	4.6%	6.0%	-3.1%	0.0%	5.4%	-1.7%

Limits: The intrarun and inter-run precision (CV) and accuracy (Bias) was $\leq 20\%$ for LLOQ and $\leq 15\%$ for all other samples.

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.)?

The bioanalytical method was adequately validated and the long term storage stability was also adequate to cover the storage stability of PK samples (see details in Table 6).

Table 6: Summary of Bioanalytical method validation

Parameter	IDP-108	H3	H4
Freeze-thaw cycles	Stable for up to 5 cycles from -70°C to room temperature		
Internal standard stability	68 Days		
Bench top stability	17 Hours	7 Hours	26 Hours
Refrigerated stability	11 Days	112 Days	92 Days
Stability at -20°C	321 Days	431 Days	122 Days
Stability at -70°C	431 Days	431 Days	146 Days

Incurring sample reproducibility for Trial DPSI-IDP-108-P1-03: Incurred sample reproducibility (ISR) was evaluated using select samples near the C_{max} and within the elimination phase for at least 10% of the samples across various subjects for IDP-108 and H3 only. The H4 metabolite was not included. The results of ISR for IDP-108 and H3 demonstrated that at least two-thirds of these samples were within $\pm 20\%$ variability of their respective original reported values [7.0% (4 of 57) for IDP-108 and 24.6% (14 of 57) for H3 were out of acceptance criteria].

Reviewer comments: *The Sponsor did not conduct ISR on H4 concentrations and this seems reasonable since exposure to metabolite H4 was $\leq 25\%$ of the parent drug and were BLQ in the majority of subjects. The results of ISR which demonstrated that at least two-thirds of these samples were within the $\pm 20\%$ variability of their original reported values is acceptable.*

Incurring sample reproducibility for Trial DPSI-IDP-108-P1-02: ISR was evaluated for clinical samples using select samples near the C_{max} and within the elimination phase for at least 10% of the samples across all subjects. The results of the ISR demonstrated that at least two-thirds of these samples were within $\pm 20\%$ bias of their respective original reported values.

Reviewer comments: *The results of ISR which demonstrated that at least two-thirds of these samples were within the $\pm 20\%$ variability of their original reported values is acceptable.*

3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling that was submitted on October 17, 2012. The bold and underlined text indicates insertion recommended by the reviewer and the ~~strike through~~ text indicates recommended deletion.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(See Microbiology 12.4)

12.2 Pharmacodynamics

The pharmacodynamics of TRADENAME (b) (4) ~~is~~ are unknown.

12.3 Pharmacokinetics

Systemic absorption of efinaconazole in 18 adult subjects (b) (4) with severe onychomycosis was determined after application of TRADENAME (b) (4) once daily for 28 days to patients (b) (4) 10 toenails and 0.5 cm adjacent skin. The concentration of efinaconazole in plasma was determined at multiple time points over the course of 24-hour periods on days 1, 14, and 28. Efinaconazole mean \pm SD plasma Cmax on Day 28 was 0.67 ± 0.37 ng/mL and the mean AUC was 12.15 ± 6.91 ng*h/mL. The (b) (4) plasma concentration versus time profile at steady state was generally flat over a 24-hour dosing interval. (b) (4) In a separate study of healthy volunteers, the plasma half-life of efinaconazole (b) (4) following daily applications to all 10 toenails for 7 days was 29.9 hours.

Drug Interactions

TRADENAME (b) (4) is considered a non inhibitor (b) (4) of the CYP450 enzyme family. In *in vitro* studies using human liver microsomes, efinaconazole did not inhibit (b) (4) CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 enzyme activities at expected clinical systemic concentrations. (b) (4)

In vitro studies in human primary hepatocytes showed that efinaconazole did not induce CYP1A2 or CYP3A4 activities. (b) (4)

12.4 Microbiology

Mechanism of Action

Efinaconazole is a (b) (4) Efinaconazole inhibits fungal lanosterol 14 α -demethylase involved in (b) (4)

Activity *In Vitro* and *In Vivo*

Efinaconazole has been shown to be active against isolates of the following microorganisms, both *in vitro* and in clinical infections. Efinaconazole exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.06 μ g/mL or less against most (\leq 90%) isolates of the following microorganisms:

Trichophyton mentagrophytes
Trichophyton rubrum

(b) (4)

(b) (4)

Resistance

Efinaconazole drug resistance development was studied *in vitro* against *T. mentagrophytes*, *T. rubrum* and *C. albicans*. Serial passage of fungal cultures in the presence of sub-growth inhibitory concentrations of efinaconazole increased the MIC by up to 4-fold [REDACTED] (b) (4). The clinical significance of these *in vitro* results is unknown.

4. INDIVIDUAL STUDY REVIEW

Trial Number: DPSI-IDP-108-P1-03 (Maximal use PK trial)

Title: A Phase 1a Open-Label Study Evaluating the Absorption and Systemic Pharmacokinetics of Topically Applied IDP-108 Solution in Patients with Severe Onychomycosis of the Toenails

Bio-analytical CRO: [REDACTED] (b) (4)

Study Objectives:

- Safety of IDP-108 administered topically once daily for 28 days
- Systemic exposure of topically applied IDP-108 when applied once daily for 28 days

Study Drug: IDP-108 (supplied in 10 mL bottles with fill volume of 10 mL) (Lot#: DP1453F1C)

Study Design: This was a single-center, open-label study designed to evaluate the safety and PK of a once daily topical application of IDP-108 in subjects with severe onychomycosis of the toenails. The study consisted of three phases:

- Screening
- Treatment
- Post-treatment

The screening phase included two visits (Screening [Day -30 to 0] and Day 0 [within 30 days of Screening]), the treatment phase included 28 visits (Day 1 [Baseline] through Day 28), and the post-treatment phase included one end of treatment visit (Day 29 or Early Termination) and one two-week post-treatment follow-up visit (Day 42 or 2 weeks after the last application of study drug).

At the Screening Visit, subjects underwent an examination of their feet to visually ascertain the presence of onychomycosis and subjects also underwent an examination of their hands to rule out the presence of tinea manum or fingernail dermatophytosis. A direct microscopic examination for the hyphae associated with dermatophytes was performed using potassium hydroxide (KOH) on toenail scrapings collected from both great toenails. Subjects with KOH-positive samples from at least one great toenail had their great toenails trimmed back to the distal groove and underwent clinical assessments of the great toenails, including measurements of the lengths of the unaffected (healthy) great toenails and determinations of the percent involvement of the great toenails and measurements of great toenail thicknesses. Finally, all subjects reported their onychomycosis histories, underwent physical examinations and assessments of vital signs (blood pressure, heart rate, respiration rate, and temperature). Blood and urine specimens were collected for chemistry, hematology, and urinalysis evaluations.

At the Day 0 visit, which was scheduled to occur within 30 days of the Screening Visit, all subjects updated their medical histories and concomitant medication uses and were re-screened to confirm that they continued to meet the inclusion/exclusion criteria. Female subjects of childbearing potential had urine pregnancy tests performed. A negative pregnancy test was required for female subjects of childbearing potential.

After confirming eligibility, subjects participated in the treatment phase of the study (Day 1 through Day 28). Specifically during each treatment visit, at approximately the same time each morning, the subjects had the study drug (0.42 mL measured and delivered from a disposable syringe) applied to all 10 toenails and 0.5cm of adjacent skin by a trained nurse or study technician. The PK evaluations were conducted on Day 1-2, Day 14-15, and Day 28-29. Additionally, a single blood sample was collected for PK analyses at any time during the two-week post-treatment follow-up visit.

Evaluations of safety were conducted during the treatment phase and also during the post-treatment phase. This included assessment of AEs and localized skin reactions. In addition, the same vital sign measurements and clinical laboratory evaluations obtained at the Screening Visit were repeated at the Day 1 and Day 14 visits and Day 29 visit. Female subjects of childbearing potential underwent urine pregnancy testing on Day 29.

The clinical assessments of the great toenails which included absolute change from baseline in the percent of affected and unaffected great toenail were conducted to Day 29 and prior to exit at the two-week post-treatment follow-up visit.

PK Blood Sampling Time: PK plasma samples for the determination of drug (IDP-108) and metabolite (H3 and H4) levels were collected at the following time points:

- Days 1-2: Pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after the first dose of study drug on Day 1
- Days 14-15: Pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after the dose of study drug on Day 14
- Days 28-29: Pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after the last dose of study drug on Day 28
- Two-week post-treatment visit: any time during the visit

PK Parameters: PK endpoints were calculated from the individual plasma concentrations on Days 1 to 2, 14 to 15, and 28 to 29. These endpoints included plasma concentrations of IDP-108 and its metabolite(s), as well as calculations of C_{\max} (observed peak drug concentration), T_{\max} (time at which C_{\max} occurs), C_{\min} (observed minimum drug concentration), and AUC (area under the concentration-time curve).

Subjects: Approximately 20 adult male and female subjects between 18 to 70 years of age were enrolled at a single clinic in the United States. Subjects had to have clinical diagnoses of severe onychomycosis affecting both great toenails defined as clinical involvement of 80% or more of the area of each great toenail and onychomycosis on at least four toenails other than the great toenails to be enrolled in this trial. The reason for

subject discontinuation was on subject request and none of the subjects discontinued due to any AE. Subjects that discontinued were Subject 01-01 and Subject 01-15. Further Subject 01-01 also had unexplained pre-treatment (pre-dose baseline on Day 1) concentration of 0.337 ng/mL on Day 1. Both the subjects were not included in the PK analysis.

Subject demographics and a summary of baseline characteristics at enrollment are shown in Table 7 and Table 8.

