

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

To: NDA 203567
From: Linda S. Pellicore, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara A. Hill, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date: 12/20/2013, 1/16/2014 and 2/4/2014
SDN: 21, 22 and 23
Submission type: Resubmission Class 2
Drug: JUBLIA (efinaconazole) Topical Solution, 10%
Drug class: Azole antifungal
Indication: Onychomycosis
Route: Topical
Sponsor: Dow Pharmaceutical Sciences

Background:

Efinaconazole is a new molecular entity (NME) and an azole antifungal drug. The applicant is seeking an indication for once daily topical treatment of onychomycosis in adults with JUBLIA (efinaconazole) topical solution, 10%. 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 nonclinical information submitted with the original application was found acceptable, provided the applicant adequately addressed the labeling comments (see Primary Nonclinical Review dated March 5, 2013, in DARRTS).

On December 20, 2013 the applicant re-submitted their NDA to address the CMC deficiencies. The applicant changed the container closure system. No new nonclinical information was submitted.

The sponsor resubmitted draft labeling information to the NDA on January 16, 2014. This nonclinical review pertains only to the sponsor's resubmitted draft labeling.

Review of proposed labeling:

Nonclinical detailed labeling recommendations were provided in the original NDA Primary Nonclinical Review (see review dated March 5, 2013 in DARRTS). In this cycle, the sponsor's proprietary name, JUBLIA, was found acceptable (see Proprietary Name Review dated March 26, 2014, in DARRTS). Other than adding the proprietary name to the sponsor's proposed label, no additional edits were made to the resubmitted draft labeling. Nonclinical labeling edits that are being proposed in this review cycle are provided below.

Conclusion:

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the JUBLIA (efinaconazole) Topical Solution 10% label reproduced below. The pharmacologic class designation for efinaconazole for the treatment onychomycosis is azole antifungal.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

JUBLIA ^{(b) (4)} azole antifungal ^{(b) (4)} indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton mentagrophytes* and *Trichophyton rubrum*. ^{(b) (4)} (1)

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with JUBLIA topical solution in pregnant women-^{(b) (4)}. JUBLIA topical solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

^{(b) (4)}

12.1 Mechanism of Action

JUBLIA topical solution is an azole antifungal [See *Clinical Pharmacology* (12.4)].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) A 2 year dermal carcinogenicity study in mice, was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons) (b) (4)

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay) (b) (4)

(b) (4)

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

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/s/

LINDA S PELLICORE
05/09/2014

BARBARA A HILL
05/09/2014

Pharmacology/Toxicology Supervisory Memorandum

NDA number: 203567
Supporting document: 1
CDER Stamp Date: July 26, 2012
Type of submission: Original NDA
Applicant: Dow Pharmaceutical Sciences
Supervisor name: Barbara Hill
Review Division: Dermatology and Dental Products
Date: March 5, 2013
Product: Efinaconazole Topical Solution, 10%
Pharmacologic class: Azole antifungal
Indication: Onychomycosis

General comments:

- I concur with the conclusions contained in Dr. Linda Pellicore's Pharmacology/Toxicology review for this drug product.
- I concur that there are no nonclinical approval issues for this drug product and that this NDA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended for this NDA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Pellicore for this drug product contained in section 1.3.3 of her review including that the appropriate Pregnancy Category is C.

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/s/

BARBARA A HILL
03/05/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203567
Supporting document/s: SDN 1 and 2
Applicant's letter date: July 25, 2012 and August 6, 2012
CDER stamp date: July 26, 2012 and August 6, 2012
Product: Efinaconazole Topical Solution, 10%
Indication: Onychomycosis
Applicant: Dow Pharmaceutical Sciences
Review Division: Dermatology and Dental Products
Reviewer: Linda Pellicore, Ph.D.
Supervisor/Team Leader: Barbara Hill, Ph.D.
Division Director: Susan Walker, M.D.
Project Manager: Strother Dixon

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Efinaconazole is a new molecular entity. Efinaconazole is a triazole antifungal agent that apparently has a low keratin binding affinity. The sponsor believes that efinaconazole's low keratophilicity will provide an important pharmacokinetic advantage for topical antifungal treatment of onychomycosis. The sponsor states that binding to keratin within the nail and skin is believed to inactivate antifungal agents and may explain the poor success of topical therapies. The sponsor expects that the low affinity of efinaconazole for keratin and ready release when bound will result in an effective topical antifungal treatment.

1.2 Brief Discussion of Nonclinical Findings

Repeat-dose systemic rodent toxicity and developmental and reproductive toxicity studies were conducted with subcutaneous administration of efinaconazole dissolved in propylene glycol. Efinaconazole appeared well tolerated but subcutaneous administration of propylene glycol was not well tolerated and resulted in significant injection site toxicity.

The primary toxicity noted in the 6 month repeat dose subcutaneous toxicity study in rats conducted with doses up to 30 (males) and 40 (females) mg/kg/day efinaconazole was injection site toxicity noted in all dose groups including the vehicle (propylene glycol) control group.

Efinaconazole solution was evaluated in a 9 month dermal toxicity study in minipigs with repeated daily dermal administration of up to 30% efinaconazole solution. The efinaconazole solution used in the chronic dermal minipig study was similar to the to-be-marketed formulation. The minor differences in a few excipients in the formulation were determined to not be of toxicological significance. The vehicle and efinaconazole solution produced mild skin irritation. Mild skin irritation (modest microscopic hyperkeratosis, acanthosis, and localized inflammation) was noted in all dose groups including the vehicle control group. No systemic toxicity was noted at topical doses up to 30% efinaconazole solution, which is the maximum feasible concentration.

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

A dermal mouse carcinogenicity study was conducted with the to-be-marketed efinaconazole solution. Severe skin irritation was noted at the treatment site in all dose groups including the vehicle control group. This study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. No treatment

related increase in the incidence of neoplasms was observed in this study. However, the skin effects of the propylene glycol vehicle confounded assessment of any skin effects due to efinaconazole.

Reproductive and developmental toxicology studies have been conducted with efinaconazole in rats and rabbits.

In a subcutaneous rat fertility study skin thickening at the injection site was noted in all efinaconazole treated groups and the vehicle control group. No treatment related effects on male or female fertility parameters were noted at doses up to 25 mg/kg/day efinaconazole in this study. A tendency to slightly prolong the estrous cycle was noted in 25 mg/kg/day treated females but the copulation index was 100% in all dose groups.

A subcutaneous embryofetal development study in rats was conducted with doses up to 50 mg/kg/day efinaconazole. Skin thickening at the treatment site, an 11% decrease in maternal body weight gain, complete embryo resorption in two dams and an increased incidence of embryofetal death were noted at the 50 mg/kg/day dose. Embryofetal resorption and/or embryofetal death may be related to the effects seen in the placenta noted at the 50 mg/kg/day dose. However, no drug-related malformations were noted at doses up to 50 mg/kg/day efinaconazole in this study.

A subcutaneous embryofetal development study in rabbits was conducted with doses up to 10 mg/kg/day efinaconazole. Injection site reactions were noted in all treatment groups including the vehicle control group. A decrease in body weight gain was noted in does at 10 mg/kg/day. There were no indications of test article related embryofetal toxicity or malformations at doses up to 10 mg/kg/day efinaconazole in this study.

A subcutaneous pre- and post-natal development study in rats was conducted with doses up to 25 mg/kg/day efinaconazole. Injection site swelling and masses were noted in all dose groups including the vehicle control group. Prenatal pup mortality was increased at 25 mg/kg/day. There were no toxicologically significant effects on duration of gestation or the ability of dams to deliver litters. No treatment related effects on postnatal development of F₁ offspring were noted at doses up to 25 mg/kg/day efinaconazole in this study.

Single dermal application of up to 10% efinaconazole solution to rabbits did not elicit dermal irritation in intact skin but was a mild irritant to abraded skin. Efinaconazole solution, 10%, was a mild ocular irritant in rabbit eyes. Efinaconazole solution did not elicit a photoirritation response in guinea pigs.

1.3 Recommendations

1.3.1 Approvability

Efinaconazole Topical solution, 10%, is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the TRADENAME (efinaconazole) Topical Solution 10% label reproduced below. The pharmacologic class designation for efinaconazole for the treatment onychomycosis is azole antifungal.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

^{(b) (4)} TRADENAME (~~efinaconazole~~) Topical Solution is ^{(b) (4)} azole antifungal ^{(b) (4)} indicated for the topical treatment of onychomycosis ^{(b) (4)} (1)

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with TRADENAME Topical Solution in pregnant women ^{(b) (4)}. TRADENAME Topical Solution ^{(b) (4)} should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

(b) (4)

12.1 Mechanism of Action

TRADENAME Topical Solution is an azole antifungal (b) (4) see Clinical Pharmacology (12.4)].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) A 2 year dermal carcinogenicity study in mice was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons). (b) (4)

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay). (b) (4)

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the

estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

2 Drug Information

2.1 Drug

CAS Registry Number
164650-44-6

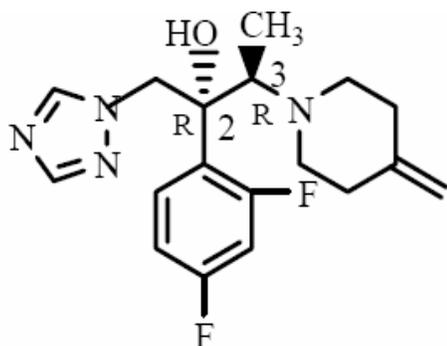
Generic Name
Efinaconazole

Code Name
KP-103; IDP-108

Chemical Name
(2R, 3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

Molecular Formula/Molecular Weight
 $C_{18}H_{22}F_2N_4O$ / 348.4

Structure



Pharmacologic Class
Azole antifungal

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77732: IDP-108 (KP-103) topical solution for the treatment of onychomycosis. Division of Dermatology and Dental Products. Sponsor: Dow Pharmaceutical Sciences, Inc.

DMF 21870: KP-103 as manufactured in Yamagata, Japan. Kaken Pharmaceutical Co Ltd. A letter authorizing the Agency to refer to the chemistry information provided in DMF 21870. No Pharmacology/Toxicology information was contained in DMF 21870.

2.3 Drug Formulation

The sponsor made several changes to the drug formulation during development. Initially the active moiety was referred to as KP-103 by Kaken Pharmaceutical. Subsequently the active moiety is referred to as IDP-108 by Dow Pharmaceuticals. Early prototype formulations include (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted] (b) (4)

The quantitative composition of IDP-108 (also referred to as IDP-108A) is provided in the table below.

Ingredient	% w/w					
IDP-108	0.00	1.00	3.00	5.00	10.00	30.00
(b) (4) Alcohol, USP						
Cyclomethicone (b) (4) NF						
Diisopropyl Adipate						
C12-15 Alkyl Lactate						
(b) (4)						
Butylated Hydroxytoluene						

Except for the dermal mouse carcinogenicity study, which was conducted with the to-be-marketed drug product, the pivotal GLP toxicity studies were conducted with IDP-108.

The difference between IDP-108, the formulation used in the pivotal GLP toxicity studies and the to-be-marketed formulation used in the GLP dermal mouse carcinogenicity study, (b) (4)

The small amount of (b) (4)

is not expected to significantly change the study results from a Pharmacology/Toxicology perspective.

The quantitative composition of the to-be-marketed drug product is provided below in the sponsor's table.

Ingredient	Grade	Function	Concentration (% w/w)
Efinaconazole	N/A	(b) (4)	10.0
Cyclomethicone	NF		(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		

The dermal mouse carcinogenicity study was conducted with the to-be-marketed formulation.

The Chemistry Manufacturing and Controls (CMC) Reviewer identified some drug product container issues (i.e., leaking containers) that may result in a Complete Response (CR) for this NDA. However, these containers were not used in any of the submitted Pharmacology/Toxicology studies. Therefore, these CMC issues do not affect the integrity of the Pharmacology/Toxicology data package.

2.4 Comments on Novel Excipients

C12-15 alkyl lactate is not listed in the CDER inactive ingredients database. Therefore, C12-15 alkyl lactate is a novel excipient. The sponsor provided additional information to qualify C12-15 alkyl lactate for use at the 10% level in this topical drug product.

2.5 Comments on Impurities/Degradants of Concern

Two impurities (b) (4) and two degradants (b) (4) have been identified in the drug substance. The structures for the impurities/degradants are provided in the table below.

Drug-Related Impurity	Structure	Origin
(b) (4)	(b) (4)	Synthesis
		Synthesis
		Degradation
		Degradation

The sponsor's proposed specifications for the impurities/degradants in the drug substance are provided below.

(b) (4) NMT (b) (4) %; (b) (4) NMT (b) (4) %; (b) (4): NMT (b) (4) % and (b) (4) NMT (b) (4) %; each additional impurity: NMT (b) (4) % and total impurities: NMT (b) (4) %. The sponsor's proposed specifications for the impurities/degradants in the drug substance are acceptable since they are all below the ICH qualification thresholds.

2.6 Proposed Clinical Population and Dosing Regimen

Efinaconazole, a triazole antifungal agent, is indicated for the topical treatment of onychomycosis. Efinaconazole solution, 10%, is a clear solution for topical application. Efinaconazole solution should be topically applied once daily using the built-in flow through brush applicator provided. It is important to ensure that the nail, the nail folds, nail bed, and hyponychium are covered.

2.7 Regulatory Background

An End of Phase 2 (EOP2) meeting was conducted on August 4, 2009. The EOP2 meeting minutes were relayed to the sponsor on August 17, 2009.

A pre-meeting communication for a Pre-NDA meeting was sent to the sponsor on April 11, 2012. The sponsor canceled the Pre-NDA meeting scheduled for April 17, 2012 after receipt of the Division's pre-meeting communication. The Pre-NDA final responses were relayed to the sponsor on May 14, 2012.

The dermal mouse carcinogenicity study protocol that was submitted as a SPA and the supporting 3 month dermal mouse dose range finding study were discussed during an Exec CAC meeting on December 9, 2008. The Executive CAC meeting minutes were relayed to the sponsor on December 15, 2008.

The sponsor submitted a request to modify the dermal mouse carcinogenicity study on November 11, 2009. Comments concerning appropriate modifications of the dermal mouse carcinogenicity study that received Executive CAC concurrence were relayed to the sponsor on November 24, 2009. The sponsor submitted a request for early termination of the dermal mouse carcinogenicity study on February 18, 2011. Comments concerning appropriate criteria for early termination of a particular dose group that received Executive CAC concurrence were relayed to the sponsor on February 25, 2011. The sponsor submitted a second request for early termination of the dermal mouse carcinogenicity study on April 11, 2011. Comments concerning early termination of the dermal mouse carcinogenicity study that received Executive CAC concurrence were relayed to the sponsor on April 18, 2011.

The sponsor submitted a waiver request for conduct of a systemic carcinogenicity study on November 25, 2009. A letter was sent to the sponsor on April 14, 2010 granting the waiver request for conduct of a systemic carcinogenicity study.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Efinaconazole

1. General pharmacology of KP-103. Study No. KOP001
2. hERG Block comparator study: Effects of IDP-108 on cloned hERG potassium channels expressed in mammalian cells. Study No. DSIN-7001-A6HP-11-08.

Metabolite H3

1. Effect of H3 on cloned hERG potassium channels expressed in mammalian cells. Study No. DSIN-7001-A6HP-23-09.

Pharmacokinetics/ADME/Toxicokinetics

Absorption

1. Absorption, distribution and excretion studies of KP-103 in rats and dogs. Study No. PK9533.

Distribution

1. Plasma protein binding of ¹⁴C-KP-103 in rats and dogs. Study No. SA950310.
2. Plasma protein binding of ¹⁴C-KP-103 in humans. Study No. SA950311.
3. Feto-placental transfer and excretion into milk after a single subcutaneous administration of ¹⁴C-KP-103 to female rats. Study No. P101077.

Metabolism

1. *In Vitro* metabolism study of ¹⁴C-KP-103. Study No. SA970103.
2. Determination of KP-103 metabolites after subcutaneous administration of ¹⁴C-KP-103 to rats. Study No. SA960307.
3. Identification of KP-103 metabolites. Study No. SA970108.
4. Identification of IDP-108 metabolites in the presence of human and minipig hepatocytes. Study No. IAS-07-MS-15-DM.
5. Determination of KP-103 metabolites after subcutaneous administration of ¹⁴C-KP-103 to dogs. Study No. P101078.
6. *In Vitro* metabolism study of ¹⁴C-KP-103 by rat, dog, minipig and human cryopreserved hepatocytes. Study No. M100202.
7. *In Vitro* assessment of reaction phenotyping for human cytochrome P₄₅₀ enzymes by IDP-108. Study No. DSIN-7001-A6HP-25-09.
8. Determination of the potential for IDP-103 to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activities in human liver microsomes. Study No. DSIN-7001-A6HP-02-06.
9. Inhibitory effects of KP-103 and its metabolite S-35345 (H3) against nine isoforms of cytochrome P₄₅₀ in human liver microsomes. Study No. M090201.
10. *In Vitro* enzyme induction of KP-103 in human hepatocytes. Study No. P101080.

Excretion

1. Urinary and fecal excretion studies of KP-103 after percutaneous administration of ¹⁴C-KP103 to rats. Study No. SA970109.