Table 7: Subject Demographics

Number of subjects	19
Age (years)	
N	19
Mean	49.3
Standard deviation	12.5
Median	51.0
Minimum to maximum	21 to 70
Weight (kg)	
N	19
Mean	78.4
Standard deviation	6.4
Median	78.3
Minimum to maximum	69.8 to 92.3
Sex, n (%)	
Male	13 (68.4)
Female	6 (31.6)
Ethnicity, n (%)	
Hispanic/Latino	7 (36.8)
Not Hispanic/Latino	12 (63.2)
Race, n (%)	
White	15 (78.9)
Black/African American	4 (21.1)

Table 8: Summary of baseline characteristics

	<u>Left Great Toenail</u>	<u>Right Great Toenail</u>
Potassium hydroxide result		
Number of great toenails	9	10
Positive, n (%)	9 (100.0%)	10 (100.0%)
Negative, n (%)	0 (0.0%)	0 (0.0%)
Percent toenail affected		
N	19	19
Mean	90.0	88.9
Standard deviation	8.7	9.2
Median	90.0	85.0
Minimum to maximum	80.0 to 100.0	80.0 to 100.0
Distance from proximal toenail fold to proximal onychomycotic margin (mm)		
N	19	19
Mean	0.2	0.7
Standard deviation	0.4	1.0
Median	0.0	0.0
Minimum to maximum	0.0 to 1.0	0.0 to 3.0
Toenail thickness (mm)		
N	19	19
Mean	4.5	3.9
Standard deviation	1.9	1.7
Median	4.0	4.0
Minimum to maximum	1.0 to 10.0	1.0 to 8.0

PK results: The PK parameters of the drug (IDP-108) and metabolites H3 and H4 in 18 subjects are shown in Table 9, 10 and 11 below

Table 9: Summary of PK parameters of parent drug (IDP-108)

	Days 1-2	Days 14-15	Days 28-29
AUC_(0-24h) (ng·h/mL)			
N	2	1	18
Mean	6.07	14.25	12.15
Geometric mean (n)	5.98 (2)	14.25 (1)	9.70 (18)
Standard deviation	1.397		6.912
Standard error of the mean	0.987		1.629
Coefficient of variation	23.02		56.90
Median	6.07	14.25	12.53
Minimum to maximum	5.08 to 7.05	14.25 to 14.25	1.46 to 25.25
AUC_(0-t) (ng·h/mL)			
N	15	18	18
Mean	1.79	10.29	12.15
Geometric mean (n)	1.05 (15)	7.80 (18)	9.70 (18)
Standard deviation	2.041	5.903	6.912
Standard error of the mean	0.527	1.391	1.629
Coefficient of variation	114.00	57.37	56.90
Median	0.86	9.62	12.53
Minimum to maximum	0.30 to 7.05	0.39 to 19.54	1.46 to 25.25
C_{min} (ng/mL)			
N		18	18
Mean		0.3280	0.3633
Geometric mean (n)		0.2794 (18)	0.3062 (18)
Standard deviation		0.17437	0.19831
Standard error of the mean		0.04110	0.04674
Coefficient of variation		53.16	54.58
Median		0.3465	0.3905
Minimum to maximum		0.102 to 0.632	0.106 to 0.715
C_{max} (ng/mL)			
N	18	18	18
Mean	0.2261	0.6149	0.6688
Geometric mean (n)	0.2351 (15)	0.5278 (18)	0.5707 (18)
Standard deviation	0.17627	0.29918	0.36830
Standard error of the mean	0.04155	0.07052	0.08681
Coefficient of variation	77.98	48.66	55.07
Median	0.2235	0.6060	0.6785
Minimum to maximum	0.000 to 0.670	0.136 to 0.988	0.184 to 1.470
T_{max} (h)			
N	15	18	18
Mean	21.01	8.93	11.45
Standard deviation	6.389	9.438	8.558
Standard error of the mean	1.650	2.224	2.017
Coefficient of variation	30.41	105.67	74.75
Median	23.92	4.55	16.00
Minimum to maximum	6.03 to 24.00	0.00 to 24.00	0.00 to 24.00

Table 10: Summary of PK parameters of H3 (Metabolite)

	Days 1-2	Days 14-15	Days 28-29
AUC_(0-24h) (ng·h/mL)			
N	2	1	18
Mean	2.74	52.10	45.80
Geometric mean (n)	2.60 (2)	52.10 (1)	35.54 (18)
Standard deviation	1.230		31.851
Standard error of the mean	0.870		7.507
Coefficient of variation	44.85	NA	69.54
Median	2.74	52.10	40.28
Minimum to maximum	1.87 to 3.61	52.10 to 52.10	8.53 to 113.40
AUC_(0-t) (ng·h/mL)			
N	6	18	18
Mean	1.50	40.03	45.80
Geometric mean (n)	1.23 (6)	29.96 (18)	35.54 (18)
Standard deviation	1.133	34.017	31.851
Standard error of the mean	0.463	8.018	7.507
Coefficient of variation	75.53	84.98	69.54
Median	1.08	28.17	40.28
Minimum to maximum	0.60 to 3.61	7.42 to 141.49	8.53 to 113.40
C_{min} (ng/mL)			
N		18	18
Mean		1.4714	1.6705
Geometric mean (n)		1.0361 (18)	1.2845 (18)
Standard deviation		1.26892	1.17095
Standard error of the mean		0.29909	0.27600
Coefficient of variation		86.24	70.10
Median		1.1250	1.4550
Minimum to maximum		0.204 to 5.070	0.289 to 4.070
C_{max} (ng/mL)			
N	18	18	18
Mean	0.0888	2.1995	2.3641
Geometric mean (n)	0.2499 (6)	1.7297 (18)	1.8508 (18)
Standard deviation	0.14170	1.72484	1.64282
Standard error of the mean	0.03340	0.40655	0.38722
Coefficient of variation	159.51	78.42	69.49
Median	0.0000	1.7850	2.1050
Minimum to maximum	0.000 to 0.443	0.579 to 7.450	0.532 to 5.550
T_{max} (h)			
N	6	18	18
Mean	23.95	1.72	2.78
Standard deviation	0.041	3.831	6.015
Standard error of the mean	0.017	0.903	1.418
Coefficient of variation	0.17	222.24	216.41
Median	23.92	1.00	0.00
Minimum to maximum	23.92 to 24.00	0.00 to 16.00	0.00 to 24.00

Table 11: Summary of PK parameters of H4 (Metabolite)

	Days 1-2	Days 14-15	Days 28-29
AUC_(0-24h) (ng·h/mL)			
N	0	0	5
Mean			1.85
Geometric mean (n)	(0)	(0)	1.07 (5)
Standard deviation			1.012
Standard error of the mean			0.452
Coefficient of variation			54.62
Median			2.23
Minimum to maximum			0.05 to 2.46
AUC_(0-t) (ng·h/mL)			
N	0	4	4
Mean		1.41	2.30
Geometric mean (n)	(0)	0.81 (4)	2.30 (4)
Standard deviation		1.335	0.110
Standard error of the mean		0.667	0.055
Coefficient of variation		95.00	4.78
Median		1.19	2.27
Minimum to maximum		0.13 to 3.10	2.21 to 2.46
C_{min} (ng/mL)			
N		18	18
Mean		0.0248	0.0298
Geometric mean (n)		0.1116 (4)	0.1070 (5)
Standard deviation		0.04789	0.04951
Standard error of the mean		0.01129	0.01167
Coefficient of variation		192.86	166.28
Median		0.0000	0.0000
Minimum to maximum		0.000 to 0.119	0.000 to 0.116
C_{max} (ng/mL)			
N	18	18	18
Mean	0.0000	0.0331	0.0454
Geometric mean (n)	(0)	0.1484 (4)	0.1569 (5)
Standard deviation	0.00000	0.06385	0.07951
Standard error of the mean	0.00000	0.01505	0.01874
Coefficient of variation	NA	193.16	174.95
Median	0.0000	0.0000	0.0000
Minimum to maximum	0.000 to 0.000	0.000 to 0.161	0.000 to 0.229
T_{max} (h)			
N	0	4	5
Mean		4.25	3.20
Standard deviation		7.848	7.155
Standard error of the mean		3.924	3.200
Coefficient of variation		184.65	223.61
Median		0.50	0.00
Minimum to maximum		0.00 to 16.00	0.00 to 16.00

Assessment of steady state: The ratio of mean AUC and Mean C_{min} on Day 14 versus Day 28 was ≤ 1.18 for the parent drug (IDP-108) and metabolite H3 suggesting that concentrations in-vivo were near steady state by Day 14 (Table 12).

Table 12: Steady state assessment for Parent drug (IDP-108) and metabolite – H3

PK parameter	Day 1-2	Day 14-15	Day 28-29	Accumulation Ratio (Day 14/Day 1)	Accumulation Ratio (Day 28/Day 14)
	Parent Drug - IDP-108				
Mean AUC _{0-t} (ng*h/mL)	1.79	10.29	12.15	5.8	1.18
Mean C _{max} (ng/mL)	0.23	0.62	0.67	2.7	1.08
Mean C _{min} (ng/mL)	0	0.33	0.36	Not calculated	1.09
Metabolite - H3					
Mean AUC _{0-t} (ng*h/mL)	1.50	40.03	45.80	26.69	1.14
Mean C _{max} (ng/mL)	0.09	2.20	2.36	24.44	1.07
Mean C _{min} (ng/mL)	0	1.47	1.67	Not calculated	1.14

Reviewer comment: Steady state assessment for metabolite H4 was not calculated because H4 was quantifiable only in 4 subjects and in those subjects it was present < 25% of the parent compound based on the ratio of the AUCs (Mean ratio = 0.14).

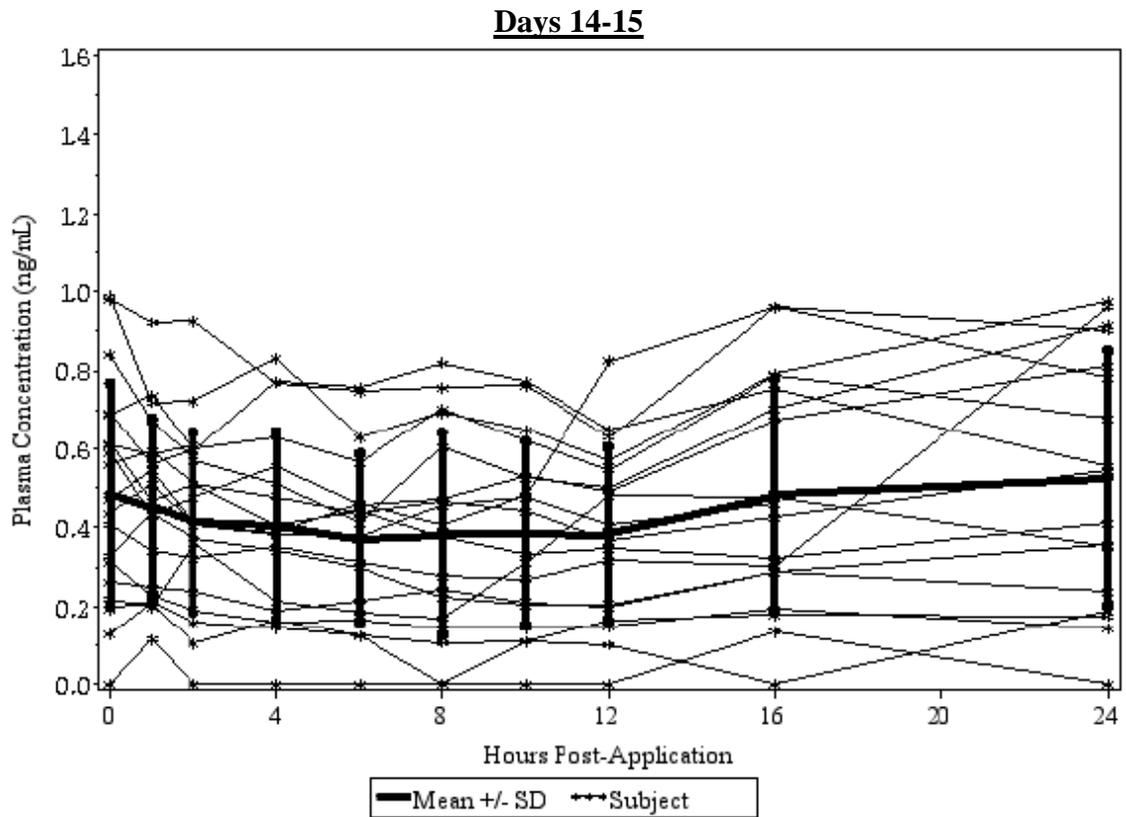
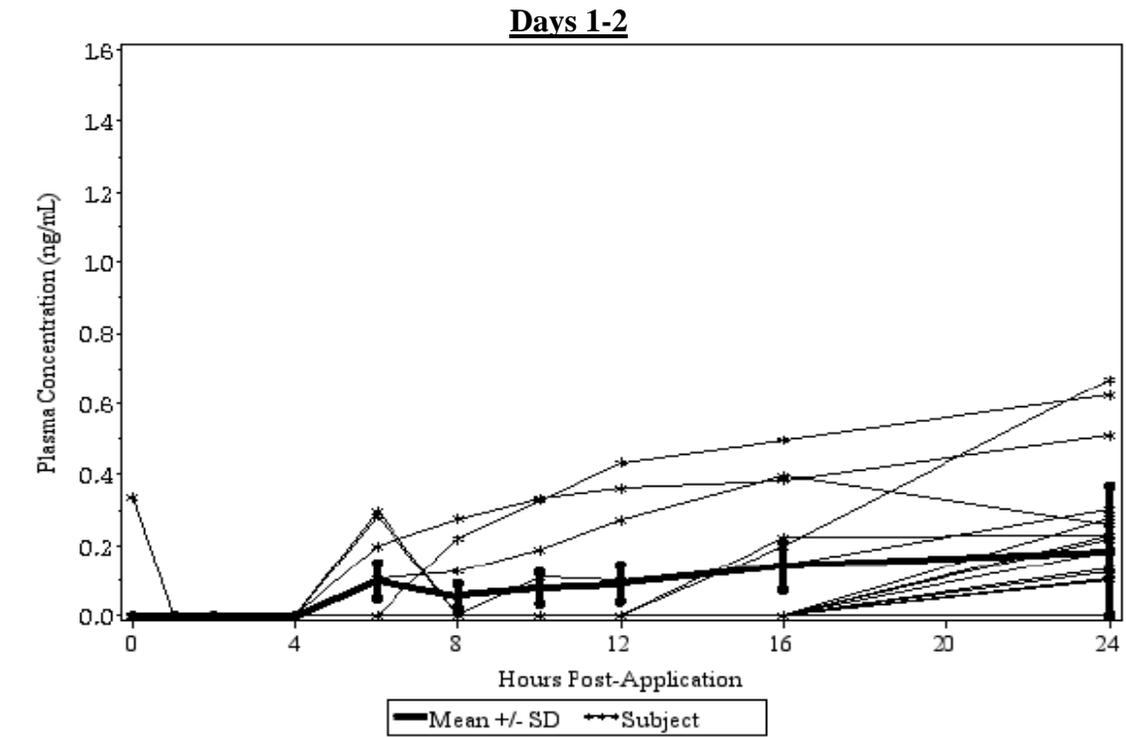
Summary of plasma concentrations of parent drug (IDP-108) are shown in Table 13 and individual subject and mean (± SD) plasma concentrations are shown in Figure 2.

Table 13: Summary of Plasma concentrations by time for parent drug (IDP-108)

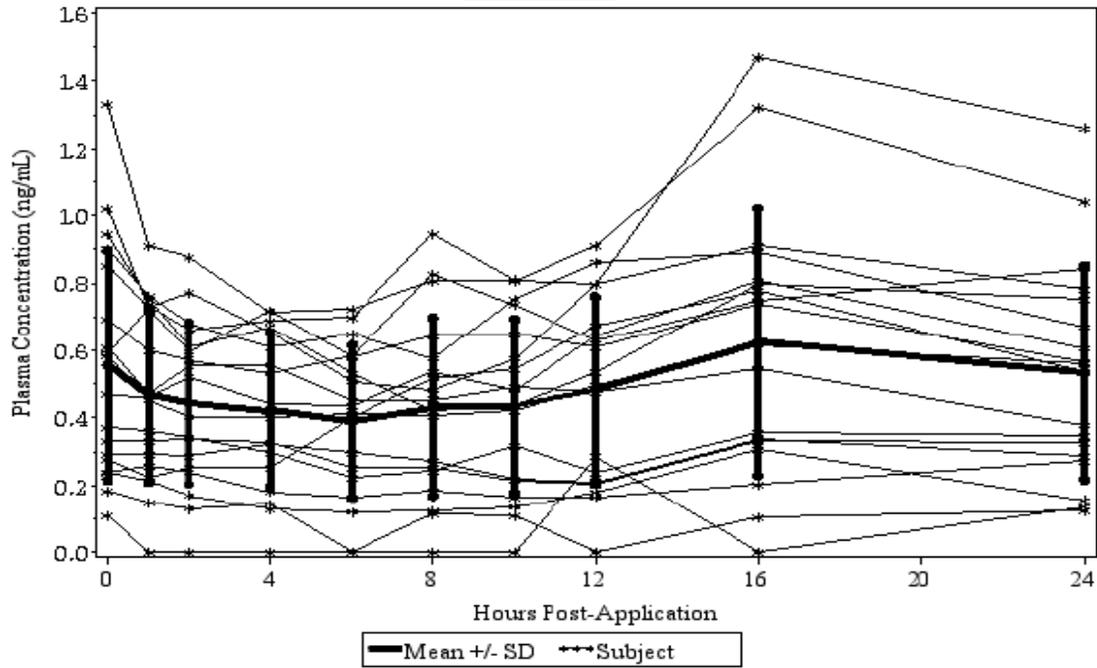
(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 1-2							
N	18	18	18	18	18	18	18
Mean	0.0000	0.0000	0.0000	0.0000	0.0491	0.0224	0.0352
SD	0.00000	0.00000	0.00000	0.00000	0.10176	0.06999	0.08986
SEM	0.00000	0.00000	0.00000	0.00000	0.02399	0.01650	0.02118
CV	NA	NA	NA	NA	207.21	312.62	255.53
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Min to Max	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.297	0.000 to 0.276	0.000 to 0.334
		12 Hours	16 Hours	24 Hours			
Days 1-2							
N		18	18	18			
Mean		0.0408	0.0750	0.1862			
SD		0.10420	0.13605	0.18242			
SEM		0.02456	0.03207	0.04300			
CV		255.53	181.41	97.96			
Median		0.0000	0.0000	0.1585			
Min to Max		0.000 to 0.361	0.000 to 0.396	0.000 to 0.670			

(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 14-15							
N	18	18	18	18	18	18	18
Mean	0.4843	0.4535	0.4154	0.4057	0.3726	0.3849	0.3869
SD	0.28367	0.22544	0.22964	0.24019	0.21552	0.25762	0.23257
SEM	0.06686	0.05314	0.05413	0.05661	0.05080	0.06072	0.05482
CV	58.58	49.71	55.28	59.21	57.84	66.93	60.11
Median	0.4530	0.4505	0.4065	0.3845	0.3940	0.3920	0.3870
Min to Max	0.000 to 0.988	0.116 to 0.923	0.000 to 0.927	0.000 to 0.832	0.000 to 0.757	0.000 to 0.820	0.000 to 0.773
Days 14-15							
		<u>12 Hours</u>	<u>16 Hours</u>	<u>24 Hours</u>			
N		18	18	17			
Mean		0.3863	0.4846	0.5291			
SD		0.22036	0.29423	0.32354			
SEM		0.05194	0.06935	0.07847			
CV		57.05	60.72	61.15			
Median		0.3865	0.4440	0.5460			
Min to Max		0.000 to 0.825	0.000 to 0.963	0.000 to 0.975			
Days 28-29							
(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 28-29							
N	18	18	18	18	18	18	18
Mean	0.5578	0.4689	0.4451	0.4250	0.3909	0.4338	0.4369
SD	0.34034	0.25821	0.23956	0.22832	0.22618	0.26362	0.25685
SEM	0.08022	0.06086	0.05647	0.05381	0.05331	0.06214	0.06054
CV	61.02	55.06	53.82	53.72	57.86	60.77	58.78
Median	0.5260	0.4580	0.4615	0.4220	0.4245	0.4380	0.4595
Min to Max	0.110 to 1.330	0.000 to 0.910	0.000 to 0.875	0.000 to 0.720	0.000 to 0.724	0.000 to 0.945	0.000 to 0.810
Days 28-29							
		<u>12 Hours</u>	<u>16 Hours</u>	<u>24 Hours</u>			
N		18	18	18			
Mean		0.4846	0.6264	0.5359			
SD		0.27704	0.39513	0.31757			
SEM		0.06530	0.09313	0.07485			
CV		57.17	63.08	59.26			
Median		0.5150	0.6785	0.5475			
Min to Max		0.000 to 0.910	0.000 to 1.470	0.124 to 1.260			
2-Week Post-Treatment							
N	18						
Mean	0.0664						
SD	0.07801						
SEM	0.01839						
CV	117.51						
Median	0.0510						
Min to Max	0.000 to 0.265						