General Toxicology

Repeat-Dose Toxicity

1. A 3 month toxicity study of IDP-108 administered by subcutaneous injection to rats. Study No. DSIN-7001-A6HP-16-08.
2. A 6 month toxicity study of IDP-108 administered by subcutaneous injection to rats. Study No. DSIN-7001-A6HP-19-08.
3. A 28 day dermal GLP toxicity study of IDP-108 in Gottingen minipigs. Study No. DSIN-7001-A6HP-05-07.
4. A 9 month dermal GLP toxicity study of IDP-108 in Gottingen minipigs. Study No. DSIN-7001-A6HP-11-07.

Genetic Toxicology**Efinaconazole**

1. Reverse mutation test of KP-103 in bacteria. Study No. SOT021.
2. Chromosomal aberration test of KP-103 in CHL/IU cells. Study No. SPT006.
3. Micronucleus test of KP-103 in mice. Study No. SPT003.

Alkyl Lactate

1. Reverse mutation test of C12-C15 alkyl lactate in bacteria. Study No. S11T006.
2. Chromosomal aberration test of C12-C15 alkyl lactate in CHL/IU cells. Study No. S11T005.
3. Micronucleus test of C12-C15 alkyl lactate in mice. Study No. S11T002.

Carcinogenicity

1. IDP-108: A 13 week dermal toxicity study in mice. Study No. DSIN-7001-A6HP-14-08.
2. A 2 year dermal carcinogenicity study in mice. Study No. DSIN-7001-A6HP-15-08.

Reproductive and Developmental Toxicology

1. Preliminary study of fertility and early embryo development to implantation in rats treated subcutaneously with KP-103. Study No. ST950305.
2. Study of fertility and early embryonic development to implantation in rats treated subcutaneously with KP-103. Study No. ST031.
3. Preliminary study of the effects on embryofetal development in rats treated subcutaneously with KP-103. Study No. ST960307.
4. Effects of subcutaneous KP-103 treatment on embryofetal development. Study No. SPT018.
5. A subcutaneous injection dose-range finding study of the effects of IDP-108 on embryofetal development in rabbits. Study No. DSIN-7001-A6HP-18-08.
6. A subcutaneous and toxicokinetic study of the effects of IDP-108 on embryofetal development in rabbits. Study No. DSIN-7001-A6HP-20-08.
7. Subcutaneous developmental and perinatal-postnatal reproduction toxicity study in rats. Study No. DSIN-7001-A6HP-26-09.

Special Toxicology Studies**Efinaconazole**

1. Primary dermal irritation study in rabbits with IDP-108. Study No. DSIN-7001-A6HP-02-07.
2. Cumulative skin irritation study of KP-103CR in rabbits. Study No. SQT021.
3. Primary ocular irritation study of KP-103CR in rabbits. Study No. SQT019.
4. Primary eye irritation study in rabbits with IDP-108. Study No. DSIN-7001-A6HP-03-07.

Alkyl Lactate

1. Primary dermal irritation study in rabbits with C12-C15 alkyl lactate. Study No. S11T003.
2. Primary eye irritation study in rabbits with C12-C15 alkyl lactate. Study No. S11T004.

3.2 Studies Not Reviewed**Pharmacokinetics/ADME/Toxicokinetics****Pharmacokinetics**

The following studies are analytical methods and validation reports and were not reviewed.

1. Measurement of KP-103 in dog plasma after a single intravenous injection. Study No. ST960102.
2. Determination of H1 in rat EDTA plasma by LC-MS-MS. Study No. DCN ISR-1465.
3. Determination of H1 in rabbit EDTA plasma by LC-MS-MS. Study No. DCN ISR-1476.
4. Determination of H1 in Gottingen minipig lithium heparinized plasma by LC-MS-MS. Study No. DCN 1002293.
5. Determination of H1 in rabbit EDTA plasma by LC-MS-MS. Study No. DCN 01160VO.
6. Determination of H1 in Sprague-Dawley rat K(2) EDTA plasma by LC-MS-MS. Study No. DCN 1003948.
7. Determination of IDP-108 and H3 in CD-1 mouse EDTA plasma by LC-MS-MS. Study No. DCN ISR-1321.
8. Determination of IDP-108 and H3 in Sprague-Dawley rat EDTA plasma by LC-MS-MS. Study No. DCN ISR-1320.
9. Determination of IDP-108 and H3 in Gottingen minipig lithium heparinized plasma by LC-MS-MS. Study No. DCN 1242.
10. Determination of IDP-108 and H3 in CD-1 mouse lithium heparinized plasma by LC-MS-MS. Study No. DCN 1002549.
11. Determination of IDP-108 and H3 in Sprague-Dawley rat K(2) EDTA plasma by LC-MS-MS. Study No. DCN 1002548.
12. Determination of IDP-108 and H3 in rabbit K(2) EDTA plasma by LC-MS-MS. Study No. DCN 1002971.
13. Determination of IDP-108 and H3 in Gottingen minipig lithium heparinized plasma by LC-MS-MS. Study No. DCN 1002247.

14. Determination of H1 in rat milk (non-GLP) by LC-MS-MS. Study No. ATM-H1-MILK-NON-GLP.
15. Determination of IDP-108 and H3 in rat milk (non-GLP) by LC-MS-MS. Study No. ATM-H3-MILK-NON-GLP.
16. Validation of an analytical method for determining KP-103 concentration in rat plasma using LC-MS/MS. Study No. M080103.
17. Sensitivity determination of modified chiral HPLC method for IDP-108 isomers to LC/MS compatible conditions. Study No. IAS-09-DW-04-MS.
18. Modification of chiral HPLC method for IDP-108 isomers to LC/MS compatible conditions. Study No. IAS-09-DW-01-MS.
19. Determination of IDP-108 and H3 in New Zealand White rabbit EDTA plasma by LC-MS-MS. Study No. DCN ISR-1412.
20. Test article impurity retrospective analysis of IDP-108 solution used in selected dermal toxicity studies. Study No. DSIN-7001-A6HP-40-12.

Absorption

A more pivotal study was conducted that is reviewed and the following studies do not provide any additional useful information.

1. Determination of KP-103 in plasma after percutaneous administration to rats. Study No. SA970105.
2. Determination of radioactivity in plasma after percutaneous administration of ¹⁴C-KP-103 to rats. Study No. SA970106.
3. Determination of plasma KP-103 concentrations after single oral administration in rats. Study No. M110102.
4. Determination KP-103 in plasma after subcutaneous administration in male rats. Study No. SA960306.
5. Determination of plasma KP-103 concentrations after single intravenous and subcutaneous administration in rats. Study No. M080107.
6. Determination of plasma KP-103 concentrations after single percutaneous administration of KP-103 formulation to rats. Study No. M100203.

Distribution

A more pivotal study was conducted that is reviewed and the following study does not provide any additional useful information.

1. Dermal distribution of KP-103 after percutaneous administration of ¹⁴C-KP-103 to guinea pigs. Study No. SA970110.

Metabolism

A more pivotal study was conducted that is reviewed and the following studies do not provide any additional useful information.

1. Quantification of IDP-108 and metabolites in minipig plasma from Study 0645-0715. Study No. IAS-07-MS-14-DM.
2. Quantification of IDP-108 and metabolites H2-H5 and estimation of concentration of novel metabolites in mouse, rat and rabbit plasma samples. Study No. IAS-09-DW-02-PK.
3. Identification of metabolites of IDP-108 in circulating mouse, rat and rabbit plasma. Study No. IAS-09-DW-03-DM.
4. Quantification of IDP-108 and metabolites in minipig plasma from Study 0645-0715. Study No. IAS-07-MS-13-DM.

5. Non-GLP determination of KP-103 and H1 in various matrices by LC-MS-MS. Study No. DCN 1003756.
6. Quantification of IDP-108 isomers in rat and human plasma samples by LC/MS/MS. Study No. IAS-09-DW-06-PK.
7. Quantification of IDP-108 and metabolites H3 and H4 and estimation of concentration of novel metabolites in mouse plasma samples. Study No. IAS-09-DW-07-PK.

General Toxicology

Single-Dose Toxicity

A more pivotal study was conducted that is reviewed and the following studies do not provide any additional useful information.

1. Acute intraperitoneal toxicity study of KP-103 in mice. Study No. ST960201.
2. TK study of KP-103 by intraperitoneal administration in mice. Study No. NT11024.
3. Toxicity tests of KP-103 on single dose subcutaneous and percutaneous administration in rats. Study No. SOT007.
4. Toxicity study of KP-103 on single dose percutaneous administration in dogs. Study No. SOT006.

Repeat-Dose Toxicity

A more pivotal study was conducted that is reviewed and the following studies do not provide any additional useful information.

1. IDP-108: A 2 week dermal toxicity study in mice. Study No. DSIN-7001-A6HP-24-09.
2. IDP-108: A 2 week dermal toxicity study in mice. Study No. DSIN-7001-A6HP-13-08.
3. A 7 day oral and subcutaneous pilot study of IDP-108 in male Sprague-Dawley rats. Study No. DSIN-7001-A6HP-12-07.
4. Repeated subcutaneous dose local toxicity study of KP-103, a candidate for onychomycosis, for 4 weeks in rats. Study No. NT09003.
5. A 1 month repeated subcutaneous dose toxicity study and 1 month recovery study of KP-103 in rats. Study No. SOT019.
6. Toxicity test of KP-103 on 1 month repeated percutaneous administration in rats and 1 month recovery test. Study No. B-3151.
7. A 4 day dermal range-finding study of IDP-108 in Gottingen minipigs. Study No. DSIN-7001-A6HP-04-07.
8. A 2 week repeated percutaneous dose toxicity study of KP-103 in dogs. Study No. ST950106.
9. A 1 month repeated percutaneous dose toxicity study and 1 month recovery study of KP-103 in dogs. Study No. SPT001.

Special Toxicology Studies

A more pivotal study was conducted that is reviewed or the study was conducted with an early prototype formulation and the following studies do not provide any additional useful information.

Efinaconazole

1. Skin sensitization test of KP-103 in guinea pigs. Study No. ST960202.
2. Delayed contact hypersensitivity in guinea pigs with IDP-108. Study No. DSIN-7001-A6HP-01-07.
3. Primary skin irritation study of KP-103L in rabbits. Study No. SQT017.
4. Primary skin irritation study of KP-103L in rabbits. Study No. SQT020.
5. Cumulative skin irritation study of KP-103L in rabbits. Study No. SQT018.
6. Primary ocular irritation study of KP-103L in rabbits. Study No. SQT016.
7. Epi-ocular MTT viability assay. Study No. DSIN-7001-A6HP-01-06.

Computational Assessments

The following studies were not reviewed because the Agency does not rely on computational assessments for these types of toxicity assessments and nonclinical toxicity studies were conducted to determine the toxicity profile of IDP-108.

1. Test article impurity retrospective analysis of IDP-108 solution used in selected dermal toxicity studies. Study No. DSIN-7001-A6HP-40-12.
2. Computational Toxicity assessment using the Leadscope model applicer for query 1(3). Study No. DSIN-7001-A6HP-32-11.

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5. 

13. Derek evaluation of the toxicity of KP-103. Study No. NJD004-KP-103.

3.3 Previous Reviews Referenced

Pharmacology/Toxicology Reviews under IND 77732

Statistical Review and Evaluation of NDA 203567 reviewed by Dr. Mohammad Atiar Rahman, DARRTS date 12/6/2012.

4 Pharmacology

4.1 Primary Pharmacology

Efinaconazole has potent *in vitro* antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Candida albicans*.

The antifungal mechanism of action of efinaconazole, like other triazole antifungal therapeutics, is attributed to lanosterol 14 α -demethylase inhibition resulting in blockage of ergosterol synthesis. Fungal cell membrane structure and function is compromised by the resulting ergosterol depletion and accumulation of 14- α methyl sterols.

In a keratin binding assay, adsorption rate of IDP-108 to keratin in physiological saline containing 5% keratin was low and the release rate was high compared to that of butenafine hydrochloride (BTF) and lanoconazole (LCZ). The low keratinophilic property of IDP-108, compared to other marketed antifungal drugs suggests that IDP-108 may be more active at the site of the nail fungal infection than other drugs and, therefore may be an effective drug treatment for onychomycosis.

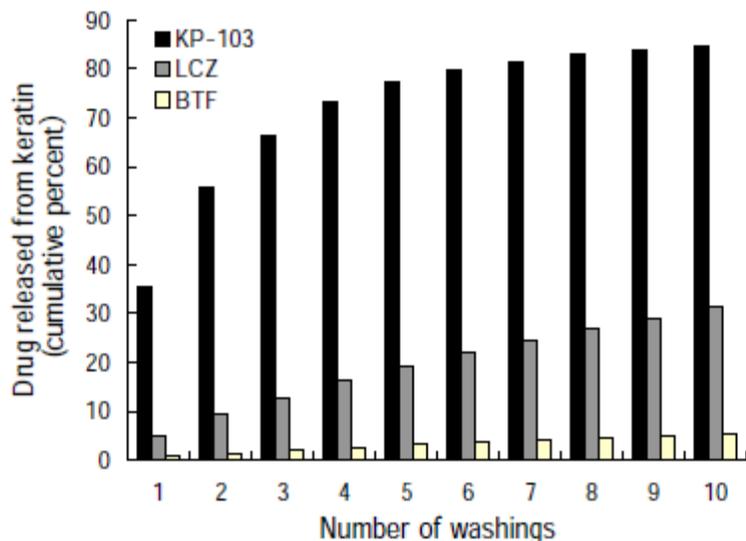
The table below contains the adsorption rates of IDP-108 (KP-103), BTF, and LCZ to keratin.

Table 1. Adsorption rates of the test compounds to keratin

Compound	Rate of adsorption to keratin (%)
KP-103	60.3
LCZ	94.9
BTF	99.4

The figure below contains the cumulative release rates of IDP-108 (KP-103), BTF, and LCZ when keratin that adsorbed the test compounds was washed 10 times with physiological saline.

Figure 1. Cumulative release rates of the test compounds when keratin that adsorbed the test compounds was washed 10 times with physiological saline



4.2 Secondary Pharmacology

NA

4.3 Safety Pharmacology

General pharmacology of KP-103. Study No. KOP001

Neurological effects:

Single subcutaneous doses of 0, 1, 10 and 100 mg/kg IDP-108 (vehicle: 0.5% methylcellulose) were administered to mice. A general condition test (i.e., evaluation of clinical signs) was performed on 6 mice/dose. A spontaneous locomotion test was performed on 18 mice/dose. A pain intensity test was conducted on 15 mice/dose. An effect on prolongation of sleep with either hexobarbital or thiopental was performed on 10 mice/dose. Possible convulsive effects were evaluated with examination of cooperative effect with pentetrazol, antagonism against penetrazol or maximum electric shock (10 mice/dose). Possible analgesic effect using the acetic acid writhing method was evaluated on 15 mice/group.

Vocalization was noted in 3/6 high dose mice in the general condition study. No treatment related effects on motor activity were noted in the spontaneous

locomotion test. Prolongation of sleep time was noted in mid and high dose mice treated with hexobarbital but no treatment related effects on sleep time were noted in mice treated with thiopental. A potentiation of convulsive effects caused by pentetrazol was noted in high dose mice, but no effect on electrically induced convulsions was noted. No treatment related effects on analgesic effects were noted in mice.

Single subcutaneous doses of 0, 1, 10 and 100 mg/kg IDP-108 (vehicle: 0.5% methylcellulose) were administered to rats (8/dose). No treatment related effects on body temperature were noted in rats.

Cardiovascular and pulmonary Effects:

The cardiovascular (blood pressure, heart rate, femoral blood flow and electrocardiograms) and pulmonary (respiration) effects of single intravenous doses of 0, 0.3, 3 and 30 mg/kg IDP-108 were evaluated in anesthetized dogs (4/dose). A transient increased in respiratory rate, heart rate and femoral artery blood flow was noted in high dose animals. Decreased blood pressure peaking at 1 minute after iv infusion was noted in high dose dogs. Decreased ECG R-wave amplitude was noted in 1/4 high dose dogs.

Reviewer's comment: Typically cardiovascular parameters are evaluated in unanesthetized dogs. Although the evaluation of cardiovascular parameters in anesthetized dogs is not an optimal study design, this study does not need to be repeated due to low systemic exposures after maximal clinical use conditions.

hERG Block comparator study: Effects of IDP-108 on cloned hERG potassium channels expressed in mammalian cells. Study No. DSIN-7001-A6HP-11-08. This study was conducted under GLP conditions.

A hERG assay was conducted with concentrations of 1 and 10 μ M IDP-108 using Human Embryonic Kidney (HEK293) cells. The percent hERG inhibition rates were 3.4% (n = 3) and 16.6% (n = 3) at 1 and 10 μ M IDP-108, respectively. The positive control, 90 nM cisapride, inhibited hERG current by 77.7% (n = 2). The vehicle for IDP-108 and positive control was HEPES buffered physiological saline.

The IC_{50} value for hERG inhibition by IDP-108 is above 10 μ M. Therefore, IDP-108 does not pose a significant QT prolongation risk in humans.

Reviwer's Comments: The sponsor requested and was granted a waiver for a thorough QT/ QT_c for IDP-108 based on the low systemic bioavailability of IDP-108 and its major metabolite, H3. (Refer to QT-Interdisciplinary Review Team (IRT) Consult to IND 77732 entered into DARRTS on 8/3/2009 and IND 77732 Advice Letter entered into DARRTS on 4/14/2010.)

Effect of H3 on cloned hERG potassium channels expressed in mammalian cells. Study No. DSIN-7001-A6HP-23-09. This study was conducted under GLP conditions.