Figure 2: Individual subject and mean (\pm SD) plasma concentrations for IDP-108



Days 28-29



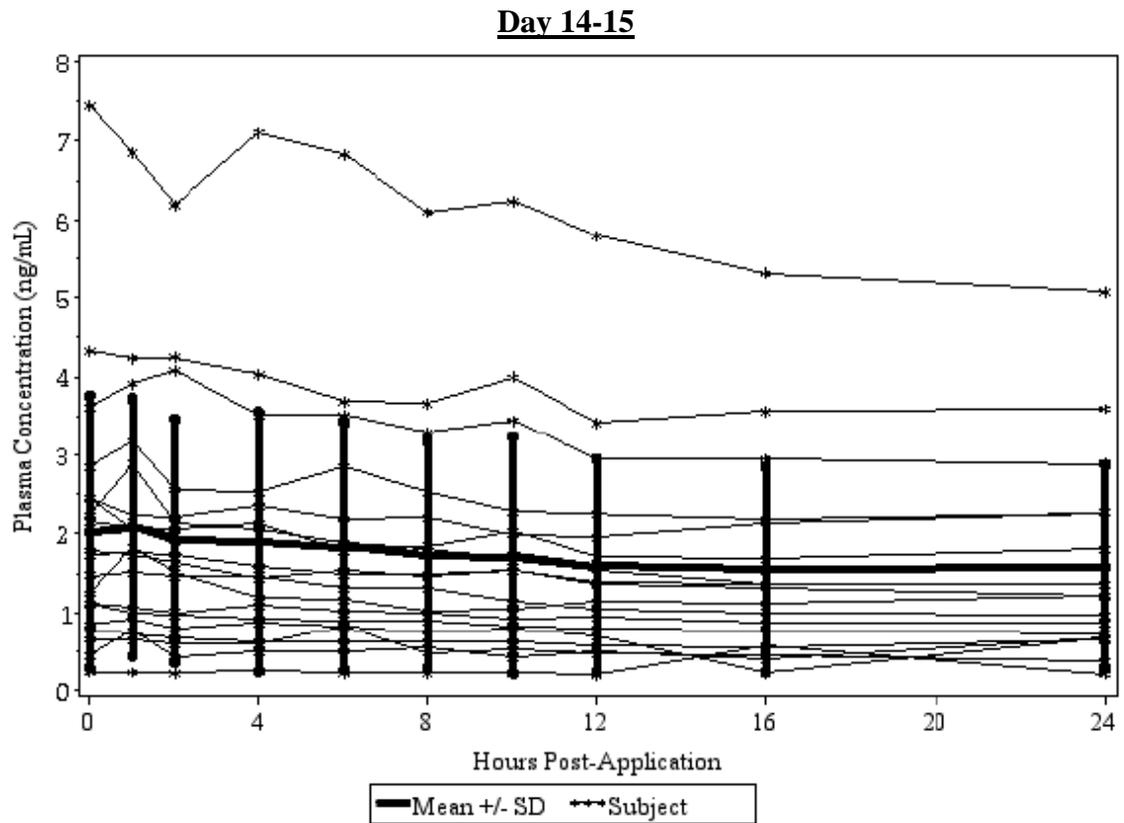
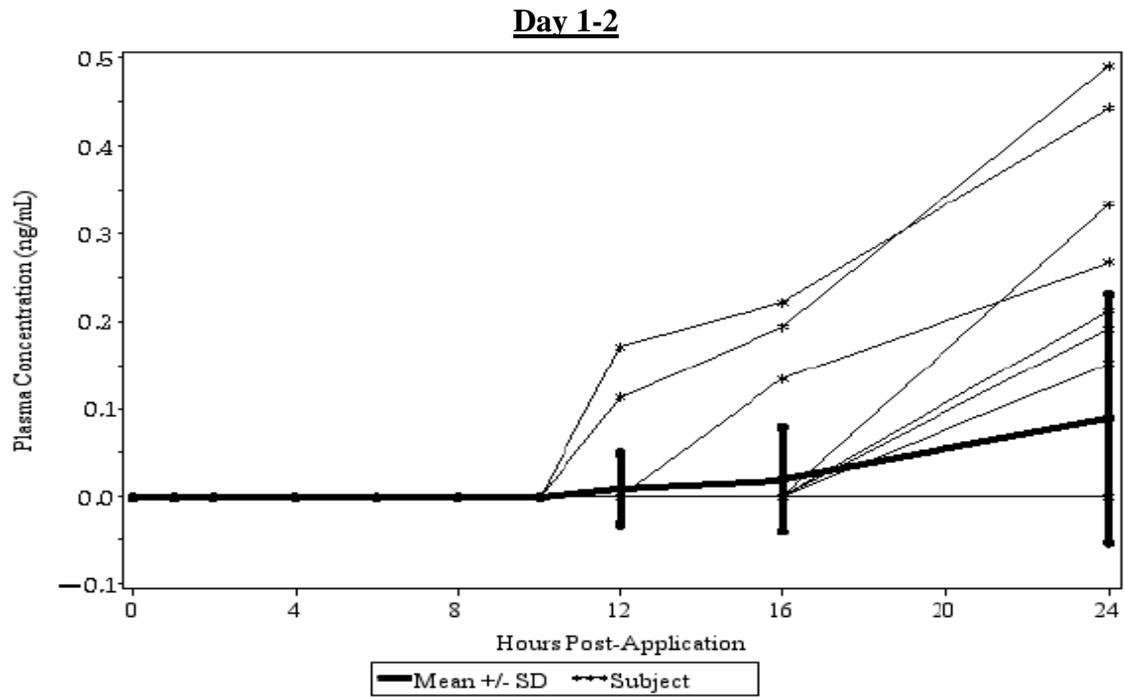
For metabolite H3, Table 14 shows the summary of plasma concentrations and individual subject and mean (\pm SD) plasma concentrations are shown in Figure 3.

Table 14: Summary of Plasma concentrations by time for metabolite H3

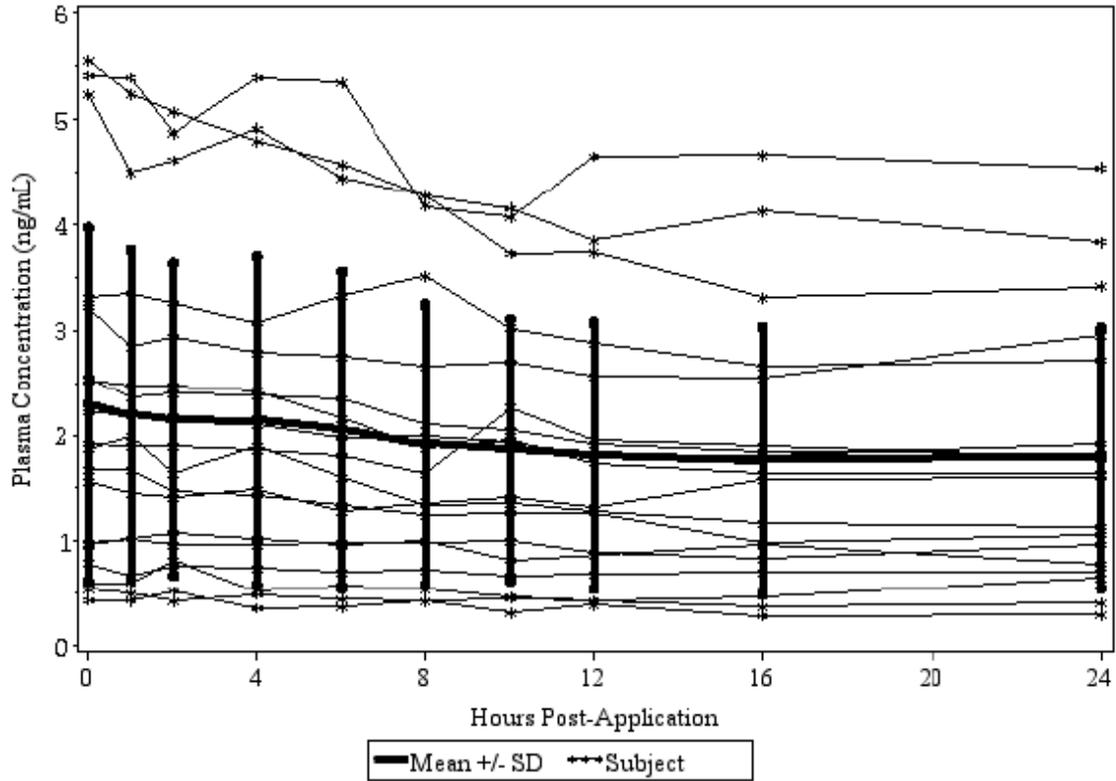
(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 1-2							
N	18	18	18	18	18	18	18
Mean	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SD	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
SEM	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
CV	NA	NA	NA	NA	NA	NA	NA
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Min to Max	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000
		12 Hours	16 Hours	24 Hours			
Days 1-2							
N		18	18	18			
Mean		0.0095	0.0197	0.0888			
SD		0.04031	0.05931	0.14170			
SEM		0.00950	0.01398	0.03340			
CV		424.26	300.71	159.51			
Median		0.0000	0.0000	0.0000			
Min to Max		0.000 to 0.171	0.000 to 0.221	0.000 to 0.443			

(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 14-15							
N	18	18	18	18	18	18	18
Mean	2.0322	2.0918	1.9202	1.9067	1.8458	1.7393	1.7373
SD	1.73717	1.64271	1.54754	1.65648	1.58324	1.44724	1.50770
SEM	0.40946	0.38719	0.36476	0.39044	0.37317	0.34112	0.35537
CV	85.48	78.53	80.59	86.88	85.77	83.21	86.78
Median	1.6050	1.7550	1.5700	1.4600	1.4050	1.3950	1.3350
Min to Max	0.240 to 7.450	0.237 to 6.860	0.226 to 6.190	0.244 to 7.110	0.229 to 6.830	0.224 to 6.100	0.229 to 6.230
		12 Hours	16 Hours	24 Hours			
Days 14-15							
N		18	18	17			
Mean		1.5989	1.5514	1.5790			
SD		1.35384	1.30105	1.29372			
SEM		0.31910	0.30666	0.31377			
CV		84.67	83.86	81.93			
Median		1.2550	1.2300	1.2200			
Min to Max		0.204 to 5.790	0.226 to 5.310	0.213 to 5.070			
(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 28-29							
N	18	18	18	18	18	18	18
Mean	2.2977	2.2009	2.1553	2.1477	2.0558	1.9208	1.8691
SD	1.66697	1.55266	1.47660	1.54803	1.49658	1.32421	1.23919
SEM	0.39291	0.36597	0.34804	0.36487	0.35275	0.31212	0.29208
CV	72.55	70.55	68.51	72.08	72.80	68.94	66.30
Median	1.8950	1.9450	1.7650	1.8800	1.7050	1.5000	1.6750
Min to Max	0.439 to 5.550	0.435 to 5.390	0.426 to 5.070	0.363 to 5.390	0.372 to 5.340	0.426 to 4.270	0.320 to 4.150
		12 Hours	16 Hours	24 Hours			
Days 28-29							
N		18	18	18			
Mean		1.8149	1.7692	1.7917			
SD		1.26382	1.26199	1.23297			
SEM		0.29788	0.29745	0.29061			
CV		69.63	71.33	68.81			
Median		1.5350	1.6100	1.6200			
Min to Max		0.394 to 4.650	0.289 to 4.660	0.297 to 4.540			
2-Week Post-Treatment							
N	18						
Mean	0.3105						
SD	0.21355						
SEM	0.05033						
CV	68.77						
Median	0.2530						
Min to Max	0.000 to 0.966						

Figure 3: Individual subject and mean (\pm SD) plasma concentrations for metabolite H3



Day 28-29



For metabolite H4, Table 15 shows the summary of plasma concentrations and individual subject and mean (\pm SD) plasma concentrations are shown in Figure 4.

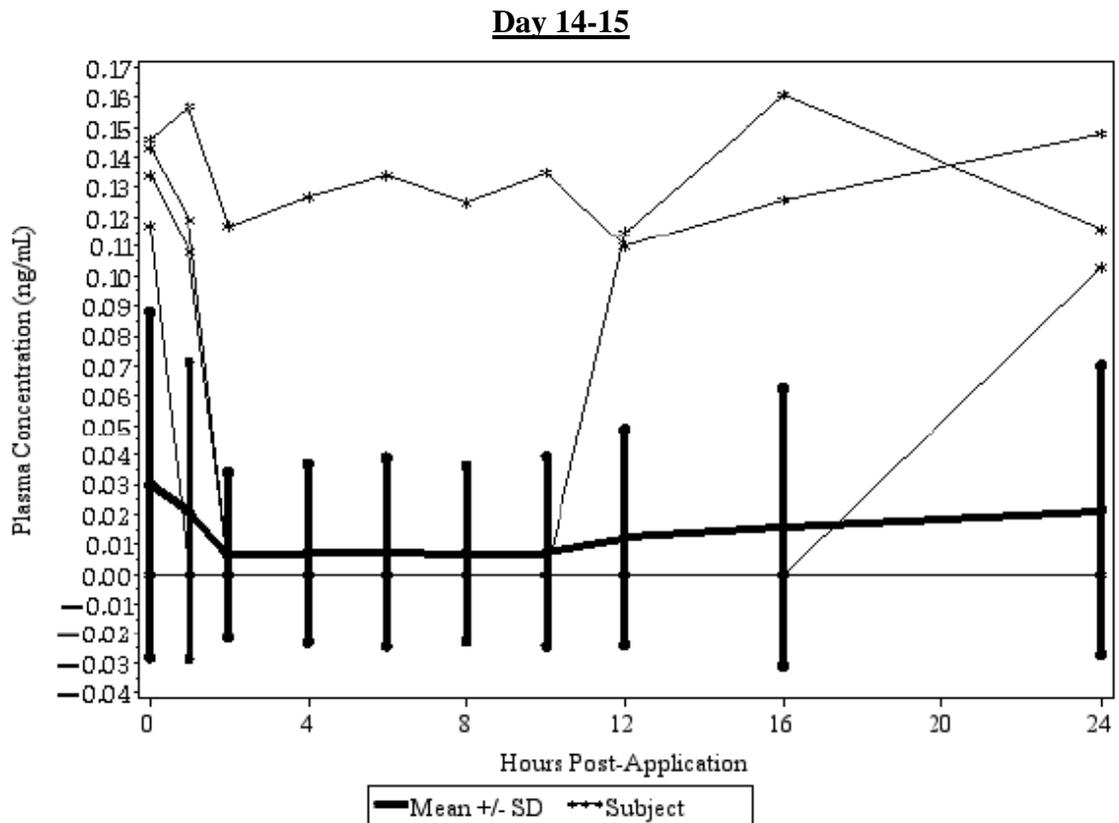
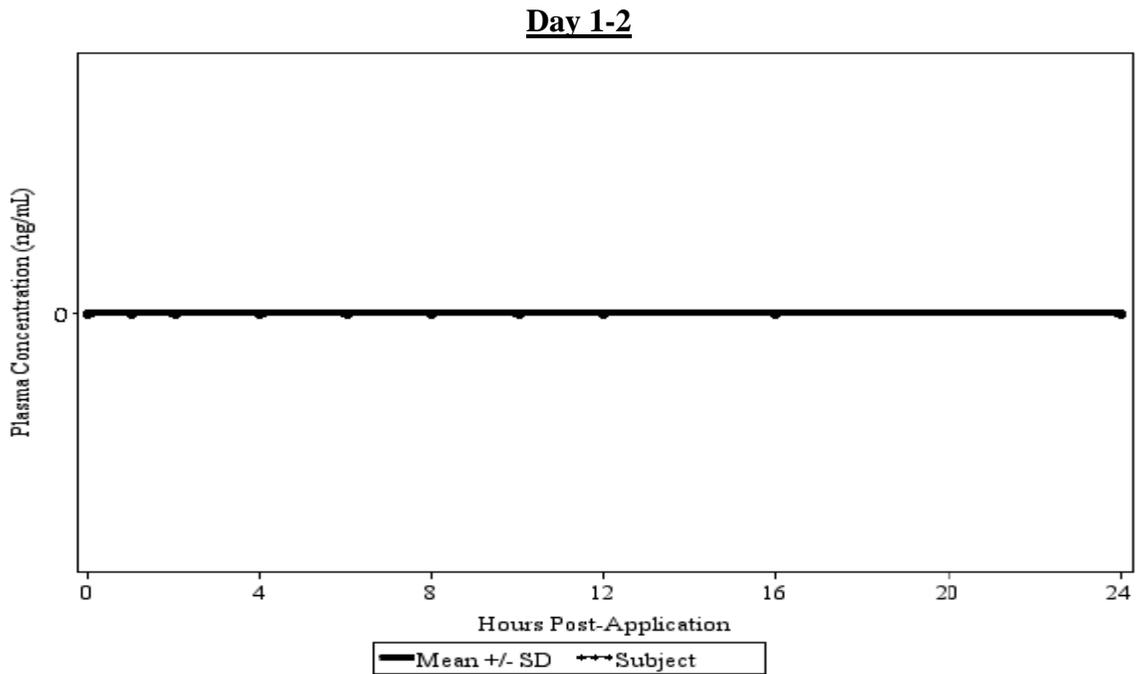
Table 15: Summary of Plasma concentrations by time for metabolite H4

(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 1-2							
N	18	18	18	18	18	18	18
Mean	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SD	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
SEM	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
CV	NA	NA	NA	NA	NA	NA	NA
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Min to Max	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000	0.000 to 0.000
		<u>12 Hours</u>	<u>16 Hours</u>	<u>24 Hours</u>			
Days 1-2							
N		18	18	18			
Mean		0.0000	0.0000	0.0000			
SD		0.00000	0.00000	0.00000			
SEM		0.00000	0.00000	0.00000			
CV		NA	NA	NA			
Median		0.0000	0.0000	0.0000			
Min to Max		0.000 to 0.000	0.000 to 0.000	0.000 to 0.000			

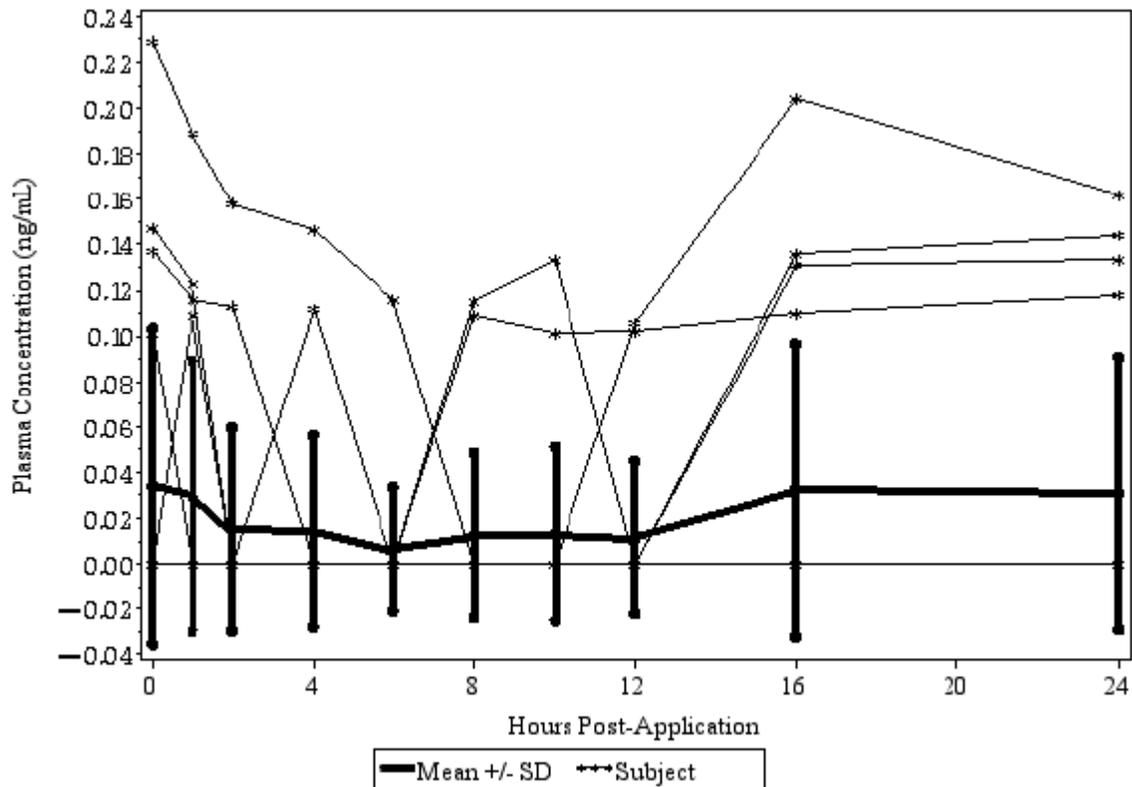
(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 14-15							
N	18	18	18	18	18	18	18
Mean	0.0300	0.0213	0.0065	0.0071	0.0074	0.0069	0.0075
SD	0.05801	0.04987	0.02758	0.02993	0.03158	0.02946	0.03182
SEM	0.01367	0.01175	0.00650	0.00706	0.00744	0.00694	0.00750
CV	193.37	233.77	424.26	424.26	424.26	424.26	424.26
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Min to Max	0.000 to 0.146	0.000 to 0.157	0.000 to 0.117	0.000 to 0.127	0.000 to 0.134	0.000 to 0.125	0.000 to 0.135
		12 Hours	16 Hours	24 Hours			
Days 14-15							
N		18	18	17			
Mean		0.0125	0.0159	0.0216			
SD		0.03639	0.04679	0.04876			
SEM		0.00858	0.01103	0.01183			
CV		291.12	293.47	225.88			
Median		0.0000	0.0000	0.0000			
Min to Max		0.000 to 0.115	0.000 to 0.161	0.000 to 0.148			