A hERG assay was conducted with concentrations of 1, 10 and 100 μM H3 metabolite using Human Embryonic Kidney (HEK293) cells. The percent hERG inhibition rates were 0.2% (n = 3), 0.2% (n = 3) and 0.8% (n = 3) at 1, 10 and 100 μM IDP-108, respectively. The positive control, 90 nM cisapride, inhibited hERG current by 75.4% (n = 2). The vehicle for H3 metabolite and positive control was HEPES buffered physiological saline.

The IC_{50} value for hERG inhibition by H3 metabolite is above 100 μM . Therefore, IDP-108 does not pose a significant QT prolongation risk in humans.

Renal effects:

The renal effects (urine volume, urine pH and electrolytes in urine) of single subcutaneous doses of 0, 1, 10 and 100 mg/kg IDP-108 (vehicle: 0.5% methylcellulose) were evaluated in rats (8/dose). Impaired renal function (decrease in urine volume and sodium and chloride excretion in urine) was noted in high dose animals.

Gastrointestinal effects:

The in vitro effect of 1, 10 and 100 μM IDP-108 on spontaneous motility was evaluated in rabbit ileum. The in vitro effect of 1, 10 and 100 μM IDP-108 on agonist (acetylcholine, histamine, barium chloride and serotonin) induced contractions was evaluated in guinea pig ileum. Agonist simulated guinea pig ileum contractions were inhibited at 10 – 100 μM IDP-108. Spontaneous rabbit ileum contractions were inhibited at 100 μM IDP-108.

The in vivo effects of single subcutaneous doses of 0, 1, 10 and 100 mg/kg IDP-108 (vehicle: 0.5% methylcellulose) on gastrointestinal transport was evaluated in mice (10/dose). No treatment related effects on gastrointestinal transport were noted in this study.

Summary

IDP-108 has been evaluated in animal safety pharmacology studies of the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems, and kidney function. With regard to the CNS, IDP-108 prolonged hexobarbital sleeping time (subcutaneous administration (sc), ≥ 10 mg/kg) and enhanced penitetrazole-induced convulsions (sc, 100 mg/kg). The study report indicates that these effects appear to be due to inhibition of cytochrome P450 (CYP) drug metabolism rather than direct CNS effects. IDP-108 (intravenous, 30 mg/kg) increased heart rate, decreased blood pressure, and increased respiration rate in anesthetized dogs. hERG studies using HEK293 cells,

conducted with IDP-108 and its major metabolite, H3, indicate IDP-108 does not pose a significant QT prolongation risk in humans. IDP-108 had no effect on gastrointestinal transit time in mice (sc, up to 100 mg/kg), but in isolated rabbit ileum preparations spontaneous and agonist induced contractions were inhibited ($\geq 10 \mu\text{M}$). IDP-108 (sc, 100 mg/kg) caused decreased urine volume and electrolyte excretion in rats. It is anticipated that the systemic exposures that caused these physiologic effects are much higher than what would be achieved after treatment with a topical IDP-108 formulation for onychomycosis. Therefore, the potential safety pharmacology effects noted for IDP-108 in the conducted studies would not be a cause for concern for use of a topical IDP-108 formulation for the treatment of onychomycosis.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Brief summary

A series of studies was conducted to evaluate the pharmacokinetics of IDP-108. The pharmacokinetics of IDP-108 was investigated in several in vitro experiments. The pharmacokinetics of IDP-108 was investigated after topical, subcutaneous and intravenous administration to rats and after subcutaneous administration to dogs. All topical applications were covered with an occlusive wrap for 24 hours. IDP-108 drug substance was dissolved in physiological saline, pH 3-4, for subcutaneous and intravenous studies. When administered by parenteral routes the dose solution concentration was 1 mg/ml for rat studies and 2 mg/ml for dog studies. The vehicle for the topical IDP-108 solution was 50% propylene glycol, 25% ethanol, 25% glycerin.

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However this formulation is acceptable for the nonclinical PK studies since definitive toxicokinetic data was obtained in minipigs using an IDP-108 formulation that is similar to the to-be-marketed formulation. The nonclinical pharmacokinetic properties of IDP-108 were studied with both ^{14}C -labeled and non-radiolabeled drug.

In the maximum use clinical PK study conducted in onychomycosis patients, the highest individual $\text{AUC}_{0-24\text{hr}}$ value was 25.15 ng·hr/ml for efinaconazole and the mean $\text{AUC}_{0-24\text{hr}}$ value was 12.15 ng·hr/ml for efinaconazole.

Absorption

The absorption after topical administration of 1% efinaconazole solution (10 mg/kg IDP-108) with ^{14}C IDP-108 was estimated to be between 6% and 15.8% of the dose in rats. This study estimated absorption based on the total radioactivity excreted in urine and feces plus the amount remaining in the carcass.

Plasma radioactivity after topical application of increasing concentrations of 0.2, 1 and 5% efinaconazole solution (2, 20 and 50 mg/kg ^{14}C IDP-108, respectively) to rats demonstrated a dose proportional increase in AUC that ranged from 2 to 50 ng eq hr/ml. Dermal absorption in rats was increased 3-fold when the stratum corneum barrier was damaged by tape stripping.

Plasma radioactivity increased rapidly after a single subcutaneous injection of 1 mg/kg ^{14}C IDP-108 to rats (T_{\max} = 0.75 hr) and declined slowly ($t_{1/2\beta}$ = 13.4 hr). In contrast, plasma IDP-108 declined rapidly after subcutaneous administration of 1 mg/kg unlabeled drug to rats ($t_{1/2\beta}$ = 2.3 hr). Comparison of PK parameters between rat subcutaneous studies conducted with radioactive labeled and unlabeled drug suggest that IDP-108 is extensively metabolized and plasma metabolites persist compared to parent drug. Ratios of C_{\max} , $\text{AUC}_{0-\infty}$, and $t_{1/2}$ determined for radiolabeled versus unlabeled drug were 2.6, 28.8 and 5.8, respectively.

The rate of absorption and elimination was slower in dogs compared to rats after subcutaneous injection of 1 mg/kg ^{14}C IDP-108. T_{\max} was 5 hours and $t_{1/2}$ was 33 hours. The sponsor indicates that during the development of the ELISA method for IDP-108 plasma drug level analysis, dogs were injected iv with 1 and 10 mg/kg IDP-108 and the samples were analyzed by HPLC and ELISA. The ELISA plasma level results were higher compared to the HPLC method for unchanged IDP-108. The sponsor indicates that this is due to the ELISA being able to detect H5 and H4 metabolites.

Distribution

Tissue distribution of ^{14}C IDP-108 was studied by both whole body autoradiography and individual tissue dissection in rats treated topically with 1% efinaconazole solution (10 mg/kg IDP-108) and subcutaneously (1 mg/kg IDP-108). Plasma protein binding was evaluated in rat, dog and human plasma. Skin distribution was evaluated in rats after topical administration of ^{14}C IDP-108 (10 mg/kg). The concentration of the topical IDP-108 dosing solution was 5 mg/ml. The dose volume was 2 ml/kg. The vehicle was propylene glycol.

Whole body radiography results

A high concentration of radioactivity was found in the dorsal skin in rats but not in other tissues 1 hour after topical application. At 12 hours after application, the highest radioactivity was found at both the dorsal skin and large intestinal contents and lower radioactivity in the liver, kidney, adrenal gland, stomach contents and small intestinal contents. At 24 hours after dosing, only dorsal skin had high levels of radioactivity and relatively low radioactivity was found in the liver, small intestinal contents and large intestinal contents. At 168 hours after dosing, radioactivity was found only at the dorsal skin site.

The highest radioactivity was detected in small intestinal contents of rats 1 hour after subcutaneous administration. The distribution of radioactivity in liver, kidney,

adrenal gland and stomach was low 1 hour after dosing with lung, brown fat and skin showing a very low level of radioactivity. At 8 hours after dosing, the highest concentration of radioactivity was found in large intestinal contents, followed by (in order) liver, kidney, adrenal gland, brown fat, stomach contents and small intestinal contents. At 168 hours after dosing, no radioactivity was detected in any tissues.

Tissue dissection and collection method results

Low levels of radioactivity were detected in the adrenal gland and liver 1 hour after topical application and distribution to other tissues was extremely low. At 12 hours after dosing, liver showed the highest levels of radioactivity, followed by (in decreasing order) adrenal gland, fat and skin. Radioactivity levels of other tissues were equal to or less than plasma. At 24 hours after dosing, liver had the highest radioactivity followed by (in decreasing order) adrenal gland, lung, fat, skin and kidney. At 72 hours after dosing, a marked decreased in radioactivity was noted in all organs and tissues. At 168 hours after dosing, only a trace amount of radioactivity was detected in lung, liver and skin.

The highest level of radioactivity noted 1 hour after subcutaneous injection was detected in liver, followed by (in decreasing order) fat, adrenal gland, harderian gland, kidney, pancreas, lung, skin, thyroid gland, prostate gland, trachea and epididymis. Radioactivity in other organs was equal to or less than plasma. At 8 hours after dosing, liver levels were still the highest followed by adrenal gland, fat and mesentery lymph node. The other organs showed the same trend as at 1 hour. At 24 hours, the liver retained the highest levels, followed by adrenal gland, lung and fat. At 72 hours, the radioactivity in all organs and tissues decreased markedly and at 168 hours only very low levels were detectable in lung, liver and kidney.

Plasma protein binding

Plasma protein binding of ^{14}C IDP-108 was examined by in vitro incubation of spiked rat, dog and human heparinized plasma. Binding was also examined in plasma samples collected from rat and dogs injected sc with radiolabeled drug. For the in vitro studies, ^{14}C IDP-108 was dissolved in 0.1 N HCl by sonication, pH adjusted to ca. 3, and the stock 1 mg/ml solution diluted to 1, 2, 10, and 50 $\mu\text{g}/\text{ml}$. Plasma samples were spiked with the stock solution to achieve a final concentration of 50, 100, 500, and 2500 ng/ml. These plasma samples containing ^{14}C IDP-108 were incubated at 37°C for 15 min, and dialyzed for 24 hours at 4°C against isotonic phosphate buffer. Reversibility of binding was studied by ethanol extraction.

Binding of IDP-108 to plasma proteins did not differ between rat, dog and human plasma, and no species differences were noted for reversibility of binding. The in vitro binding was very high, and concentration independent, in all species, approaching 100%, and reversibility of binding was rapid.

In vivo plasma protein binding after sc injection of ^{14}C IDP-108 decreased significantly over time. Samples collected 1 hour after dosing were 69.9% bound while samples collected 24 hours after dosing were less than one-third bound, i.e. 29.7%. This time-dependent decrease suggests that the metabolites bind to a lesser extent than the parent compound. There was a decrease in plasma protein binding over time following sc administration in both rats and dogs, which suggests greater amounts of weaker binding metabolites in dogs, 6 hours following administration.

Most of the plasma protein binding in human serum was considered to be associated with human serum albumin. *In vitro* studies showed only 4.4% bound to human γ -globulin and 95.2% bound to albumin.

Distribution in skin

Skin distribution of a topical dose of 10 mg/kg ^{14}C IDP-108 was evaluated in male Sprague-Dawley rats. The concentration of the IDP-108 dosing solution was 5 mg/ml. The dose volume was 2 ml/kg. The vehicle was propylene glycol. Skin at the dose site was collected at 24 and 48 hours after dosing and frozen 20 μm sections prepared for measurement of radioactivity.

At 24 hour after dosing, distribution of the radioactivity in the skin was not uniform. In the outer 300 μm layer which included the horny layer, a very high concentration of radioactivity, equivalent to 45 $\mu\text{g/g}$ of ^{14}C IDP-108, was detected. In contrast, at a depth of 1000-2000 μm very little radioactivity, approximately 1 $\mu\text{g/g}$, was present. At 48 hours after dosing, the elimination rate of radioactivity from the skin was slow, demonstrating retention of IDP-108 at the applied site.

Metabolism

The *in vivo* metabolism of IDP-108 was evaluated in rats after subcutaneous administration of 10 mg/kg ^{14}C IDP-108. IDP-108 was rapidly metabolized after subcutaneous administration in rats and the plasma metabolites exceed the amount of unchanged IDP-108. IDP-108 was oxidatively metabolized, cleaved and conjugated with glucuronic acid. All metabolite levels are based on total, i.e., free plus conjugated forms, since all samples were incubated with β -glucuronidase to hydrolyze conjugates. Metabolite structures were initially proposed based on LC/MS/MS analysis and confirmed with synthetic reference standards. The level of unchanged IDP-108 declined to a small percent of plasma radioactivity by 8 hours while metabolites H1 and H3 increased. At 8 hours after subcutaneous injection, H3 was the predominant plasma and kidney metabolite while H4 was the major form in liver. The percent of urinary metabolites excreted over 24 hours was H1>H2>H3>H4>H5. In bile the order was H2>H3>H4>H5>H1. No unchanged IDP-108 was detected in bile or urine. The level of IDP-108 metabolites in plasma, liver and kidney is provided in the sponsor's table (below).

Table 2.6.4.5.1 IDP-108 Metabolites in Rat Tissues

	% of radioactivity in tissue ¹					
	plasma ²		liver		kidney	
	1hr	8hr	1hr	8hr	1hr	8hr
IDP-108	26.9	1.2	1.6	0.2	30.4	3.5
H1	9.6	39.0	1.0	3.0	2.9	22.6
H2	N.D.	N.D.	9.2	4.2	14.1	11.5
H3	32.1	48.0	14.2	12.0	16.1	29.8
H4	7.1	2.0	45.9	60.6	9.3	4.0
H5	N.D.	N.D.	1.4	2.4	1.5	0.6
others	24.3	9.8	26.7	17.6	25.7	28.0

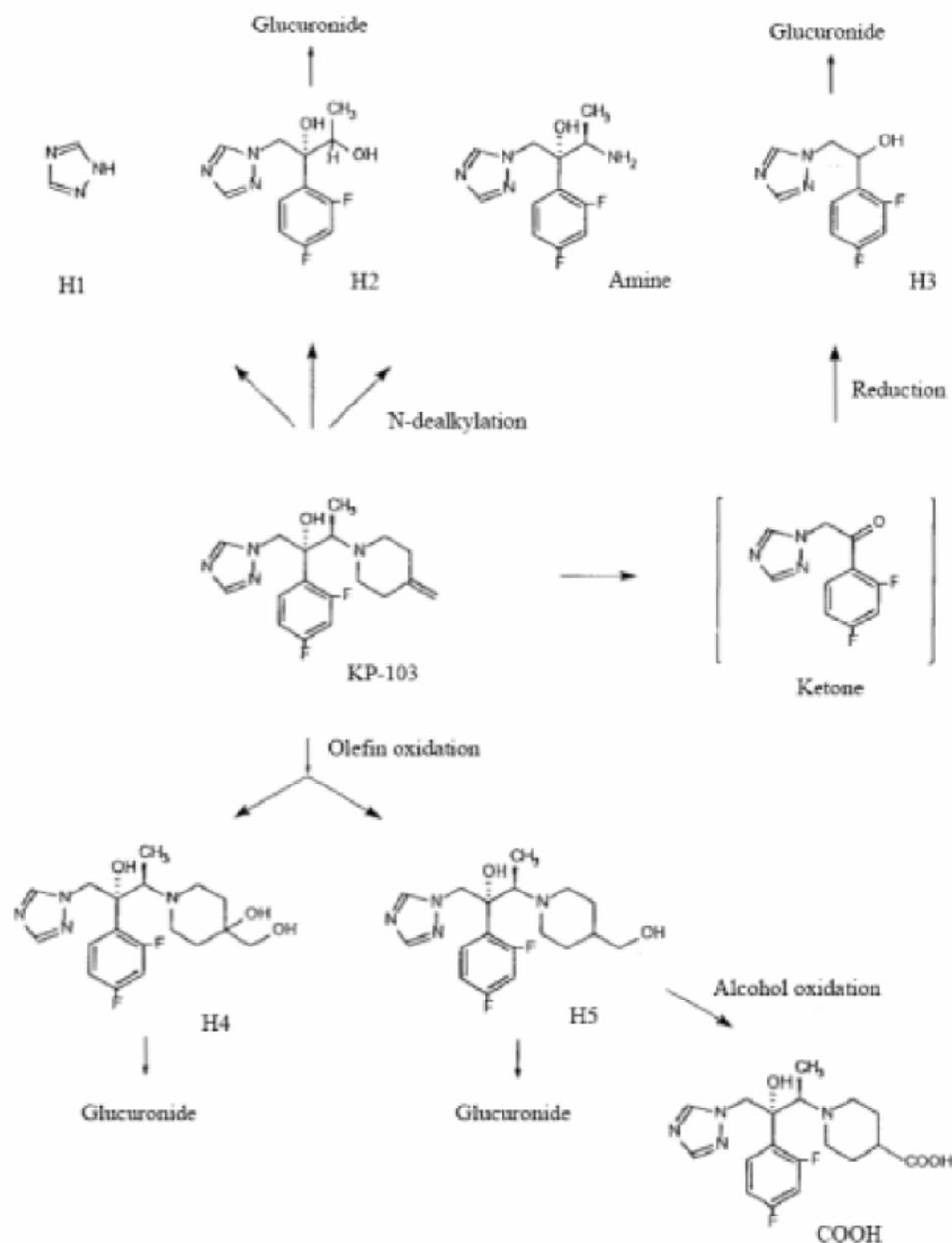
1 Rat tissue homogenates pooled from 3 animals was extracted (83% or greater extraction rates), incubated with β -glucuronidase and analyzed by HPLC. Data are expressed percentage of total radioactivity on HPLC. N.D.: Not detected.

2 Data are expressed only as unconjugated unchanged drug or metabolites

The *in vitro* metabolism of IDP-108 was evaluated in rat, dog and human liver microsome and S9 fraction incubations. ¹⁴C IDP-108 was mainly metabolized to H4 in rats at both 2 and 20 μ g/ml concentrations and the reaction did not proceed further. This *in vitro* result contrasts with the *in vivo* rat urinary metabolite pattern in which H1, H2 and H3 and other forms were major metabolites rather than H4. The metabolism of ¹⁴C IDP-108 was very slow in dogs compared with rats. Considerable amounts of unchanged ¹⁴C IDP-108 were detected even after incubation for 2 hours at 20 μ g/ml with the main metabolite being H4. H4 was also the main metabolite at 2 μ g/ml, but the proportion of other metabolites was increased slightly. The metabolism of ¹⁴C IDP-108 was also slow in humans. The main metabolite was also H4. The proportion of unidentified metabolites in 2 hour human tissue incubation at 2 μ g/ml was higher than in the rat and dog and further metabolism of H4 to H2 was noted. After 2 hours of incubation of 2 μ g/ml ¹⁴C IDP-108 with human microsomes, at least 70% of radioactivity was unidentified compared to 33% in dog and 19% in rat preparations. There were no major unique human metabolites that were not present in the animal studies.

Five IDP-108 metabolites were identified in the *in vivo* subcutaneous rat study [triazole (H1), 2R, 3S-diol (H2), reduced ketone (H3), diol (H4) and exo-OH (H5)]. Eight metabolites were identified in the *in vitro* metabolism studies. Three new metabolites {2R, 3R-amine, ketone and carboxylic acid} were identified in addition to the 5 metabolites identified *in vivo*.

The sponsor proposes the following metabolic pathway of IDP-108.



Excretion

The urinary and fecal excretion rates of radioactivity were determined after single administration of ^{14}C IDP-108 either topically (10 mg/kg; 1% IDP-108 solution) or subcutaneously (1 mg/kg). The concentration of the IDP-108 dosing solution was 5 mg/ml. The dose volume was 2 ml/kg. The vehicle was propylene glycol. From 0 to 24

hours after topical administration, 5.4% of the dose of radioactivity was excreted in both urine and feces for a total excretion rate of 10.8%. By 168 hours, 8.4% and 7.4% of the dose were excreted in urine and feces, respectively. After 168 hours, 0.0% and 0.1% of the dose of radioactivity were detected in skin at the administration site and the carcass, respectively. The methanol extract of the cotton with which the administration site was wiped and the silicone rubber frame, seal and adhesive bandage contained 87.3% of the administered radioactivity. The total recovery of radioactivity after 168 hours was 103.2%.

From 0 to 24 hours after subcutaneous administration, 33.0% and 20.1% of the dose of radioactivity were excreted in urine and feces for a total excretion rate of 53.1%. The urinary and fecal excretion rates from 0 to 48 hours were 46.8% and 36.7%, respectively, for a total excretion rate of 83.5%. The urinary and fecal excretion rates from 0 to 168 hours were 56.8% and 40.8%, respectively, for a total excretion rate of 97.6%. After 168 hours, the carcass contained 0.9% of the radioactivity. The total recovery rate of radioactivity over the 168 hour time period was 98.4%.

The urinary, biliary and fecal excretion rates of radioactivity were determined after single subcutaneous administration of 1 mg/kg ¹⁴C IDP-108 to bile duct cannulated rats. At 8 hours after administration, 45.1% of the radioactivity was excreted in the bile. At 24 hours, 58.1%, 32.0% and 3.0% of the radioactive dose was excreted in bile, urine and feces, respectively. At 48 hours, 60.8%, 35.1% and 3.9% of the radioactive dose was excreted in bile, urine and feces, respectively. The total recovery rate of radioactivity over the 48 hour time period was 99.8%.

Pharmacokinetic drug interactions

The potential of IDP-108 to inhibit cytochrome P450 (CYP) enzyme activity was evaluated in vitro using human liver microsomes. Inhibition of CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) was determined by co-incubation of 5 concentrations of IDP-108 (ranged from 1 – 100 µM) with selective substrates. The calculated IC₅₀ values for each of the CYP isoforms are provided in the sponsor's table (below).

Table 2.6.4.7.1.1 In Vitro IDP-108 CYP Inhibition

CYP Isoform	IC ₅₀
CYP1A2	> 100 µM
CYP2C9	0.194 µM
CYP2C19	1.36 µM
CYP2D6	46.1 µM
CYP3A4 – Midazolam	0.731 µM
CYP3A4 – Testosterone	0.572 µM

These results indicate that IDP-108 was a potent inhibitor of multiple CYP isoforms including CYP2C9, CPY2C19 and CYP3A4.

Triazole antifungals are reversible inhibitors of CYP enzymes in humans. The degree and type of inhibition varies with each azole on the basis of its physiochemical characteristics and pharmacokinetics. Itraconazole and metabolites are very potent inhibitors for CPY3A4 with IC₅₀ values of 6, 5, 7, and 0.4 nM for itraconazole (ITZ), OH-ITZ, keto-ITZ and N-ITZ, respectively. In general, the most important drug interactions seen with azole antifungals typically arise from inhibition of CYP3A4, which plays a critical role in metabolism of many drugs. The extent of CYP inhibition of topical IDP-108 may not be as extensive due to lower systemic exposure.

5.2 Toxicokinetics

Refer to Section 6.2.

6 General Toxicology

6.1 Single-Dose Toxicity

There are no single dose toxicity studies.

6.2 Repeat-Dose Toxicity

Reviewer's comments: Efinaconazole is extremely poorly (less than 1% bioavailable) absorbed after oral administration due in part to a high first pass liver effect. However, efinaconazole is very well absorbed (essentially 100% bioavailable) after subcutaneous injection. Therefore, the sponsor chose to conduct the repeat dose systemic toxicity studies and reproductive toxicity studies via subcutaneous injection. Unfortunately, the vehicle (propylene glycol) that was used for subcutaneous injection was not well tolerated after repeat dose administration. It would have been preferable to have selected a better tolerated vehicle for repeat dose subcutaneous administration. However, it has determined that the animal studies conducted with repeat dose subcutaneous administration using the propylene glycol vehicle are minimally acceptable due to the low systemic exposure after maximal clinical use conditions of efinaconazole solution for the treatment of onychomycosis.

Study 1 A 3 month repeat dose subcutaneous study of IDP-108 conducted in rats (Study No. 7001-A6HP-16-08).

The sponsor conducted a 3 month subcutaneous toxicity study in rats with 3, 10 and 30 mg/kg/day IDP-108 to identify dose levels of IDP-108 to be used in a subsequent 2 year subcutaneous carcinogenicity study in rat. Subcutaneous injection of the control vehicle, propylene glycol, or the test article (IDP-108) at doses of 3, 10, or 30 mg/kg/day for 90 days resulted in significant injection site changes. Gross pathology findings at injection

sites correlated microscopically with hemorrhage, fibrosis, necrosis, cystic cavities, ulceration, chronic inflammation and other less common changes. No gender differences were observed. Treatment related findings were attributed to vehicle injection.

A summary of the mean pharmacokinetic parameters for IDP-108 measured in this study is provided in the following table.

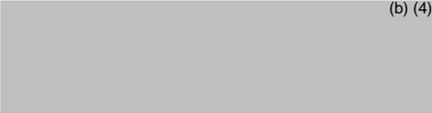
Table 5. Pharmacokinetic Parameters for IDP-108 in Rats

Sex	Dose (mg/kg/day)	Day	C _{max} (µg/mL)	T _{max} (hr)	AUC ₀₋₂₄ (µg•hr/mL)	r ²	t _{1/2} (hr)
M	3	1	93.8	1	616	0.9814	3.69
		90	281	1	1,230	0.9406	4.64
		% change	193%		100%		
M	10	1	347	4	2,289	0.9787	3.05
		90	532	1	3,300	0.9949	6.11
		% change	53%		44%		
M	30	1	460	4	4,393	0.9717	6.71
		90	1,323	0.5	9,002	0.9379	9.52
		% change	188%		96%		
F	3	1	125	0.5	472	0.9994	3.13
		90	305	0.5	996	0.9480	5.60
		% change	144%		111%		
F	10	1	177	4	1,537	0.9915	3.75
		90	843	0.5	3,841	0.9083	4.39
		% change	376%		150%		
F	30	1	437	4	4,969	0.9887	7.34
		90	1,658	1	9,389	0.9988	9.56
		% change	279%		89%		

Peak exposure to IDP-108, as measured by C_{max}, and total daily exposure, as measured by AUC₀₋₂₄, increased with increasing dose for both sexes on both sampling days. The increases were approximately linear for AUC₀₋₂₄, but less than directly dose-proportional for C_{max}. Between Day 1 and Day 90, there were increases in C_{max} and AUC₀₋₂₄ values for IDP-108 for both sexes and all dose groups. There was a trend for apparent t_{1/2} to be higher on Day 90 than on Day 1 and to be higher at the highest dose level. Overall, the differences in apparent t_{1/2} for IDP-108 were modest, with the values ranging from 3.1 to 9.7 hr. There was no apparent effect of the sex of the rats in this study on the pharmacokinetic parameters of IDP-108.

Study 2

Study title: A 6 month toxicity study of IDP-108 administered by subcutaneous injection to rats.

Study no.:	DSIN-7001-A6HP-19-08
Study report location:	SDN 1
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	July 30, 2008
GLP compliance:	Yes.
QA statement:	Yes.
Drug, lot #, and % purity:	IDP-108, lot# DFP-001, 99.9% Propylene glycol, lot# 081395, 99.8%

Key Study Findings

IDP-108 administered by subcutaneous injection to rats once daily for 180 days did not induce any test article-related systemic toxicity. However, repeated subcutaneous administration of the propylene glycol vehicle induced severe dermal effects. Microscopic evaluation of the injection site revealed ulceration and surface crusts involving the epidermis and hemorrhage, cystic spaces, necrosis, fibrosis, chronic inflammation, mineralization and abscess formation in the subcutaneous tissues. The incidence and severity of the injection site reactions was similar among control and treated groups with the exception of a slight increase in injection site reactions noted in high-dose males. Increased mortality was noted in high-dose males. Body weights were lower in the high-dose males due to reduced body weight gain. Based on the increased high-dose mortality and the decrease in body weight and body weight gain in high-dose males, the no-observed-adverse-effect-level (NOAEL) for IDP-108 is 10 mg/kg/day in males and 40 mg/kg/day in females.

The vehicle used in this study was not acceptable for repeat dose subcutaneous administration due to the injection site reactions noted in all treatment groups. However, systemic exposure following dermal administration is negligible under conditions of maximal clinical use. Therefore, it is not necessary to repeat this 6 month subcutaneous rat study with another vehicle that would be better tolerated after repeat dose subcutaneous administration.

Methods

Doses: 0, 3, 10, 40/30*, 40 mg/kg/day
* Beginning on Day 92, the dose level of the high dose male group was decreased to 30 mg/kg/day

Frequency of dosing: Once daily for 180 days.

Route of administration: Subcutaneous injection to one of four dorsal test sites clipped free of hair.

Dose volume: 2 ml/kg

Formulation/Vehicle: Propylene glycol

Species/Strain: Sprague Dawley Crl:CD(SD) rat

Number/Sex/Group: 15/sex/group for 0, 10, 40/30 (males) and 40 (females) mg/kg/day groups and 20/sex/group for 3 mg/kg/day group.
12/sex/group for 0, 3, 10, 40/30 (males), 40 (females) mg/kg/day for toxicokinetic analysis.

Age: 7 Weeks

Weight: Males: 232-286 grams
Females: 174-217 grams

Satellite groups: 5/sex/group for 0, 10, 40/30 and 40 mg/kg/day groups for 28 day recovery.

Unique study design: None

Deviation from study protocol: Beginning on Day 92, the dose level of the high dose male group was decreased to 30 mg/kg/day due to apparent test article-induced toxicity in the high dose male group.

Observations and Results

Mortality

Mortality and moribundity checks were performed on all animals twice daily during the study.

Seven males in the high-dose group were found dead from Days 53-171 and two males were euthanized moribund on Day 52 and Day 145. One male was found dead and one male was euthanized moribund in each of the control, low- and mid-dose male groups.

All control females and all low-dose females survived until scheduled necropsy. One female in the mid-dose group was found dead on Day 38. One female in the high-dose group was found dead on Day 9 and one female in the high-dose group was found dead on Day 142.

The cause of the increased mortality in the high dose group is unknown.

Clinical Signs

Detailed clinical observations were performed on all animals prior to treatment and weekly during treatment and recovery periods. Cage-side observations were performed daily within 3 hours of dosing.

Treatment-related clinical signs were primarily limited to findings at or near the injection sites, and included scabs, raised areas, swelling and open lesions. Scabs were observed at the injection sites of all animals in all groups. Swelling and open lesions were observed in all groups including the control groups. Raised areas were observed in all groups but were observed at a higher frequency in the high-dose male group.

Impaired mobility was observed prior to death or moribund euthanasia in four (3 high-dose and 1 mid-dose) males found to have spinal cord necrosis and urinary tract disease.

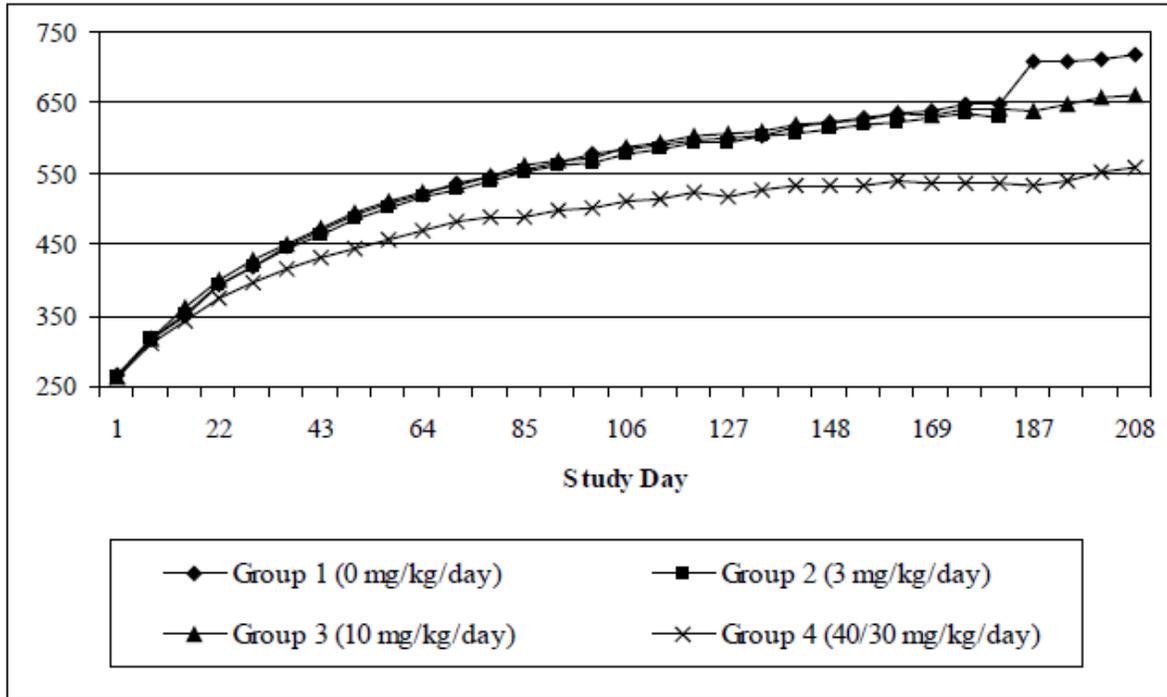
Body Weights

Individual body weights of all animals were recorded on the day of randomization and weekly throughout the treatment and recovery periods.

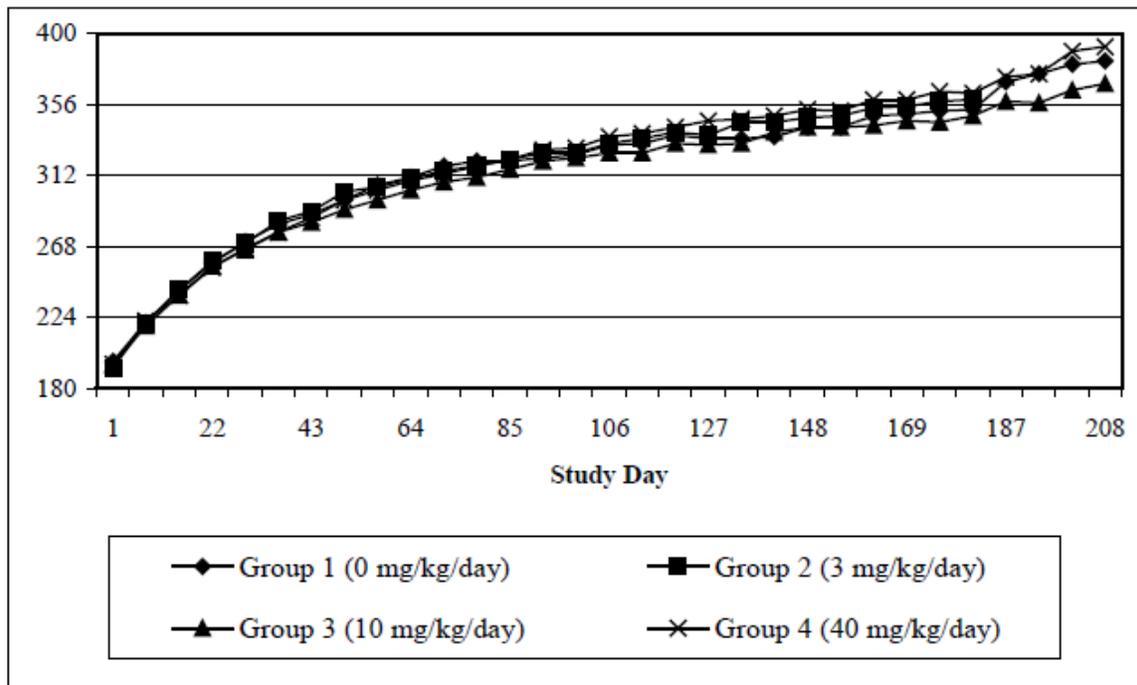
Male and female body weight growth curves are presented in the figures below.