(ng/mL)	Pre-Application	Post-Application (Nominal Time)					
		1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Days 28-29							
N	18	18	18	18	18	18	18
Mean	0.0341	0.0298	0.0151	0.0143	0.0064	0.0124	0.0130
SD	0.06948	0.05949	0.04449	0.04212	0.02734	0.03623	0.03823
SEM	0.01638	0.01402	0.01049	0.00993	0.00644	0.00854	0.00901
CV	203.70	199.41	295.52	293.87	424.26	291.16	294.09
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Min to Max	0.000 to 0.229	0.000 to 0.189	0.000 to 0.158	0.000 to 0.146	0.000 to 0.116	0.000 to 0.115	0.000 to 0.133
		12 Hours	16 Hours	24 Hours			
Days 28-29							
N		18	18	18			
Mean		0.0116	0.0323	0.0309			
SD		0.03364	0.06445	0.06008			
SEM		0.00793	0.01519	0.01416			
CV		291.10	199.68	194.14			
Median		0.0000	0.0000	0.0000			
Min to Max		0.000 to 0.106	0.000 to 0.204	0.000 to 0.162			
2-Week Post-Treatment							
N		18					
Mean		0.0000					
SD		0.00000					
SEM		0.00000					
CV		NA					
Median		0.0000					
Min to Max		0.000 to 0.000					

Figure 4: Individual subject and mean (\pm SD) plasma concentrations for metabolite H4



Day 28-29



Efficacy results: The mean change from screening to Day 29 in the percent of the affected toenail ranged from -0.8% (left great toenail) to -0.3% (right great toenail). The mean change from screening to the two-week post-treatment follow-up visit in the percent of the affected toenail ranged from -1.1% (left great toenail) to -1.9% (right great toenail). Separately, the mean change from screening to Day 29 in the measurement of the unaffected toenail ranged from 0.2 mm (left great toenail) to 0.0 mm (right great toenail). The mean change from screening to the two-week post-treatment follow-up visit in the measurement of the unaffected toenail ranged from 0.1 mm (left great toenail) to 0.3 mm (right great toenail). Overall, these results showed that there were no meaningful changes from screening in the percent of the affected toenail or the measurement of the unaffected toenail due to the short duration of this study.

Brief Summary of AEs: Of the 19 subjects who used the study drug, 4 experienced at least 1 AE. These events included upper respiratory tract infection, skin laceration, arthralgia, and back pain. None of the events were serious or related to the study drug. All 4 of the events resolved, 2 with the use of concomitant therapy and 2 without the need for concomitant therapy. One of the events (skin laceration) was severe and one of the events (arthralgia) was moderate; the other 2 events (back pain and upper respiratory tract infection) were mild. No subject discontinued use of the study drug, had a change in the frequency of study drug application, or discontinued from the study because of an AE.

According to the Sponsor, none of the reported AEs were serious which led to discontinuation of the study or study drug. These AEs were considered not related to the study drug. No deaths were reported in this trial.

Localized skin reactions: The localized skin reactions included redness and swelling as well as burning, itching, and vesiculation. According to the Sponsor few localized skin reactions were reported by any of the subjects. At approximately half of the study visits, 1 to 2 subjects (up to 10.5% of the subjects) reported the presence of burning and/or itching. According to the Sponsor, the results of the localized skin reaction evaluations indicated that IDP-108 was well tolerated. A summary of local skin reactions is shown in Table16.

Table 16: Summary of local skin reactions

	Redness		Swelling		Burning		Itching		Vesiculation	
	Last	Worst	Last	Worst	Last	Worst	Last	Worst	Last	Worst
N	19	19	19	19	19	19	19	19	19	19
None	19 (100.0%)	18 (94.7%)	19 (100.0%)	19 (100.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
Mild	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	19 (100.0%)	17 (89.5%)	19 (100.0%)	17 (89.5%)	19 (100.0%)	19 (100.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)						
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)						

Reviewer comments: For further information on drug safety, please see Clinical review by medical officer Dr. Gary Chiang.

Trial Number: DPSI-IDP-108-P1-02 (Healthy subject PK trial)

Title: A Phase 1, Randomized, Open-Label, Crossover Study Evaluating the Pharmacokinetics of Topically Applied IDP-108 Solution, 10% in Healthy Volunteers

Bio-analytical work done by: [REDACTED]

(b) (4)

Study Objectives: This study was designed to:

- To evaluate the systemic exposure and characterize the plasma PK profile of IDP-108 and its major metabolite, H3, following single and 7 days of daily administration of 10% IDP-108 solution applied topically to the toenails and back of healthy volunteers
- To evaluate accumulation and time-dependent PK linearity of IDP-108 between single and multiple dose administrations
- To evaluate the safety of topically administered IDP-108, 10% solution in healthy volunteers

Study Design: This was a single-center, randomized, open-label, two-period, crossover study. Subjects were randomized to one of the following two treatment sequences

- Sequence A: IDP-108 solution, 10% was to be applied to all 10 toenails during Period I and the skin on the back during Period II
- Sequence B: IDP-108 solution, 10% was to be applied to the skin on the back during Period I and to all 10 toenails during Period II

Subjects were required to complete a washout of at least 7 days between the last dose of study drug on Day 10 of Period I and the first dose of study drug on Day 1 of Period II. During each treatment period, the study drug was to be applied once on Day 1 and once daily Day 4 through Day 10 (7 consecutive days of dosing). No study drug applications were to occur on Days 2 and 3. Blood and urine samples for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) were to be obtained at Screening, Day 0 (each treatment period), and during each period on Days 10 and 13. All female subjects were to have a urine pregnancy test performed and recorded at Screening, Day 0 (each treatment period), and upon study exit.

PK blood sampling time: Plasma samples for pharmacokinetic (PK) analysis were collected at the following time points for the determination of the concentrations of IDP-108 and its major metabolite, H3:

- Days 1-4: Pre-dose (prior to the Day 1 morning application) and 1, 2, 4, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48 and 72 hours after dosing
- Days 6 and 8: Pre-dose (prior to the morning application)
- Days 10-13: Pre-dose (prior to the Day 10 morning application) and 1, 2, 4, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48 and 72 hours after dosing

PK parameter estimation: The PK parameters were computed from the plasma concentration data using actual sampling times were C_{max} (observed peak drug concentration), T_{max} (time at which C_{max} occurs), C_{min} (observed minimum drug concentration - trough level at pre-dose), $t_{1/2}$ (apparent terminal half-life), AUC_{0-t} (area under the concentration-time curve from time zero up to the sampling time corresponding

to the last quantifiable concentration), AUC_{24h} (area under the concentration-time curve from time zero through 24 hours -corresponding to the dosing interval), AUC_{inf} (area under the concentration-time curve from time zero extrapolated to infinity for Day 1 only), F_{rel} (relative systemic bioavailability of IDP 108 applied to the back relative to the dose applied to the toenails) and R_o (accumulation ratio).

Dose administered: 2.5 mL on back skin; 0.42 mL on all 10 toenails

Approximate daily dose: ~42 mg (toenail treatment); ~250 mg (back treatment)

Route of administration: Topical

Number of subjects: A total of 10 subjects were randomized to study drug (5 subjects in each sequence), and 9 subjects completed the study as planned. Subject 03 (Sequence B) withdrew prior to Period II dosing due to schedule conflict. Table 17 shows the summary of subject disposition by sequence and Table 18 shows the summary of subject disposition by study period. Subject demographics are shown in Table 19.

Table 17: Summary of Subject Disposition by Sequence

	Sequence		Total
	A	B	
Subjects Randomized	5	5	10
Subjects Who Successfully Completed the Study	5	4	9
Subjects Who Withdrew Consent	0	1	1
Subjects Dropped by the Sponsor	0	0	0
Subjects Excluded from PK Analysis	0	0	0

Sequence A (toenail application) and B (back application)

Table 18: Summary of Subject Disposition by study period

	Total	Period I	Period II
Number of Subjects Randomized	10	10	9
Number of Subjects Who Completed the Period/Study	10	10	9
Number of Subjects Discontinued by Medical Investigator	0	0	0
Number of Subjects Discontinued by the Sponsor	0	0	0
Number of Subjects Who Withdrew Consent	1	1	0

Table 19: Subject demographics

Parameters	All Subjects N = 10	Females N = 4	Males N = 6
Age	29.1 (22 - 42)	25.8 (24 - 28)	31.3 (22 - 42)
Weight (lbs)	167.6 (112.0 - 229.0)	142.0 (112.0 - 208.0)	184.7 (136.5 - 229.0)
Height (in.)	68.7 (58.3 - 74.7)	63.7 (58.3 - 69.1)	72.0 (69.8 - 74.7)
BMI	24.6 (19.7 - 30.6)	24.2 (20.7 - 30.6)	24.9 (19.7 - 28.9)
Race ¹			
Asian:	-	-	-
African American:	2 (20.0%)	1 (25.0%)	1 (16.7%)
Native Hawaiian or Other Pacific Islander:	-	-	-
American Indian or Alaskan Native:	1 (10.0%)	1 (25.0%)	-
White:	7 (70.0%)	2 (50.0%)	5 (83.3%)

¹Subjects used in final statistical report.