A test article-related decrease in body weight gain was observed in the high-dose males and lower body weights compared to controls were observed from Day 29 to the end of the study.

Male Group Mean Body Weights (g)



Female Group Mean Body Weights (g)



Feed Consumption

Feed consumption measurements for all animals were recorded weekly throughout the treatment and recovery periods.

Feed consumption in the low- and mid-dose groups and in the high-dose female group was comparable to the control groups.

The high-dose male group had lower feed consumption values compared to controls throughout the study. This is consistent with the decrease in body weight gain in the high-dose male group.

Ophthalmoscopy

Ophthalmological examinations were performed on all animals prior to study initiation and during the last week of dosing.

Corneal crystals were noted in one or both eyes of several animals at pretest and on Day 178.

No test-article related ophthalmological effects were observed.

ECG

NA

Hematology

Blood samples were collected via the vena cava prior to study initiation and prior to scheduled or recovery necropsies. A complete battery of hematology and coagulation parameters was evaluated.

Slight fluctuations in red cell parameters and individual white cell populations were noted. However, all of these parameters were within the normal historical control range and are regarded as incidental findings.

There were no test-article related effects on hematology parameters.

Clinical Chemistry

Blood samples for clinical chemistry analysis were collected via the vena cava prior to study initiation and prior to scheduled or recovery necropsies. A complete battery of clinical chemistry parameters was evaluated.

Slight fluctuations in protein and albumin/globulin ratios were noted. However, most of these parameters were within the normal historical control range.

There were no test-article related effects on clinical chemistry parameters.

Urinalysis

Animals were individually housed in stainless steel urine collection cages and urine was collected by cage pan drainage overnight. A complete battery of urinalysis parameters was evaluated.

There were no test-article related effects on urinalysis parameters.

Gross Pathology

All toxicity and recovery phase animals were subjected to a complete gross necropsy examination.

There were numerous gross pathology findings at multiple injection sites of animals in all groups, including the control group. Injection site changes included discoloration, scabbing, thickening and nodules. There was no difference in the incidence or severity of these changes among groups. Therefore, these injection site findings are vehicle-related.

Adhesions in the abdominal cavity involving spleen, liver, stomach, fat or body wall were observed in animals of all groups. Although the cause of these adhesions is unknown, adhesions in the abdominal cavity are absent at the end of the 28 day recovery phase.

Organ Weights

The following organs were weighed for all toxicity and recovery phase animals at scheduled necropsy.

Organ Weights

Adrenal gland ^a	Prostate gland
Brain	Salivary gland ^a
Epididymis ^a	Seminal vesicle ^a
Heart	Spleen
Kidney ^a	Testis ^a
Liver	Thymus
Lung	Thyroid gland with parathyroid gland ^a
Ovary ^a	Uterus
Pituitary gland	
^a Paired organ weight.	

There were no test article related effects on organ weight in males or females.

Histopathology

Adequate Battery

Yes. All tissues and organs collected at necropsy from control and high-dose animals and animals found dead or euthanized *in extremis* and gross lesions from the low- and mid-dose animals were processed and examined microscopically.

Tissue Collection and Preservation

Adrenal gland (paired)	Lymph node, mesenteric
Animal identification	Mammary gland
Aorta	Nerve, optic ^b
Bone, femur	Nerve, sciatic
Bone, sternum	Ovary (paired)
Bone marrow, sternum	Pancreas
Bone marrow smear ^a	Parathyroid gland ^c
Brain (cerebrum, cerebellum, brain stem, medulla)	Pituitary gland
Cervix	Prostate gland
Epididymis (paired)	Salivary gland (paired)
Esophagus	Seminal vesicle (paired)
Eye (paired) ^b	Skeletal muscle (thigh)
Harderian gland (paired)	Skin (mammary)
Heart	Spinal cord (cervical, thoracic, lumbar)
Injection sites	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch ^c	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
^a Bone marrow smears were collected from the femur at scheduled necropsies only for possible examination. The smears were not examined and were archived with the other study specimens. ^b Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin. ^c Examined only if present in the routine section.	

Peer Review

No. However, this did not affect interpretation of the study results.

Histological Findings

Microscopic evaluation of the injection site revealed ulceration and surface crusts involving the epidermis and hemorrhage, cystic spaces, necrosis, fibrosis, chronic inflammation, mineralization and abscess formation in the subcutaneous tissues. The incidence and severity of the injection site reactions was similar among control and treated groups.

Following the 28 day recovery period, the incidence and severity of injection site reactions was decreased.

Special Evaluation

None

Toxicokinetics

Toxicokinetics animals were divided into subgroups of 3 animals/sex/group and blood samples were collected according to the following table.

TK Sample Collection Schedule – Days 1, 89, and 90

Group No.	Subgroup	No. of Males/ Females	Sample Collection Time Points (Hours Post-Dose) on Days 1, 89 ^a , and 90					
			0 hr ^b	1 hr	4 hr	6 hr	8 hr	24 hr
1 ^a	A	3/3	x			x		
	B	3/3		x			x	
	C	3/3			x			x
	D ^c	3/3						
2	A	3/3	x			x		
	B	3/3		x			x	
	C	3/3			x			x
	D ^c	3/3						
3	A	3/3	x			x		
	B	3/3		x			x	
	C	3/3			x			x
	D ^c	3/3						
4	A	3/3	x			x		
	B	3/3		x			x	
	C	3/3			x			x
	D ^c	3/3						

Note: "x" = scheduled sample collection.
^aSample Collection Day 89 was for Group 1 animals only. Group 1 animals did not have samples collected on Day 90.
^bSamples collected prior to dosing.
^cSubset D animals were bled in place of any animals in Subsets A-C that died during the study.

Similar to the main study, test article-related mortality was observed in the high-dose male toxicokinetic group. One high-dose male was found dead on Day 103 and one high-dose male was found dead on Day 161. One mid-dose male was euthanized moribund on Day 158. Control and low-dose toxicokinetic males and all toxicokinetic females survived until scheduled euthanasia.

For IDP-108 (see the table below), increases in AUC₀₋₂₄ were directly proportional to dose; however, the increases in C_{max} were less than the increase in dose. From Day 1 to Day 90, there were increases in C_{max} and AUC₀₋₂₄ followed by a decrease from Day 90 to Day 180. T_{max} occurred at 1 or 4 hours for males and females in the low- and mid-dose groups. T_{max} occurred at 4 or 6 hours for the high-dose group. Elimination half-life values determined on Day 180 with collections out to 72 hours ranged from 20.3 to 34.0 hours.

Sex	Dose (mg/kg/day)	Day	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng•hr/mL)	AUC ₀₋₇₂ (ng•hr/mL)	r ²	t _{1/2} (hr) based on 0 - 24 hr data	t _{1/2} (hr) based on 0 - 72 hr data	
M	3	1	81	1	361		0.9749	4.01		
		90	335	1	1,123		0.9830	4.70		
		180	86	4	570	730	<i>0.5171</i>		<i>39.2</i>	
M	10	1	201	1	1,157		0.9457	4.22		
		90	421	1	3,618		0.9607	5.35		
		180	189	1	1,883	2,527	0.8665		20.3	
M	40	1	403	4	4,781		0.9145	9.90		
		40	90	1,578	4	15,191		0.8271	9.33	
		30	180	443	6	5,751	9,001	0.9968		34.0
F	3	1	210	1	695		0.9973	3.34		
		90	203	1	886		0.9157	7.58		
		180	78	1	469	531	<i>0.7574</i>		<i>20.5</i>	
F	10	1	297	4	1,944		1.0000	3.58		
		90	480	1	2,821		0.9098	6.88		
		180	258	1	1,668	1,879	0.8398		25.2	
F	40	1	568	4	6,325		0.9730	7.69		
		90	1,682	4	13,214		0.9187	9.68		
		180	519	6	5,338	7,502	0.8891		30.5	

Value for t_{1/2} in bold italics is considered unreliable since r² < 0.8.

For the H3 metabolite (see the table below), C_{max} and AUC_{0-24} increased proportionally with dose. C_{max} and AUC_{0-24} increased between Day 1 and Day 90. Most of the T_{max} values occurred at 6 or 8 hours. C_{max} and AUC_{0-24} values for the H3 metabolite were lower for females than for males.

Sex	Dose (mg/kg/day)	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	AUC_{0-72} (ng•hr/mL)	r^2	$t_{1/2}$ (hr) based on 0 - 24 hr data	$t_{1/2}$ (hr) based on 0 - 72 hr data
M	3	1	122	6	1,442		0.9190	10.1	
		90	257	6	4,487		0.9947	18.5	
		180	342	6	4,827	7,814	0.9220		25.1
M	10	1	310	8	5,907		nc	nc	
		90	1,126	8	20,881		nc	nc	
		180	975	8	17,080	27,748	0.9645		24.3
M	40	1	862	24	16,508		nc	nc	
		90	7,250	8	135,104		nc	nc	
		30	180	3,253	8	65,789	111,041	0.9537	
F	3	1	47.3	6	684		0.9982	8.03	
		90	75.8	6	1,132		0.9873	12.6	
		180	67.3	6	1,008	1,443	0.9982		12.9
F	10	1	136	6	1,574		0.8991	11.4	
		90	201	6	3,411		1.0000	14.5	
		180	225	6	3,354	5,060	0.9051		13.7
F	40	1	220	8	4,266		nc	nc	
		90	729	6	15,327		0.9857	65.3	
		180	826	4	16,395	31,615	<i>0.7534</i>		<i>21.4</i>

nc = could not be calculated.

Value for $t_{1/2}$ in bold italics is considered unreliable since $r^2 < 0.8$.

For the H1 metabolite (see the table below), increases in C_{max} and AUC_{0-24} were less than proportional to dose. Between Day 1 and Day 90, C_{max} and AUC_{0-24} increased, but the increases were less than those observed for IDP-108 and the H3 metabolite. For the H1 metabolite, the values of C_{max} and AUC_{0-24} on Day 180 were similar to those on Day 90. The production of the H1 metabolite is sustained resulting in T_{max} values of 8 or 24 hours on Day 1. Estimated half-life values ranged from 16 to 41 hours. No measurable concentrations of the H1 metabolite were observed on Day 209. C_{max} and AUC_{0-24} values for the H1 metabolite were lower for females than for males.

Sex	Dose		C_{max} (ng/mL)	% Change in C_{max} from		AUC_{0-24} (ng•hr/mL)	% Change in AUC from		
	(mg/kg/day)	Day		Day 1	Day 90		Day 1	Day 90	
M	3	1	55.8			1,008			
		90	54.0	-3%		1,123	11%		
		180	74.9	34%	39%	1,289	28%	15%	
M	10	1	161			3,028			
		90	265	65%		5,397	78%		
		180	268	66%	1%	5,076	68%	-6%	
M	40	1	617			7,785			
		40	90	657	6%		12,797	64%	
		30	180	610	32%	24%	9,759	67%	2%
F	3	1	15.3			204			
		90	28.6	87%		451	120%		
		180	23.0	50%	-20%	371	81%	-18%	
F	10	1	30.5			591			
		90	51.3	68%		966	63%		
		180	51.6	69%	1%	949	60%	-2%	
F	40	1	77.1			1,144			
		90	137	78%		2,952	158%		
		180	139	80%	1%	2,893	153%	-2%	

^a Calculated using dose-normalized values to adjust for dose change.

Dosing Solution Analysis

All dosing solutions were analyzed and were found between 99.7% and 100.3% of target concentrations.

Study 3

A 28 day dermal GLP toxicity study of IDP-108 in Gottingen minipigs. Study No. DSIN-7001-A6HP-05-07.

IDP-108 solution was dermally administered once daily to groups of 4 Gottingen minipigs/sex/group at concentrations of 0 (vehicle), 1%, 10% and 30% for 28 (males) or 29 (females) consecutive days. Approximately 20 $\mu\text{L}/\text{cm}^2$ IDP-108 solution was applied to 10% of the total body surface area. On the day following the last dose, all animals were euthanized, necropsied, and tissues were collected. Parameters for evaluation included daily clinical and dermal observations, body weights, food consumption, physical and ophthalmic examinations, clinical pathology determinations, macroscopic pathology, organ weights, and microscopic pathology. Systemic exposure was determined by quantifying IDP-108 concentrations in plasma samples collected on Days 1, 7, and 27.

All animals survived to scheduled necropsies. Animals given the vehicle and IDP-108 were noted with rubbing against the cage partition and/or the cage floor immediately after dosing on most treatment days. The rubbing was resolved approximately two to three minutes after dosing. Beginning on Day 21 and continuing to the scheduled necropsy, all animals including controls were noted with hyperkeratosis. Both of these clinical observations are related to the vehicle and not a direct effect of IDP-108 solution. There were no test article related effects on dermal observations, body weights, body weight changes, food consumption, hematology, coagulation, clinical chemistry, or electrocardiogram parameters nor were there any effects on gross pathology findings or organ weights. Microscopic modest hyperkeratosis, acanthosis, and localized inflammation was similar for treated skin sites from minipigs administered vehicle or IDP-108 solutions and is consistent with clinical signs of hyperkeratosis noted during the last week of this study. There was no histological evidence of systemic toxicity associated with any of the administered IDP-108 solutions.

The toxicokinetic parameters for efinaconazole, H3 metabolite and H1 metabolite from this study are provided in the following table.

Day	Dose Group (%)					
	1		10		30	
	M	F	M	F	M	F
Efinaconazole Mean AUC ₀₋₂₄ (ng • h/mL)						
1	169	626	756	750	2217	1917
7	1501	816	2380	2879	3463	7499

Day	Dose Group (%)					
	1		10		30	
	M	F	M	F	M	F
27	651	546	1670	4064	2821	3366
Metabolite H3 Mean AUC ₀₋₂₄ (ng • h/mL) ^a						
1	97 (0.6)	50 (0.1)	379 (0.5)	302 (0.4)	762 (0.3)	516 (0.3)
7	831 (0.6)	430 (0.5)	2155 (0.9)	1611 (0.6)	3027 (0.9)	3148 (0.4)
27	910 (1.4)	298 (0.5)	2335 (1.4)	2275 (0.6)	3258 (1.2)	2910 (0.9)
Metabolite H1 Mean AUC ₀₋₂₄ (ng • h/mL) ^a						
1	NC	NC	0 (0.0)	0 (0.0)	0 (0.0)	19 (0.0)
7	NC	NC	36 (0.0)	185 (0.1)	77 (0.0)	339 (0.1)
27	NC	NC	34 (0.0)	191 (0.1)	72 (0.0)	257 (0.1)

^a Values in parenthesis indicate plasma AUC₀₋₂₄ metabolite/parent ratios
 NC = not calculated

After IDP-108 administration, IDP-108 plasma concentrations increased gradually. Time to maximum concentration was highly variable, ranging on average between 2 and 19 hrs. Likewise, half-life was highly variable, with an average range of 6 to 159 hrs.

Plasma exposure of IDP-108, measured by C_{max} and AUC_t, increased with increasing the dose and was generally similar between male and female minipigs. Concentrations of IDP-108 were quantified in the control group suggesting some exposure to the control animals. The highest C_{max} and AUC_t of IDP-108 in the control group were 76 ng/ml and 421 ng·h/ml, respectively. This finding cannot be explained. Following a thorough investigation, no cause was determined for this unexpected finding, and it is suspected that some environmental contamination was the cause of the exposure. The increase in average AUC_t with dose appeared less than dose proportional. The highest average C_{max} and AUC_t of IDP-108 were 852 ng/ml and 7499 ng·h/ml, respectively, both observed at the highest dose group (30% IDP-108 solution) on Day 7 in females. No obvious gender related differences were observed in the pharmacokinetics of IDP-108. Accumulation was observed upon repeat once daily administration of IDP-108. The compound appeared to reach steady state by Day 7.

The dose of 30% IDP-108 solution (approximately 200 mg/kg/day) is considered the NOAEL for dermal and systemic toxicity in this study.

Study 4

Study title: A 9 month dermal GLP toxicity study of IDP-108 in Gottingen minipigs.

Study no.:	DSIN-7001-A6HP-11-07
Study report location:	SDN 1
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	12/10/2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	1% IDP-108, LB07145, 99.0% 5% IDP-108, LB08032, 101.2% 10% IDP-108, LB07146, 100.2% 30% IDP-108, LB07147, 103.0% 30% IDP-108, LB08020, 100.7%

Key Study Findings

Gottingen minipigs were administered once daily dermal doses of IDP-108 Solution (0%, 1/5%, 10%, and 30%) for 39 Weeks at an application rate of 20 $\mu\text{L}/\text{cm}^2$ applied to 10% of the total body surface area. Slight hyperkeratosis was noted in skin from dose sites and pathology was similar for tissues from minipigs from vehicle control or IDP-108 treated groups. The high dose (30% IDP-108 solution), is the no-observed-adverse-effect level (NOAEL) for dermal and systemic toxicity.

The topical formulation used in this study is similar to the to-be-marketed formulation. The difference between the topical formulation used in this study and the to-be-marketed formulation is the addition of two stabilizers, 0.1% Citric Acid and 0.00025% Edetate Disodium, and the removal of Vitamin E in to-be-marketed formulation. The small amount of 0.1% Citric Acid and 0.00025% Edetate Disodium added to the to-be-marketed formulation and the removal of Vitamin E are not expected to significantly change the study results from a Pharmacology/Toxicology perspective.

Methods

Doses: 0 (vehicle), 1% (Day 1 to 163)/5% (Day 164 to 273), 10% and 30% IDP-108 Solution.
 Frequency of dosing: Once daily for 273 consecutive days.
 Route of administration: Dermal, unoccluded dorsal skin, 10% BSA
 (adjusted weekly: Total BSA(cm²)=734(BW_{kg})^{0.656})
 Dose volume: 0.020ml/cm²
 Formulation/Vehicle: (b) (4) Alcohol, USP, (b) (4)
 Cyclomethicone (b) (4) NF, (b) (4)
 Diisopropyl Adipate, (b) (4)
 C12-15 Alkyl Lactate, (b) (4)
 (b) (4)
 Butylated Hydroxytoluene, NF, (b) (4)
 Species/Strain: Minipig (*Sus scrofa*)/ Gottingen
 Number/Sex/Group: 5 Minipigs/sex/study group
 Additional 2 Minipigs/sex/control recovery group
 (25 Days)
 Additional 2 Minipigs/sex/high dose recovery
 group (25 Days)
 Additional 2 Minipigs/sex as sentinel animals
 Age: 3-5 Months
 Weight: 8.2-11.6 kg
 Satellite groups: NA
 Unique study design: NA
 Deviation from study protocol: Yes, but the deviations did not affect the integrity
 of the study or the interpretation of the study
 results.

Observations and Results**Mortality**

All animals were observed at least twice daily for morbidity and mortality.
 All animals survived to their respective scheduled necropsies.

Clinical Signs

All animals were observed for general signs of toxicity at least once daily.
 There were no clinical observations noted that were considered related to IDP-108
 treatment.

Application sites of all animals were examined and scored once daily during Week 1,
 and once weekly for the remainder of the study.
 Most animals, including controls, were noted to rub against the cage immediately after
 dosing on most treatment days. The rubbing resolved two to three minutes after dosing.

No signs of edema were noted in control animals or animals treated with IDP-108 solution. Many animals, including controls, were noted with erythema. The majority of erythema findings occurred during the first 3 months of the study; erythema was less common during the last 6 months of the dosing phase. None of the animals had more than minimal erythema at completion of 39 Weeks of dosing and following a 25 Day recovery.

There were no signs of blanching, ulceration, or fissuring noted in control or IDP-108 animals during the study. At the end of the study, slight eschar was noted in control and IDP-108 animals. Eschar involved less than one-third of the application site regardless of treatment group and is considered vehicle related.

Incidence and severity of erythema.

Dose Group (%)	Placebo	1/5	10	30
Dermal Finding				
Males				
# of animals/group	7	5	5	7
Erythema				
Very slight	3	2	4	5
Well-defined	1	3	1	1
Moderate	-	-	-	-
Severe	-	2	-	-
# animals affected	3	3	5	5
Females				
# of animals/group	7	5	5	7
Erythema				
Very slight	3	4	3	6
Well-defined	1	1	3	4
Moderate	-	1	1	1
Severe	1	-	-	1
# animals affected	5	4	4	6

Body Weights

Body weights were recorded for all animals once weekly until scheduled sacrifice. There were no test article-related changes in body weight or body weight gain.

Feed Consumption

Feed consumption estimates (0%, 25%, 50%, 75%, or 100%) were recorded for all animals once weekly until scheduled sacrifice.

There were no test article-related changes in feed consumption.

Ophthalmoscopy

Ophthalmic examinations were performed on all animals pretest, prior to scheduled necropsy, and prior to recovery necropsy.

On Day 268, the lens of the left eye of one control male and the lens of both eyes of one high dose male were noted with pigmented opacity.

On Day 301, the lens of the right eye of one control male and the lens of both eyes of one high dose female were noted with pigmented opacity.

These findings are not considered related to IDP-108 since they are also noted in the control animals.

ECG

Electrocardiograms were conducted on all animals at pretest, Weeks 39, and 43.

At Week 39, the PR interval in high dose female minipigs was 16 msec shorter compared to control females. This change was not considered dose related since recovery ECG traces were within normal limits.

Hematology

Whole blood was collected from all animals at pretest, Weeks 13, 39, and 43.

At Week 13, elevated red blood cell counts (20%) and hematocrit values (15%) were noted in high dose males. At Week 13, elevated red blood cell counts were noted in low, mid and high dose females (17%, 16%, and 14% respectively) and during Week 39 (13%) in high dose females. At Week 39, elevated white blood cell counts were noted in mid and high dose males (29% and 36%, respectively). At Week 39, elevated white blood cell counts were noted in mid and high dose males (29% and 36%, respectively). All of these parameters resolved following a 25 Day recovery period.

Some hematology parameters (mean cell hemoglobin, platelet counts, and reticulocyte counts in females) were slightly elevated compared to the control group. These parameters are not considered to be related to IDP-108 treatment and are not clinically significant because the changes are within the range of normal reference values, and are not dose related.

Clinical Chemistry

Serum was processed from all animals at pretest, Weeks 13, 39, and 43.

At Week 39, elevated serum potassium concentrations were noted in mid and high dose males (44% and 34%, respectively). At Week 39 elevated serum calcium concentrations were noted in mid and high dose males (9% and 10%, respectively). Both of these parameters were resolved following a 25 Day recovery period.

Some clinical chemistry parameters (alkaline phosphatase and alanine aminotransferase activities in females) were slightly elevated compared to the control group. These changes are not clinically significant, and are not considered to be related to IDP-108 treatment because the changes are within the range of normal reference values.

Urinalysis

Urine was collected from all animals at pretest, Weeks 13, 39, and 43. There were no treatment related effects on urinalysis parameters.

Gross Pathology

All animals were examined for external abnormalities. The abdominal, thoracic, and cranial cavities and their contents were examined for abnormalities and the organs removed, examined, and, where specified in the table below, fixed in 10% neutral buffered formalin.

No treatment related gross anomalies were observed.

Organ Weights

Organ weights were expressed as absolute values and as organ weight:body weight and organ weight:brain weight ratios.

Some organ weights (absolute and relative splenic weight in IDP-108 males and lung weight relative to brain weight in low dose males) were slightly different from the control group. These parameters are not clinically significant, and not considered to be related to IDP-108 treatment because the changes are not dose related.

There were no IDP-108 treatment related effects on organ weight parameters.

Histopathology

Microscopic examinations were performed on sections of tissues indicated in the following table.

Tissue	Organ Weight Taken	Collected and Preserved in 10% NBF	Microscopic Examination
Adrenal glands*	X	X	X
Aorta (thoracic)		X	X
Brain	X	X	X
Cecum		X	X
Cervix		X	X
Colon		X	X
Duodenum		X	X
Epididymides		X	X
Esophagus		X	X
Eyes		X	X
Femur, proximal		X	
Gallbladder		X	X
Heart	X	X	X
Identification (ear)		X	
Ileum		X	X
Jejunum		X	X
Kidneys*	X	X	X
Lacrimal gland		X	X
Lesion(s)		X	X
Liver	X	X	X
Lungs	X	X	X
Lymph node - cervical		X	X
Lymph node - mesenteric		X	X
Mammary gland (region)		X	X
Muscle (biceps femoris)		X	X
Optic nerve		X	X

Tissue	Organ Weight Taken	Collected and Preserved in 10% NBF	Microscopic Examination
Ovaries*	X	X	X
Pancreas		X	X
Pituitary	X	X	X
Prostate	X	X	X
Salivary gland, mandibular		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skin (treated and untreated)		X	X
Spinal cord – cervical, thoracic		X	X
Spleen	X	X	X
Sternum with marrow		X	X
Stomach		X	X
Testes*	X	X	X
Thymus (region)	X	X	X
Thyroid		X	X
Tongue		X	
Trachea		X	X
Urinary bladder		X	X
Uterus	X	X	X
Vagina		X	X

Adequate Battery

Yes.

Peer Review

No. However the lack of peer review did not prevent evaluation of the study.

Histological Findings

Beginning on Day 91 and continuing to the scheduled necropsy, all animals, including controls, were noted with slight hyperkeratosis at the application site. Slight hyperkeratosis persisted throughout the 25 Day recovery period. Slight hyperkeratosis is considered related to the vehicle and not a direct response to IDP-108 since it is also noted in the control animals.

At Week 39, one mid dose male was observed at necropsy with nonglandular mucosa ulceration at the cardiofundic junction of the stomach. An ulceration of the glandular

mucosa in the pyloric area of the stomach was observed in one sentinel male housed with the IDP-108 animals. One control female was observed with glandular mucosa ulceration in the fundic area of the stomach after the recovery phase. The ulceration in the one mid dose male is not considered related to IDP-108 treatment since a similar lesion was observed in a control female and a sentinel male that was negative for the presence of IDP-108 in plasma samples collected on Days 298 and 273, respectively.

One mid dose male was observed with several (2-10) dark foci on the atrium of the heart at Week 39.

The remainder of the macroscopic findings noted at Week 39 are commonly observed in minipigs and are not considered IDP-108 treatment related.

Slight hyperkeratosis, acanthosis, and localized inflammation were noted in skin from dose sites and pathology was similar for tissues from minipigminipigs from vehicle or IDP-108 groups. Other microscopic findings that occurred in both control and IDP-108 treated minipigminipigs included kidney (focal interstitial inflammatory cellular infiltrate), optic nerve (focal axonal neuropathy), heart (perivascular or coronary fat inflammatory cellular infiltration), testes (focal seminiferous tubule hypoplasia) and lung (macrophage foci). Stromal hemorrhage and/or inflammation noted in several thymus and thyroid glands was attributed to inadvertent trauma associated with multiple blood sampling procedures. Splenic red pulp congestion was likely associated with barbiturate euthanasia. Other microscopic findings were considered incidental and unrelated to IDP-108. There was no histomorphologic evidence of systemic toxicity associated with up to 30% IDP-108 administered to minipigminipigs by dermal application once daily for 39 weeks in this study.

Special Evaluation

NA

Toxicokinetics

IDP-108 and metabolite H3 were not detected in plasma samples from the control group. IDP-108 and metabolite H3 were found at detectable levels (maximal concentrations of 11.6 ng/ml and 24.1 ng/ml for IDP-108 and H3, respectively) in plasma samples from the sentinel animals housed with the IDP-108 treatment animals, indicating that the sentinel animals were indirectly exposed to IDP-108.

Plasma concentrations of IDP-108, measured by C_{max} and AUC_t , increased with dose but, in a less than dose proportional manner. Systemic exposures of IDP-108 were generally similar between genders with higher exposure in females in the mid and high dose groups, while the exposure of H3 was higher in males across all three dose groups. Accumulation of IDP-108 and H3 was observed with repeated once daily administration of IDP-108. The accumulation ratio (mean repeat dose AUC_t / Day 1 AUC_t) was higher for H3 (1.95 to 12.38) compared to IDP-108 (1.28 to 7.65). Plasma concentrations of both IDP-108 and H3 were measurable in all animals on Days 28, 91 and 273 and were similar across each dose group, indicating that steady state was likely attained within 28 days of repeated once daily dosing. Concentrations of IDP-108

and H3 were still quantifiable in the recovery animals 25 Days after the last drug application, an indication of the long half-life of both IDP-108 and H3.

Table 1 Average (SD) Toxicokinetic Parameters of IDP-108 Obtained After Daily Administration of IDP-108 for Nine Months to Mini-Pigs

Dose	Day	t_{max} (h)		C_{max} (ng/mL)		AUC_t (ng•h/mL)		Dose-Normalized C_{max}		Dose Normalized AUC_t		Mean Accumulation Ratio*	
		F	M	F	M	F	M	F	M	F	M	F	M
1%/ 5%	1	7.200 (1.789)	6.000 (2.828)	4.760 (2.120)	11.40 (6.833)	70.29 (25.47)	121.6 (37.97)	4.760 (2.120)	11.40 (6.833)	70.29 (25.47)	121.6 (37.97)	NA	NA
	28	4.000 (2.449)	4.400 (3.286)	26.20 (13.65)	25.18 (10.68)	395.2 (107.8)	412.8 (82.61)	26.20 (13.65)	25.18 (10.68)	395.2 (107.8)	412.8 (82.61)	NC	NC
	273#	1.600 (3.578)	2.400 (1.673)	159.4 (91.67)	144.0 (39.29)	1844 (1019)	2226 (337.4)	31.88 (18.33)	28.80 (7.858)	368.8 (203.8)	445.2 (67.48)	NC	NC
10%	1	10.40 (7.797)	3.600 (2.608)	136.6 (160.2)	45.68 (32.10)	1591 (1637)	377.6 (102.8)	13.66 (16.02)	4.568 (3.210)	159.1 (163.7)	37.76 (10.28)	NA	NA
	28	3.000 (2.828)	1.800 (0.4472)	194.8 (72.88)	141.7 (97.68)	2974 (729.4)	2304 (940.5)	19.48 (7.288)	14.17 (9.768)	297.4 (72.94)	230.4 (94.05)	1.869	6.102
	273	2.200 (1.643)	5.200 (2.683)	318.8 (114.2)	243.1 (170.2)	3462 (747.6)	2890 (1362)	31.88 (11.42)	24.31 (17.02)	346.2 (74.76)	289.0 (136.2)	2.176	7.654
30%	1	10.57 (9.431)	16.00 (10.07)	291.5 (173.3)	187.9 (104.6)	3553 (2100)	2010 (1294)	9.717 (5.777)	6.263 (3.487)	118.4 (70.00)	67.00 (43.13)	NA	NA
	28	8.430 (7.525)	6.710 (8.261)	285.6 (77.75)	254.0 (90.68)	4536 (1051)	4270 (969.6)	9.520 (2.592)	8.467 (3.023)	151.2 (35.03)	142.3 (32.32)	1.277	2.124
	273	6.570 (8.284)	4.570 (3.409)	647.7 (599.4)	378.3 (191.1)	5693 (3491)	4817 (2635)	21.59 (19.98)	12.61 (6.370)	189.8 (116.4)	160.6 (87.83)	1.602	2.397

Notes: NA = not applicable; NC = not calculated; # = The higher exposure measured on Day 273 can partially be explained by the dose increased occurring on Day 164; * = based on the ratio of the mean AUC_t from Days 28 and 273 to Day 1 for 10% and 30% dose levels only.

Table 2 Average (SD) Toxicokinetic Parameters of H3 Obtained After Daily Administration of IDP-108 for Nine Months to Mini-Pigs

Dose	Day	t_{max} (h)		C_{max} (ng/mL)		AUC_t (ng•h/mL)		AUC_M/AUC_P		Dose-Normalized C_{max}		Dose Normalized AUC_t		Mean Accumulation Ratio*	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M
1%/ 5%	1	24.00 (0.000)	24.00 (0.000)	2.410 (0.8629)	4.890 (1.803)	31.97 (11.07)	64.01 (22.26)	0.4778 (0.185)	0.5898 (0.3475)	2.410 (0.8629)	4.890 (1.803)	31.97 (11.07)	64.01 (22.26)	NA	NA
	28	0.2000 (0.4472)	6.800 (10.16)	19.02 (3.773)	29.20 (9.003)	395.9 (84.56)	639.2 (195.2)	1.021 (0.1696)	1.577 (0.4389)	19.02 (3.773)	29.20 (9.003)	395.9 (84.56)	639.2 (195.2)	NC	NC
	273#	6.400 (10.43)	14.60 (12.88)	59.78 (15.72)	104.3 (32.55)	1241 (354.9)	2249 (635.7)	0.7693 (0.2495)	1.044 (0.3865)	11.96 (3.144)	20.86 (6.510)	248.2 (70.98)	449.8 (127.1)	NC	NC
10%	1	24.00 (0.000)	24.00 (0.000)	19.32 (9.196)	26.02 (9.654)	245.1 (96.83)	328.0 (101.1)	0.2822 (0.2573)	0.8926 (0.2268)	1.932 (0.9196)	2.602 (0.9654)	24.51 (9.683)	32.80 (10.11)	NA	NA
	28	0.6000 (0.8944)	1.600 (3.578)	109.4 (31.98)	154.2 (54.17)	2220 (667.4)	3025 (974.0)	0.7429 (0.1237)	1.394 (0.4903)	10.94 (3.198)	15.42 (5.417)	222.0 (66.74)	302.5 (97.40)	9.058	9.223
	273	9.600 (13.15)	19.20 (10.73)	119.7 (50.29)	170.0 (40.71)	2335 (730.0)	3362 (659.8)	0.7330 (0.4007)	1.370 (0.6518)	11.97 (5.029)	17.00 (4.071)	233.5 (73.00)	336.2 (65.98)	9.527	10.25
30%	1	24.00 (0.000)	24.00 (0.000)	25.50 (9.104)	36.39 (5.977)	299.4 (108.1)	492.7 (119.7)	0.1266 (0.1135)	0.3672 (0.2963)	0.8500 (0.3035)	1.213 (0.1992)	9.980 (3.603)	16.42 (3.990)	NA	NA
	28	9.710 (10.23)	4.140 (8.877)	157.0 (28.55)	251.3 (70.51)	3417 (605.6)	5459 (1551)	0.8125 (0.3211)	1.314 (0.4113)	5.233 (0.9517)	8.377 (2.350)	113.9 (20.19)	182.0 (51.70)	11.41	11.08
	273	7.710 (7.868)	11.43 (11.82)	174.1 (77.77)	285.4 (114.4)	3705 (1738)	5845 (2323)	0.8066 (0.3943)	1.493 (1.029)	5.803 (2.592)	9.513 (3.813)	123.5 (57.93)	194.8 (77.43)	12.38	11.86

Notes: NA = not applicable; NC = not calculated; # = The higher exposure measured on Day 273 can partially be explained by the dose increased occurring on Day 164; * = based on the ratio of the mean AUC_t from Days 28 and 273 to Day 1 for 10% and 30% dose levels only.