PK results for parent drug (IDP-108):

Single dose: Table 20 summarizes the mean PK parameters of IDP-108 following single application of the drug on toenails and on the back on Day 1.

Table 20: Summary of mean PK parameters of IDP-108 following single application

Parameter	Toenails ^a		Back ^b	
	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)
AUC _t (ng·hr/mL)	6.70	10.19 (7.79)	31.32	37.73 (23.07)
AUC _{24h} (ng·hr/mL)	1.40	2.64 (2.85)	20.16	23.56 (14.30)
AUC _{inf} (ng·hr/mL)	N/A	N/A (N/A)	43.30	47.92 (26.28)
C _{max} (ng/mL)	0.261	0.382 (0.387)	1.467	1.914 (1.756)
T _{max} (hr)	17.93	24.00* (6.00 - 28.00)	12.75	12.00* (8.00 - 24.00)
λz (Kel) (1/hr)	N/A	N/A (N/A)	0.0356	0.0381 (0.0165)
t _{1/2} (hr)	N/A	N/A (N/A)	19.48	20.62 (6.79)

^a Applied dose volume for toenails was 0.420 mL of IDP-108 solution, 10% (~40 mg IDP-108)

^b Applied dose volume for back skin was 2.5 mL of IDP-108 solution, 10% (~200 mg IDP-108)

*Median value (Range)

SD - Standard deviation

N/A - Not available

Multiple dose: Table 21 summarizes the mean PK parameters of IDP-108 on Day 10 following multiple applications of the drug on toenails and on the back for 7 days.

Table 21: Summary of mean PK parameters of IDP-108 following multiple applications

Parameter	Toenails ^a		Back ^b	
	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)
AUC _{24h} (ng·hr/mL)	8.82	9.48 (3.86)	44.55	54.45 (36.99)
C _{max} (ng/mL)	0.501	0.542 (0.217)	2.676	3.529 (3.056)
T _{max} (hr)	N/A	10.00* (0.00 - 24.00)	N/A	11.00* (0.00 - 24.00)
C _{min} (ng/mL)	0.441	0.469 (0.178)	1.371	1.601 (0.849)
λz (Kel) (1/hr)	0.0232	0.0232 (N/A)	0.0284	0.0292 (0.0074)
t _{1/2} (hr)	29.91	29.91 (N/A)	24.41	25.07 (6.12)

^a Applied dose volume to toenails was 0.420 mL of IDP-108 solution, 10% (~40 mg IDP-108)

^b Applied dose volume to back skin was 2.5 mL of IDP-108 solution, 10% (~200 mg IDP-108)

* Median value (Range)

SD - Standard deviation

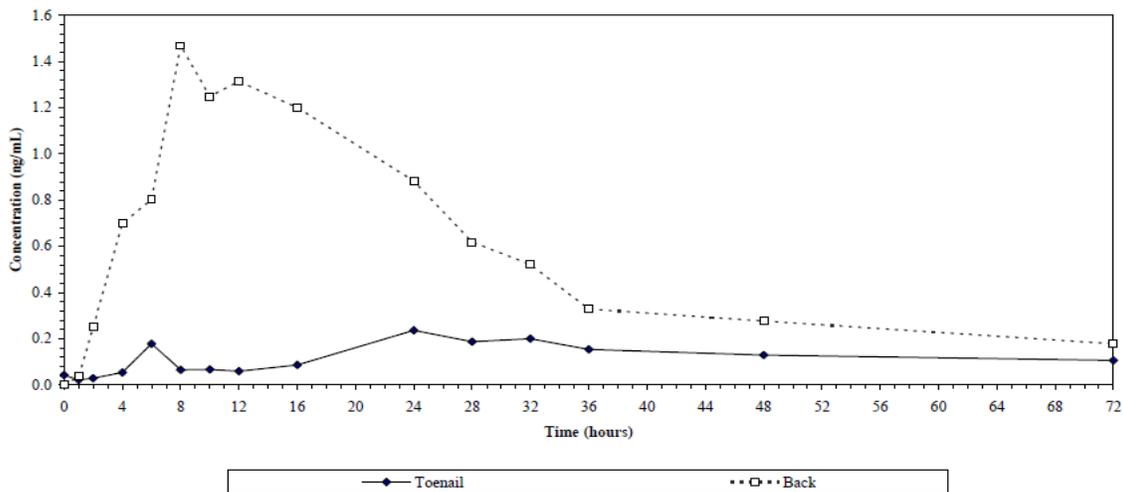
N/A - Not available

The accumulation ratios for IDP-108 from applications of 10% drug solution on toenails and on the back from Day 1 to Day 10 are shown in Table 22 and mean plasma concentration profile is shown in Figure 5.

Table 22: Summary of Accumulation Ratios – IDP-108

Toenails			
PK Parameter	Day 1	Day 10	Accumulation Ratio (Ro) (AUC _{24h} Day10/AUC _{24h} Day1)
C _{max}	0.382	0.542	3.59
T _{max}	20.25	9.56	
AUC _{24h}	2.64	9.48	
Back			
PK Parameter	Day 1	Day 10	Accumulation Ratio (Ro) (AUC _{24h} Day10/AUC _{24h} Day1)
C _{max}	1.914	3.529	2.31
T _{max}	13.40	11.60	
AUC _{24h}	23.56	54.45	

Figure 5: Mean plasma concentrations of IDP-108 following single application



PK results for metabolite H3:

Single dose: Table 23 summarizes the mean PK parameters of metabolite H3 following single application of the drug on toenails and on the back on Day 1.

Table 23: Summary of mean PK parameters of H3 following single application

Parameter	Toenails ^a		Back ^b	
	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)
AUC _t (ng·hr/mL)	16.32	21.31 (17.67)	65.45	73.43 (33.13)
AUC _{24h} (ng·hr/mL)	2.77	5.65 (5.30)	16.59	18.86 (8.37)
AUC _{inf} (ng·hr/mL)	N/A	N/A (N/A)	86.71	101.83 (50.86)
C _{max} (ng/mL)	0.348	0.436 (0.360)	1.41	1.61 (0.77)
T _{max} (hr)	28.37	48.00* (2.00 - 72.00)	26.27	26.00* (24.00 - 32.00)
C _{min} (ng/mL)	N/A	0.171 (0.230)	N/A	0.04 (0.08)
λz (Kel) (1/hr)	N/A	N/A (N/A)	0.0222	0.0224 (0.0030)
t _{1/2} (hr)	N/A	N/A (N/A)	31.25	31.48 (3.97)

^a Applied dose volume to toenails was 0.420 mL of IDP-108 solution, 10% (~40 mg IDP-108)

^b Applied dose volume to back skin was 2.5 mL of IDP-108 solution, 10% (~200 mg IDP-108)

*Median value (Range)

SD - Standard deviation

N/A - Not available

Multiple dose: Table 24 summarizes the mean PK parameters of metabolite H3 on Day 10 following multiple applications of the drug on toenails and on the back for 7 days.

Table 24: Summary of mean PK parameters of H3 following multiple applications

Parameter	Toenails ^a		Back ^b	
	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)
AUC _{24h} (ng·hr/mL)	29.04	32.52 (14.70)	102.08	117.22 (57.96)
C _{max} (ng/mL)	1.422	1.628 (0.798)	4.70	5.46 (2.81)
T _{max} (hr)	N/A	1.00* (0.00 - 28.00)	7.53	10.00* (1.00 - 24.00)
C _{min} (ng/mL)	1.340	1.544 (0.767)	4.16	4.78 (2.40)
λz (Kel) (1/hr)	0.0089	0.0095 (0.0037)	0.0187	0.0193 (0.0049)
t _{1/2} (hr)	77.37	82.42 (31.52)	37.08	38.14 (9.58)

^a Applied dose volume to toenails was 0.420 mL of IDP-108 solution, 10% (~40 mg IDP-108)

^b Applied dose volume to back skin was 2.5 mL of IDP-108 solution, 10% (~200 mg IDP-108)

* Median value (Range)

SD - Standard deviation

The accumulation ratios for H3 from applications of 10% drug solution on toenails and on the back from Day 1 to Day 10 are shown in Table 25 and mean plasma concentration profile is shown in Figure 6.

Table 25: Summary of Accumulation Ratios – H3

Toenails			
PK Parameter	Day 1	Day 10	Accumulation Ratio (Ro)
			(AUC _{24h} Day10/AUC _{24h} Day1)
C _{max}	0.436	1.628	5.75
T _{max}	44.44	7.67	
AUC _{24h}	5.65	32.52	
Back			
PK Parameter	Day 1	Day 10	Accumulation Ratio (Ro)
			(AUC _{24h} Day10/AUC _{24h} Day1)
C _{max}	1.614	5.460	6.21
T _{max}	26.40	11.20	
AUC _{24h}	18.86	117.22	

Figure 6: Mean Plasma Concentrations of H3 (0 – 72 hours) (N = 10)

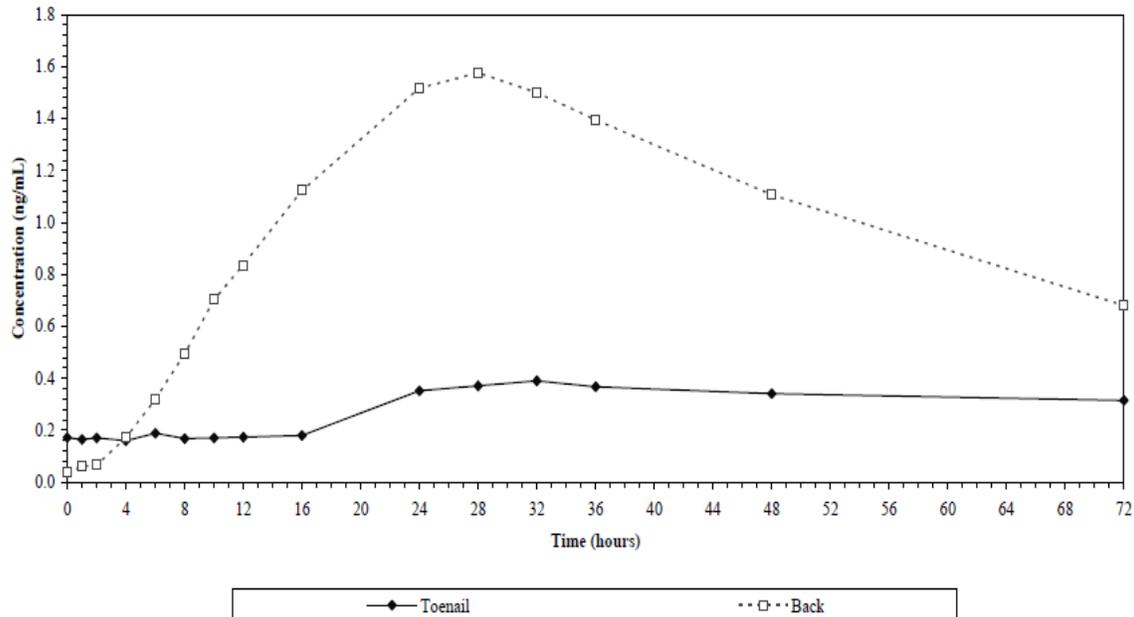


Table 26 compares the ratio of metabolite-to-parent for IDP-108 applications on the toenails vs. back for Day 1 and Day 10.