Dosing Solution Analysis

All dosing solutions were evaluated and were found within the appropriate target concentrations.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Efinaconazole

Study title: Reverse mutation test of KP-103 in bacteria.

Study no.: SOT021

Study report location: SDN 1

Conducting laboratory and location:



Date of study initiation: 12/4/1995

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: KP-103, Lot# 94Z22

Key Study Findings

KP-103 was not mutagenic in the Ames test, under the conditions of this experiment.

Methods

Strains: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *Escherichia coli* strain WP2 *uvrA*

Concentrations in definitive study: 9.8, 20, 39, 78, 156 and 313 µg/plate (-S9) for TA100 and WP2 *uvrA*.
 2.4, 4.9, 9.8, 20, 39, and 78 µg/plate (-S9) for TA98, TA1535 and TA1537.
 39, 78, 156, 313, 625 and 1250 µg/plate (+S9; S9 derived from Aroclor 1254 induced rat liver homogenate) for TA100.
 9.8, 20, 39, 78, 156, 313 µg/plate (+S9) for TA98, TA1535, TA1537 and WP2 *uvrA*.
 Growth inhibition was noted in the highest concentration tested in each strain (± S9). 3 plates/dose.

Basis of concentration selection: Dose range finding study conducted with 5, 20, 78, 313, 1259 and 5000 µg/plate for all tester strains (± S9; S9 derived from Aroclor 1254 induced rat liver homogenate); 1 plate/dose.
 Minimal precipitate was noted at the highest concentration.
 Growth inhibition was noted at doses ≥313 µg/plate for TA100 and WP2*uvrA* and at doses ≥78 µg/plate for TA1535, TA98 and TA1537 without metabolic activation.
 Growth inhibition was noted at doses ≥1250 µg/plate for TA100 and at doses ≥313 µg/plate for TA1535, TA98, TA1537 and WP2*uvrA* with metabolic activation.

Negative control: DMSO
 Positive controls: See Table below.
 Formulation/Vehicle: DMSO
 Incubation & sampling time: Plates were incubated at 37 ± 2°C for 2 days (*S. typhimurinum*) or 3 days (*E. coli*) after treatment.
 Plates were counted for colony formation by automated colony counter and/or by hand after completion of the incubation period.

Test strain	S9 mix	Positive control	Dose ($\mu\text{g}/\text{plate}$)
TA 98	+	Benzo[a]pyrene	5.0
TA 98	-	2-nitrofluorene	1.0
TA 100	+	Benzo[a]pyrene	5.0
TA 100	-	ENNG	3.0
TA 1535	+	2-aminoanthracene	2.0
TA 1535	-	ENNG	5.0
TA 1537	+	Benzo[a]pyrene	5.0
TA 1537	-	9-aminoanthracene	80
WP2 _{uvrA}	+	2-aminoanthracene	10
WP2 _{uvrA}	-	ENNG	2.0

Study Validity

A test article was considered to be positive if it produced at least a 2-fold increase in the mean revertants per plate for tester strains TA98, TA100 or WP2_{uvrA} or if it produced at least a 3-fold increase in mean revertants per plate for tester strains TA1535 or TA1537. This increase in the mean number of revertants per plate had to be accompanied by a dose response to increasing concentrations of the test article.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate showing a mean reversion frequency that was three times or greater than the mean reversion frequency of the solvent control plates. The dose range selected for the definitive study was appropriate according to ICH guidelines.

Results

The test article produced a negative response in the presence and absence of S-9 activation. All tester strains treated with the test article exhibited a mean reversion frequency that was similar to the corresponding solvent control.

Alkyl Lactate**Study title:** Reverse mutation test of C12-C15 alkyl lactate* in bacteria

Study no.: S11T006

Study report location: SDN 1

Conducting laboratory and location:



Date of study initiation: 09/13/2011

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: C12-C15 alkyl lactate,
 Lot# 01100265392,
 Purity 95-99%

*This excipient is widely used in cosmetics. Refer to Section 11 of this review for a more detailed discussion of this excipient.

Key Study Findings

Alkyl lactate was not mutagenic in the Ames test, under the conditions of this experiment.

Methods

Strains: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *Escherichia coli* strain WP2 *uvrA*

Concentrations in definitive study: 0.78, 1.6, 3.1, 6.3, 13, 25, and 50 µg/plate (-S9) for TA100 and TA1537.
 160, 310, 630, 1300, 2500, and 5000 µg/plate (-S9) for TA98, and WP2 *uvrA*.
 20, 39, 78, 160, 310, 630, and 1300 µg/plate (-S9) for TA1535.
 39, 78, 160, 310, 630 and 1300 µg/plate (+S9; S9 derived from Aroclor 1254 induced rat liver homogenate) for TA1537.
 20, 39, 78, 160, 310, 630, and 1300 µg/plate (+S9) for TA100.
 310, 630, 1300, 2500, and 5000 µg/plate (+S9) for TA98, TA1535, and WP2 *uvrA*.
 Growth inhibition was noted in the highest concentration tested in each strain (± S9). 3 plates/dose.

Basis of concentration selection: Dose range finding study conducted with up to 50 µg/plate (-S9) for TA100 and TA1537, up to 1300 µg/plate (-S9) for TA1535, and up to 5000 µg/plate (-S9) for TA98 and WP2 *uvrA*, 1 plate/dose. Dose range finding study conducted with up to 1300 µg/plate (+S9; S9 derived from Aroclor 1254 induced rat liver homogenate) for TA100 and TA1537, and up to 5000 µg/plate (+S9) for TA98, TA1535, and WP2 *uvrA*, 1 plate/dose. Minimal precipitate was noted at the highest concentration for all tester strains except WP2 *uvrA*. Growth inhibition was noted at doses ≥ 21 µg/plate for TA100 and TA1537, at doses ≥ 556 µg/plate for TA1535, and ≥ 5000 µg/plate for TA98 without metabolic activation. Growth inhibition was noted at doses ≥ 556 µg/plate for TA100 and TA1537 with metabolic activation.

Negative control: DMSO

Positive controls: See Table below.

Formulation/Vehicle: DMSO

Incubation & sampling time: Plates were incubated at $37 \pm 2^\circ\text{C}$ for 2 days (*S. typhimurinum*) or 3 days (*E. coli*) after treatment. Plates were counted for colony formation by automated colony counter and/or by hand after completion of the incubation period.

Positive control article	Solvent	Concentration (µg/mL)	Lot No. *
2AA	Dimethyl sulfoxide (DMSO)	5.0	101111A205
		10	101111A210
		20	101111A220
		100	101111A2100
AF-2	DMSO	0.1	101112AF01
		1.0	101112AF10
NaN ₃	water for injection	5.0	101111N
9AA	DMSO	800	101112A9

2AA: 2-aminoanthracene

AF-2: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide

NaN₃: Sodium Azide

9AA: 9-aminoacridine hydrochloride hydrate

Study Validity

A test article was considered to be positive if it produced at least a 2-fold increase in the mean revertants per plate for tester strains TA98, TA100 or WP2*uvrA* or if it produced at least a 3-fold increase in mean revertants per plate for tester strains TA1535 or TA1537. This increase in the mean number of revertants per plate had to be accompanied by a dose response to increasing concentrations of the test article.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate showing a mean reversion frequency that was three times or greater than the mean reversion frequency of the solvent control plates. The dose range selected for the definitive study was appropriate according to ICH guidelines.

Results

The test article produced a negative response in the presence and absence of S-9 activation. All tester strains treated with the test article exhibited a mean reversion frequency that was similar to the corresponding solvent control.

7.2 *In Vitro* Assays in Mammalian Cells

Efinaconazole

Study title: Chromosomal aberration test of KP-103 in CHL/IU cells

Study no.: SST006

Study report location: SDN 1

Conducting laboratory and location:



Date of study initiation: 6/10/1999

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: KP-103, Lot# 23047

Key Study Findings

KP-103 was negative in the Chinese hamster lung fibroblast cell chromosomal aberration assay with and without S9 activation, under the conditions of this assay.

Methods

Cell line: Chinese hamster lung fibroblast cells

Concentrations in definitive study: Concentrations of 0.0188, 0.0375, 0.075, and 0.15 mg/ml KP-103 were used for the 6 hr incubations (\pm S9); 2/concentration. Concentrations of 0.0125, 0.025, 0.05 and 0.1 mg/ml KP-103 were used for the 24 hr incubation (- S9); 2/concentration. Concentrations of 0.01, 0.02, 0.04 and 0.08 mg/ml KP-103 were used for the 48 hr incubation (- S9); 2/concentration

Basis of concentration selection: The concentrations selected for analysis of chromosomal aberrations was based on the level of toxicity noted for the incubations.

The high dose was selected so that 50% reduction in the growth rate relative to the solvent control was noted.

The 0.125 and 0.25 mg/ml KP-103 concentrations exhibited a 37.5% and 100% growth rate reduction, respectively, for the 6 hour incubation (-S9).

The 0.125 and 0.25 mg/ml KP-103 concentrations exhibited a 24% and 92% growth rate reduction, respectively, for the 6 hour incubation (+S9).

The 0.125 mg/ml KP-103 concentration exhibited a 57% and 90% growth rate reduction for the 24 and 48 hour incubations (-S9), respectively.

Negative control: DMSO

Positive control: Mitomycin C (-S9):

0.05 µg/ml for 6 hour exposure,

0.02 µg/ml for 24 and 48 hour exposure.

Cyclophosphamide (+S9):

8 µg/ml for 6 hour exposure

Formulation/Vehicle: DMSO

Incubation & sampling time: Cell cultures were incubated with test article ± S9 for 6 hours and harvested 18 hours after treatment initiation.

Cell cultures were incubated with test article -S9 for 24 or 48 hours and then harvested for analysis.

Slides were prepared from the harvested cultures and stained with 5% Giemsa solution for the analysis of mitotic index and chromosomal aberrations.

Study Validity

A test article was considered to be positive for inducing chromosomal aberrations if a significant increase (the difference was considered significant when $p \leq 0.05$) in the number of cells with chromosomal aberrations is observed at one or more concentrations and a linear trend test demonstrates a dose response relationship.

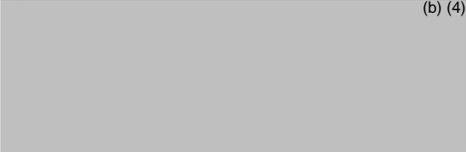
Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate for this assay. The dose range selected for the initial and confirmatory assays were appropriate according to ICH guidelines.

Results

No significant increase in cells with chromosomal aberrations was noted in the analyzed cultures.

Alkyl Lactate

Study title: Chromosomal aberration test of C12-C15 alkyl lactate in CHL/IU cells

Study no.:	S11T005
Study report location:	SDN 1
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	09/02/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C12-C15 alkyl lactate, Lot# 01100265392, Purity 95-99%

Key Study Findings

Alkyl lactate was negative in the Chinese hamster lung fibroblast cell chromosomal aberration assay with and without S9 activation, under the conditions of this assay.

Methods

Cell line:	Chinese hamster lung fibroblast cells
Concentrations in definitive study:	Concentrations of 60, 40, 26.7, 17.8, and 11.9 µg/ml Alkyl lactate were used for the 6 hr incubations (- S9); 2/concentration. Concentrations of 600, 300, 150, 75, and 37.5 µg/ml Alkyl lactate were used for the 6 hr incubations (+ S9); 2/concentration. Concentrations of 40, 26.7, 17.8, 11.9, and 7.9 µg/ml Alkyl lactate were used for the 24 hr incubation (± S9); 2/concentration. Concentrations of 40, 20, 10, 5, and 2.5 µg/ml Alkyl lactate were used for the 48 hr incubation (± S9); 2/concentration

Basis of concentration selection: The concentrations selected for analysis of chromosomal aberrations was based on the level of toxicity noted for the incubations.

The high dose was selected so that 50% reduction in the growth rate relative to the solvent control was noted.

Concentrations of Alkyl lactate from 61.7-1667 µg/ml exhibited a 50% growth rate reduction for the 6 hour incubation (+S9). The 20.6 µg/ml Alkyl lactate concentrations exhibited a 58% and 56% growth rate reduction, respectively for the 24 and 48 hour incubations (± S9), respectively.

Negative control: DMSO

Positive control: Mitomycin C (-S9):
1 µg/ml for 6 hour exposure,
0.4 µg/ml for 24 and 48 hour exposure.
Cyclophosphamide (+S9):
0.1 mg/ml for 6 hour exposure

Formulation/Vehicle: DMSO

Incubation & sampling time: Cell cultures were incubated with test article ± S9 for 6 hours and harvested 18 hours after treatment initiation.
Cell cultures were incubated with test article ± S9 for 24 or 48 hours and then harvested for analysis.
Slides were prepared from the harvested cultures and stained with 5% Giemsa solution for the analysis of mitotic index and chromosomal aberrations.

Study Validity

A test article was considered to be positive for inducing chromosomal aberrations if a significant increase (the difference was considered significant when $p \leq 0.05$) in the number of cells with chromosomal aberrations is observed at one or more concentrations and a linear trend test demonstrates a dose response relationship.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate for this assay. The dose range selected for the initial and confirmatory assays were appropriate according to ICH guidelines.

Results

No significant increase in cells with chromosomal aberrations was noted in the analyzed cultures.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

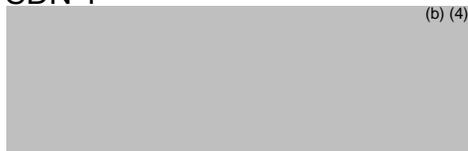
Efinaconazole

Study title: Micronucleus test of KP-103 in mice

Study no: SPT003

Study report location: SDN 1

Conducting laboratory and location:



Date of study initiation: 3/25/1996

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: KP-103, Lot# 94Z22

Key Study Findings

KP-103 was negative in the *in vivo* mouse micronucleus assay, under the conditions of this experiment. This study measured the number of micronucleated cells in peripheral reticulocytes instead of the number of micronucleated cells in bone marrow. This is an acceptable measure of *in vivo* clastogenicity per the ICH guidance.

Methods

Doses in definitive study: 0 (vehicle), 125, 250 and 500 mg/kg KP-103

Frequency of dosing: Single dose

Route of administration: Oral gavage

Dose volume: 10 ml/kg

Formulation/Vehicle: Olive oil

Species/Strain: Male CD-1 mice

Number/Sex/Group: 5 Males/dose

Satellite groups: N/A

Basis of dose selection: Preliminary toxicity study was conducted with single oral (gavage) doses of 250, 500, 1000 and 2000 mg/kg KP-103, 5 males/dose. Complete mortality (5/5) was noted in the mid-high and high dose groups. Hypokinesia was noted 6 hours after administration in mid-low dose animals but the animals recovered by the next day. No treatment related signs of toxicity were noted in low dose animals. The high dose was selected as 500 mg/kg based on the results of the preliminary toxicity study.

Negative control: Olive oil

Positive control: Mitomycin C (1 mg/kg), oral (gavage)

Study Validity

A test article was considered to be positive if a statistically significant increase in micronucleated reticulocytes with increased dose was noted in this study.

Solvent control mutant frequencies fell within established ranges. Positive control results were appropriate. The dose range selected for the definitive study was appropriate according to ICH guidelines. This study measured the number of micronucleated cells in peripheral reticulocytes instead of the number of micronucleated cells in bone marrow. This would be an acceptable measure of *in vivo* clastogenicity if the oral bioavailability of the parent compound was adequate.

The oral bioavailability of efinaconazole is very low due to extensive metabolism after oral administration. Therefore, the oral route of administration makes the relevancy of this study questionable. It would have been preferable to conduct the study by a route of administration where extensive metabolism would not have occurred. However, it is not necessary to repeat this study due to the limited extent of systemic exposure to efinaconazole after dermal application for the treatment of onychomycosis.

Results

KP-103 did not induce any statistically significant increases in micronucleated cells in peripheral reticulocytes at any of the doses or timepoints tested in this study.

Hypokinesia was noted until 6 hours after administration in high dose animals. Body weight gain was slightly inhibited on days 3 and 4 after dose administration in high dose animals. No treatment related signs of toxicity were noted in low and mid dose animals.