Table 26: PK Parameter Comparison - IDP-108 and H3

Toenails						
PK Parameter	Day 1			Day 10		
	H3	IDP-108	Ratio	H3	IDP-108	Ratio
C _{max} (ng/mL)	0.436	0.382	1.14	1.628	0.542	3.00
AUC _{24h} (ng·hr/mL)	5.65	2.64	2.14	32.52	9.48	3.43
Back						
PK Parameter	Day 1			Day 10		
	H3	IDP-108	Ratio	H3	IDP-108	Ratio
C _{max} (ng/mL)	1.61	1.914	0.84	5.46	3.529	1.55
AUC _{24h} (ng·hr/mL)	18.86	23.56	0.80	117.22	54.45	2.15

Brief Summary of AEs: According to the Sponsor, 6 subjects experienced a total of 18 AEs over the course of the study. The AEs were mild in severity and no SAEs were reported. All AEs were followed until resolution, with the exception of Subject 10, who was diagnosed with asymptomatic bacteriuria per clinical labs drawn during the study. This subject was monitored by the Medical Investigator from onset to study exit and was verbally queried on two occasions on whether she felt symptomatic. According to the Sponsor, on both occasions the subject indicated that she did not feel symptomatic. Due to the asymptomatic response from the subject, the Medical Investigator concluded it was appropriate for the subject to exit the study with no additional follow-up. This AE was considered not related to the study drug by the Medical Investigator. There were no deaths in this trial. Overall, the most common AEs reported were headache and upper abdominal pain which were considered not related to the treatment by the Investigator. Table 27 provides a summary of AEs observed in this trial.

Table 27: Summary of AEs observed in Trial DPSI-IDP-108-P1-02

Adverse Event (AE) MedDRA SOC / Preferred Term ⁺	Treatment Arm		
	Treatment A N=10	Treatment B N=10	Overall N=10
Total Number of Subjects with AEs	3 (30.00%)	3 (30.00%)	6 (60.00%)
Gastrointestinal disorders			
Abdominal pain	-	1 (10.00%) 05	1 (10.00%)
Abdominal pain upper	1 (10.00%) 04 ³	1 (10.00%) 02	2 (20.00%)
Constipation	-	1 (10.00%) 08	1 (10.00%)
Nausea	1 (10.00%) 04	-	1 (10.00%)
Infections and infestations			
Asymptomatic bacteriuria	1 (10.00%) 10	-	1 (10.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	-	1 (10.00%) 02 ³	1 (10.00%)
Nervous system disorders			
Headache	1 (10.00%) 01 ²	2 (20.00%) 02, 05 ²	3 (30.00%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (10.00%) 01	-	1 (10.00%)
Skin and subcutaneous tissue disorders			
Rash	1 (10.00%) 10	-	1 (10.00%)

Reviewer comments: For further information on drug safety, please see Clinical review by medical officer Dr. Gary Chiang.

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

/s/

CHINMAY SHUKLA
03/04/2013

DOANH C TRAN
03/04/2013

EDWARD D BASHAW
03/07/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203567	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	III	Generic Name	Efinaconazole, 10%
Medical Division	DDDP	Drug Class	Triazole antifungal
OCP Reviewer	Chinmay Shukla, Ph.D.	Indication(s)	Topical treatment of onychomycosis
OCP Team Leader	Doanh Tran, Ph.D.	Dosage Form	Solution
Pharmacometrics Reviewer	NA	Dosing Regimen	Apply once daily using the built-in flow-through brush
Date of Submission	July 26, 2012	Route of Administration	Topical
Estimated Due Date of OCP Review	March 05, 2013	Sponsor	Dow Pharmaceutical Sciences, Inc.
Medical Division Due Date	March 12, 2013	Priority Classification	Standard
PDUFA Due Date	May 26, 2013		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-				
single dose:				

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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multiple dose:	X	1		Study DPSI-IDP-108-P1-02: PK in 10 healthy subjects using to-be-marketed formulation
Patients-				
single dose:				
multiple dose:	X	1		Study DPSI-IDP-108-P1-03: Maximal use PK trial in 20 patients with severe onychomycosis using to-be-marketed formulation
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Literature References				
Total Number of Studies		9		Four Phase 1, One Phase 2, Two Phase 3 and Two Non-IND (Non-IND studies are included to provide supplemental safety data)

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	All pivotal studies are conducted with the to-be-marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Study DPSI-IDP-108-P1-03: Maximal use PK trial in 20 patients with severe onychomycosis using to-be-marketed formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Inadequate long term sample stability for Study DPSI-IDP-108-P1-03 (maximal use study).
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			The Sponsor has not submitted raw data sets of the two Non-IND Phase 1 trials.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The Sponsor has submitted (b) (4)
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	All reports are in English

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___
___ Yes ___

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

- N.A. -

Chinmay Shukla, Ph.D.

 Reviewing Clinical Pharmacologist

 Date

Doanh Tran, Ph.D.

 Team Leader

 Date

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Filing Memorandum

Clinical Pharmacology Review

NDA: 203567
Compound: (b) (4) (efinaconazole) Solution, 10%
Indication: Topical treatment of Onychomycosis
Sponsor: Dow Pharmaceutical Sciences, Inc.
Date: 07/26/2012
Reviewer: Chinmay Shukla
Related IND: 77732

Background: Efinaconazole is a new molecular entity and belongs to triazole antifungal drug class. The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway and is seeking an indication of once daily topical treatment of onychomycosis in adults with 10% solution formulation of efinaconazole. The Sponsor has also requested (b) (4)

[REDACTED]

The Clinical program consists of four Phase 1, one Phase 2 and two Phase 3 trials. The Sponsor has also submitted reports of 2 additional Phase 1 trials that were not conducted under their investigational IND 77732. The Sponsor's reason for including the non-IND trials is to provide supplemental safety data. A summary of clinical trials is shown in the table below (TBM denotes to-be-marketed solution formulation used).

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Study number	Objective	Test product and Duration of treatment	No. of subjects
<i>Phase 1</i>			
DPSI-IDP-108-P1-01	Dermal Irritation	* 1% (TBM*), 5% (TBM*) & 10% (TBM) * 21 days	55 (healthy)
DPSI-IDP-108-P1-02	PK in Healthy subjects	* 10% (TBM) * 28 days	10 (healthy)
DPSI-IDP-108-P1-03	Maximal use PK trial	* 10% (TBM) * 28 days	20 (severe disease)
DPSI-IDP-108-P1-04	Contact sensitization	* 10% (TBM) * 8 weeks	239 (healthy)
<i>Phase 2</i>			
DPSI-IDP-108-P2-01 <i>Conducted in Mexico</i>	Safety and Efficacy	* 5% (not TBM) & 10% (not TBM) * 40 weeks	135 (mild to moderate)
<i>Phase 3</i>			
DPSI-IDP-108-P3-01	Safety and Efficacy	* 10% (TBM) * 52 weeks	870 (mild to moderate)
DPSI-IDP-108-P3-02	Safety and Efficacy		781 (mild to moderate)
<i>Non-IND Phase 1 studies</i>			
KP-103-02 <i>Conducted in Japan</i>	Skin irritation and Photosensitization	* 5% (TBM*) & 10% (TBM) * 28 days	56 (healthy)
KP-103-03 <i>Conducted in Japan</i>	To investigate efinaconazole concentrations in effected vs. normal toenails as well as 1 st vs. 2 nd toenail with different thickness	* 1% (TBM*), 5% (TBM*) & 10% (TBM) * 7 days	40 (diseased)

TBM: To-be-marketed formulation of 10% strength

TBM*: Formulation similar to to-be-marketed but of strength other than 10%

Pharmacokinetic assessment: The Sponsor has evaluated PK of the parent compound as well as major metabolites H3 and H4 in healthy subjects and in subjects with onychomycosis under maximal use conditions. The parent drug and metabolites were quantifiable in almost all subjects with C_{max} of metabolite H3 approximately 3.5 times higher than the parent compound on Day 28. The C_{max} of metabolite H4 was approximately 76 % lower than the parent compound on Day 28. In addition to this, the Sponsor has also assessed metabolic pathway of efinaconazole and addressed the potential for drug-drug interaction. Bioanalytical reports and associated method validation reports are available for review for trials DPSI-IDP-108-P1-02 and DPSI-IDP-108-P1-03.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 203567 is fileable.

Comments for the Sponsor:

1. For trial DPSI-IDP-108-P1-03, we notice that the long term storage stability data provided by you appears to be inadequate. Provide long term storage stability data for the parent compound and metabolites to support the storage stability of PK samples to cover the duration from the time of PK sample collection during the trial to the time of sample analysis. In addition, clarify the duration of storage for the internal standard solution used during analysis of samples from this trial and whether there is sufficient stability data to support such duration.
2. For trial DPSI-IDP-108-P1-02, under Section 5.3.3.1.1, Study DCN-1002550 - Bioanalytical Report, it states that the “*Stock stability has been established and is reported separately.*” Provide this report for review.
3. Submit bioanalytical method validation report and bioanalysis reports for trials KP-103-02 and KP-103-03.

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

/s/

CHINMAY SHUKLA
09/14/2012

DOANH C TRAN
09/14/2012