Allyl Lactate**Study title:** Micronucleus test of C12-C15 Alkyl Lactate in mice

Study no: S11T002

Study report location: SDN 1

Conducting laboratory and location:



Date of study initiation: 10/9/2011

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: C12-C15 Alkyl Lactate, Lot#
01100265392, Purity 95-99%**Key Study Findings**

C12-C15 Alkyl Lactate was negative in the *in vivo* mouse bone marrow micronucleus assay, under the conditions of this experiment.

The relevancy of this study is questionable since the C12-C15 Alkyl Lactate excipient probably would have been rapidly degraded in stomach acid. It would have been preferable to conduct this study by an alternate route of administration. However, it is not necessary to repeat this study due to the anticipated limited extent of systemic exposure to C12-C15 Alkyl Lactate after dermal application for the treatment of onychomycosis.

MethodsDoses in definitive study: 0 (vehicle), 1141, 2283, 4565, or 9130 mg/kg
C12-C15 Alkyl Lactate

Frequency of dosing: Single dose

Route of administration: Oral gavage

Dose volume: 1.25 ml/kg, 1141 mg/kg C12-C15 Alkyl Lactate
2.5 ml/kg, 2283 mg/kg C12-C15 Alkyl Lactate
5 ml/kg, 4565 mg/kg C12-C15 Alkyl Lactate
10 ml/kg, 9130 mg/kg C12-C15 Alkyl Lactate

Formulation/Vehicle: Saline

Species/Strain: Male CD-1 mice

Number/Sex/Group: 6 Males/dose

Satellite groups: N/A

Basis of dose selection: A preliminary toxicity study was conducted with single intraperitoneal injections of 9130, 4565, 2283, or 1141 mg/kg C12-C15 Alkyl Lactate*. The highest dose volume was set at 10 ml/kg followed by 5, 2.5, and 1.25 ml/kg** with a common factor of 2.

In the preliminary study, 3 out of 13 animals died in 9130 mg/kg group within 24 hrs after administration, and surviving animals from this group showed decreases in locomotor activity and proportion of polychromatic erythrocytes in bone marrow.

In the 1141 mg/kg group, no animal showed any apparent toxic signs or symptoms.

Negative control: Saline, 10 ml/kg dose volume
Positive control: Mitomycin C (2 mg/kg), 10 ml/kg dose volume

*The doses used in this study are too high.

** It would have been preferable to vary the test article concentration and administer the same dose volume.

Study Validity

C12-C15 Alkyl Lactate was regarded as being able to induce micronuclei if the total number of micronucleated polychromatic erythrocytes in the C12-C15 Alkyl Lactate groups showed significant and dose-dependent increase compared to the negative control group.

Positive control results were appropriate. Bone marrow smears were prepared 24 hrs after administration in all groups. This study measured the number of micronucleated cells in bone marrow smears.

The validity of this study is questionable since the doses evaluated in this study were too high and elicited too much toxicity. However, it is not necessary to repeat this study due to the anticipated limited extent of systemic exposure to C12-C15 Alkyl Lactate after dermal application for the treatment of onychomycosis.

Results

Decreases in locomotor activity were observed in the mid-low, mid-high and high dose groups. There were significant decreases in body weight in the mid-low, mid-high and high dose groups. The proportions of polychromatic erythrocytes among total erythrocytes in the mid-low, mid-high and high dose groups were significantly lower than in the negative control group, and the decrease was dose-dependent. C12-C15 Alkyl Lactate had an inhibitory effect on the proliferation of myelocytes in this study.

C12-C15 Alkyl Lactate did not induce any statistically significant increases in micronucleated cells in bone marrow smears at any of the doses tested in this study.

7.4 Other Genetic Toxicity Studies

There are no additional genetic toxicity studies.

8 Carcinogenicity

The sponsor submitted a systemic carcinogenicity waiver request for IDP-108 to IND 77732 on 11/27/2009. The sponsor submitted solubility information, a preliminary pharmacokinetic study in rats with IDP-108 administered intravenously and a preliminary pharmacokinetic study in rats with IDP-108 administered orally and subcutaneously to support their justification for a waiver. The systemic carcinogenicity waiver request was granted based on the poor oral bioavailability of IDP-108 and a significantly different metabolism profile after oral versus subcutaneous/dermal administration which makes the conduct of a 2 year oral rat carcinogenicity study not informative for a topical IDP-108 solution. The decision to grant the waiver request was also based on the poor solubility of IDP-108 which makes determination of an acceptable solvent for IDP-108 that would be tolerated in a 2 year subcutaneous rat carcinogenicity study not possible. Thus, conduct of a single dermal mouse carcinogenicity study with the clinical formulation of IDP-108 solution is adequate to assess the carcinogenic potential of IDP-108 solution.

The sponsor conducted a 13 week dermal toxicity study of IDP-108 solution in CD-1 mice as a dose range-finding study prior to initiating the 2 year dermal carcinogenicity study in mice. The 13 week dermal toxicity study of IDP-108 in mice (Study No. DSIN 7001-A6HP-14-08) was previously reviewed under IND 77732.

Concentrations of 0% (vehicle), 3%, 10% and 30% IDP-108 solution were topically administered to mice (15/sex/group) once daily for 13 consecutive weeks. A dose volume of 0.1 ml/animal was used in this study. Vehicle or test article was administered to a 1 x 1 cm² treatment area on the cranial dorsal surface of each animal that was clipped free of hair. The composition of the IDP-108 solution is provided in the following table.

Ingredient	% w/w	% w/w	% w/w	% w/w
IDP-108	0.00	3.00	10.00	30.00
(b) (4) Alcohol, USP	(b) (4)			
Cyclomethicone (b) (4) NF				
Diisopropyl Adipate				
C12-15 Alkyl Lactate				
(b) (4)				
Butylated Hydroxytoluene, NF				

Blood samples for determination of the plasma concentrations of the test article were collected from TK animals (38/sex/group) in cohorts of 3 animals/sex/group prior to dosing and at 1, 2, 4, 8, and 24 hours after dosing on Days 1 and 91.

Mild irritation at the application sites was seen in the treated groups but primarily in the mid and high dose groups. A number of minor changes in clinical chemistry values were observed at the terminal evaluation primarily in the mid and high dose groups. Test article-related organ weight changes consisted of higher liver weights in all dose groups, higher thyroid/parathyroid weights in mid and high dose males, and lower ovary weights in high dose females. The only systemic test article-related microscopic finding consisted of panlobular hepatocellular hypertrophy in the liver of high dose animals. The local application of the test article and/or the vehicle alone resulted in higher incidences of hyperkeratosis, epidermal hyperplasia, and mononuclear infiltrates in the treated skin. Higher concentrations of the test article in the mid and high dose groups were associated with higher severity of these cutaneous changes. These inflammatory cutaneous changes were related to a mild irritant potential of the vehicle that was worsened by higher concentrations of the test article. The local inflammation at the skin sites resulted in higher incidence/severity of several systemic findings that were considered an adaptive response to the cutaneous inflammation and were not direct test article effects, namely granulocytic hyperplasia in the bone marrow, lymphoid hyperplasia in the mandibular lymph nodes, and increased extramedullary hematopoiesis in the spleen. On the basis of the results of this study, the systemic no-observed-adverse-effect-level (NOAEL) was considered to be the 30% concentration of IDP-108. IDP-108 in the vehicle used in this study was a mild skin irritant at all doses and particularly at 10% and 30% IDP-108. A local NOAEL was not determined for this study.

A summary of the toxicokinetic parameters for IDP-108 and the H3 metabolite obtained on day 91 in this study are provided in the two tables below.

Table K. Toxicokinetic Parameters of IDP-108 Estimated on Mean Concentration-Time Data Following Dermal Application of IDP-108 in Mice-Day 91						
Sex	Dose Level (IDP Solution)	T _{max} (hr)	C _{max} (ng/mL)	C _{max} /Dose [(ng/mL)/mg]	AUC _{last} (hr*ng/mL)	AUC ₀₋₂₄ (hr*ng/mL)
Male	3%	1.00	536	179	3421	3421
	10%	2.00	1310	131	13097	13097
	30%	4.00	1410	47.0	19502	19502
Female	3%	1.00	375	125	3332	3332
	10%	4.00	1347	135	11909	11909
	30%	2.00	1377	45.9	15832	15832

Table L. Toxicokinetic Parameters of H3 Estimated on Mean Concentration-Time Data Following Dermal Application of IDP-108 in Mice-Day 91						
Sex	Dose Level (IDP Solution)	T _{max} (hr)	C _{max} (ng/mL)	C _{max} /Dose [(ng/mL)/mg]	AUC _{last} (hr*ng/mL)	AUC ₀₋₂₄ (hr*ng/mL)
Male	3%	1.00	455	152	2354	2354
	10%	2.00	767	76.7	7788	7788
	30%	2.00	894	29.8	11626	11626
Female	3%	2.00	225	75.0	2110	2110
	10%	1.00	380	38.0	4634	4634
	30%	4.00	689	23.0	6837	6837

The T_{max} for IDP-108 occurred within 1 to 4 hours for both sexes and the T_{max} for the metabolite (H3) occurred at 2 hours for males and within 1 to 4 hours for females. The systemic exposure to IDP-108 and H3 increased with dose but the increase was lower than proportional to dose. There were no consistent gender differences in systemic exposure for both IDP-108 and H3.

Study title: IDP-108: A 2 year Dermal Carcinogenicity Study in Mice

Study no.: DSIN 7001-A6HP-15-08
 Study report location: SDN 1 and 2
 Conducting laboratory and location: (b) (4)

Date of study initiation: 4/9/2009
 GLP compliance: Yes. Signed 2/15/2012
 QA statement: Yes. Signed 2/14/2012
 Drug, lot #, and % purity:

0% (Vehicle),	DP1415	
0% (Vehicle),	LB-09059	
3% w/w IDP-108,	LB-09019,	100.7%
3% w/w IDP-108,	LB-09060,	101.2%
10% w/w IDP-108,	DP1418,	102.3%
10% w/w IDP-108,	LB-09061,	101.5%
30% w/w IDP-108,	LB-09020,	104.1%
30% w/w IDP-108,	LB-09062,	102.1%

CAC concurrence: No*.

*The sponsor conducted a dermal 3 month dose range finding study in mice with 3%, 10% and 30% IDP-108 solutions. IDP-108 solution in the vehicle used for this study caused mild skin irritation particularly in the mid and high dose groups. The sponsor proposed to conduct the 2 year dermal carcinogenicity study with a different vehicle containing an additional (b) (4). The Executive Carcinogenicity Assessment Committee (ECAC) recommended that the sponsor conduct a dose range finding study with the to-be-marketed clinical formulation, and submit the study results for consideration, if the to-be-marketed formulation differs from that used in the dose-ranging studies (ECAC meeting date: 12/9/2008). The ECAC meeting minutes were sent to the sponsor on 12/15/2008.

The 2 year dermal mouse carcinogenicity study was conducted with the to-be-marketed formulation. However, the dose-range finding study was conducted with a different formulation. The difference between the dose range-finding formulation and the to-be-marketed formulation is the addition of (b) (4) the to-be-marketed formulation.

The sponsor submitted a request to modify the dermal mouse carcinogenicity study on November 11, 2009. The sponsor indicated that the drug product formulation used in the 2 year dermal carcinogenicity study in mice is the to-be-marketed formulation and differs from the formulation used in the previously conducted 3 month dose range finding study by the addition (b) (4). The sponsor further indicated that beginning at Week 20 the animals presented with skin irritation at the dosing site and by Week 24 55% of the animals in the high dose group, 30% of the animals in the mid dose group and 30% of the animals in the low dose group exhibited severe scabbing. The scabs were generally localized to the cervical region, shoulders and forearms and appeared to be equally

severe in the mid and high dose groups. All animals were placed on a dosing holiday from Week 25 to Week 31 due to skin irritation and scabbing at all doses. At Week 31 the dose volume was decreased from 100 μ L to 50 μ L and the high dose group was terminated at Week 34 due to severe skin effects per comments relayed to the sponsor on November 24, 2009 that had received ECAC concurrence.

Key Study Findings

Skin irritation was observed in all dose groups at Week 20 in this study. The doses exceeded an acceptable skin Maximum Tolerated Dose. The skin irritation was apparently due to the vehicle used in this study. The skin irritation progressed, exacerbated by the IDP-108 test solutions, and a high rate and severity of skin abrasions and scabbing was observed at Week 24, which prompted a drug dosing holiday for all animals from Week 24 to Week 31. The high dose group was terminated at Week 34 due to severe skin reactions.

This carcinogenicity study was conducted with the to-be-marketed formulation. The vehicle used in this carcinogenicity study had severe adverse effects on the skin which resulted in the early termination of the high dose group. However, adequate numbers of mid dose animals survived and enough animals were exposed to the mid dose for a sufficient amount of time to evaluate any potential systemic neoplastic effects. Although the vehicle effects at the treatment site compromised this carcinogenicity study for evaluation of neoplastic skin effects, there were no treatment-related effects on mortality, food consumption, body weight, or body weight gain. There was no treatment related increase in the incidence of neoplasms observed in this study.

Based on the lack of treatment-related systemic effects in the 2 year dermal mouse study, and in consideration of the 9 month dermal minipig study, it is not recommended that the sponsor repeat the 2 year dermal mouse carcinogenicity study. Conduct of another 2 year dermal mouse carcinogenicity study will not provide additional useful information to address the dermal carcinogenic potential of efinaconazole solution. There appears to be no concern for the dermal carcinogenic potential of efinaconazole solution since no hyperplastic/neoplastic lesions were noted in the 9 month dermal minipig study and the extent of local and systemic exposure to efinaconazole is very limited due to the clinical conditions of use (i.e., application of the efinaconazole solution to toenails).

No treatment related effects were observed in minipigs treated with once daily dermal doses of 1/5%, 10%, or 30% IDP-108 solutions for 9 months. 20 μ L/cm² of IDP-108 solution was applied to 10% of the minipig body surface area. Slight hyperkeratosis was noted in skin from dose sites and pathology was similar for tissues from minipigs in treated and vehicle control groups. The high dose (30% IDP-108) is the no-observed-adverse-effect-level (NOAEL) for dermal and systemic toxicity in the 9 month minipig study.

The ECAC concurs with this assessment (See ECAC Meeting Minutes attached in the Appendix).

Adequacy of Carcinogenicity Study

The number of animals/sex/dose group was adequate (60 animals/sex/dose), the duration of dosing was adequate. The high dose (30% IDP-108 solution) was terminated at 34 weeks due to the high rate and severity of scabbing. However adequate numbers of the mid dose animals (10% IDP-108 solution) survived in this study. The MTD was exceeded based on the high rate and severity of scabbing in the high dose group.

Appropriateness of Test Models

The intended route of human exposure is dermal and mice are a preferred species for carcinogenicity testing. The carcinogenicity study was conducted in mice with a dermal route of exposure. The test model was appropriate.

Evaluation of Tumor Findings

No treatment-related increase in the incidence of tumors was observed in this study.

Methods

Doses: 0% (Untreated), 0% (Vehicle Control), 3%,
 10%, 30%
 Frequency of dosing: Daily
 Dose volume: Weeks 1-24, 100µl/mouse
 Weeks 25-31, 6 week drug holiday
 Weeks 34-103, 50µl/mouse
 Route of administration: Dermal (unoccluded 2x3cm² dorsal area)
 Formulation/Vehicle: (b) (4) alcohol, USP, qs (b) (4)
 Cyclomethicone, NF, (b) (4)
 Diisorpopyl adipate, (u) (4)
 C12-C15 alkyl lactate, (u) (4)
 Purified water, (b) (4)
 Butylated hydroxytoluene, NF, (b) (4)
 (b) (4)
 Basis of dose selection: Tolerability of maximum feasible concentration
 after 13 weeks of dosing
 Species/Strain: Crl:CD1(Icr) Mouse
 Number/Sex/Group: 60/sex/group
 Age: 6 Weeks
 Animal housing: Animals were housed individually.
 Paradigm for dietary restriction: Ad libitum
 Dual control employed: Yes
 Interim sacrifice: None
 Satellite groups: None
 Deviation from study protocol: Yes*

* All animals were placed on a dosing holiday from Week 25 to Week 31 due to skin irritation and scabbing at all doses. At Week 31 the dose volume was decreased from 100µL to 50µL and the high dose group (30% IDP-108 solution) was terminated at Week 34 due to severe skin effects per comments relayed to the sponsor on November 24, 2009 that had received ECAC concurrence. The sponsor followed the ECAC's advice as relayed to them during the conduct of the dermal mouse carcinogenicity study.

Observations and Results**Mortality**

Signs of morbidity and mortality of all animals were observed at least twice daily.

Survival in males and females in the low and mid dose groups was similar to the vehicle control and the untreated control groups. Three vehicle males, 4 low dose males, 13 mid dose males, and 12 mid dose females were terminated during Week 34 because of excessive scabbing and abrasions in the dorsal cervical area. All male groups were terminated at Week 102 when the number of males in the vehicle control group reached 20. All females in the mid dose group were terminated at Week 100 when the number of

females in the mid dose group declined to less than 20 females and the remaining female groups were terminated at week 102 when the number of females in the vehicle control group was below 20.

Survival at study termination for males was 35.1%, 55.2%, 44.6%, and 42.6% in the vehicle control, untreated control, low and mid dose groups, respectively. Survival at study termination for females was 30.0%, 44.1%, 35.0%, and 31.3% in the vehicle control, untreated control, low and mid dose groups, respectively.

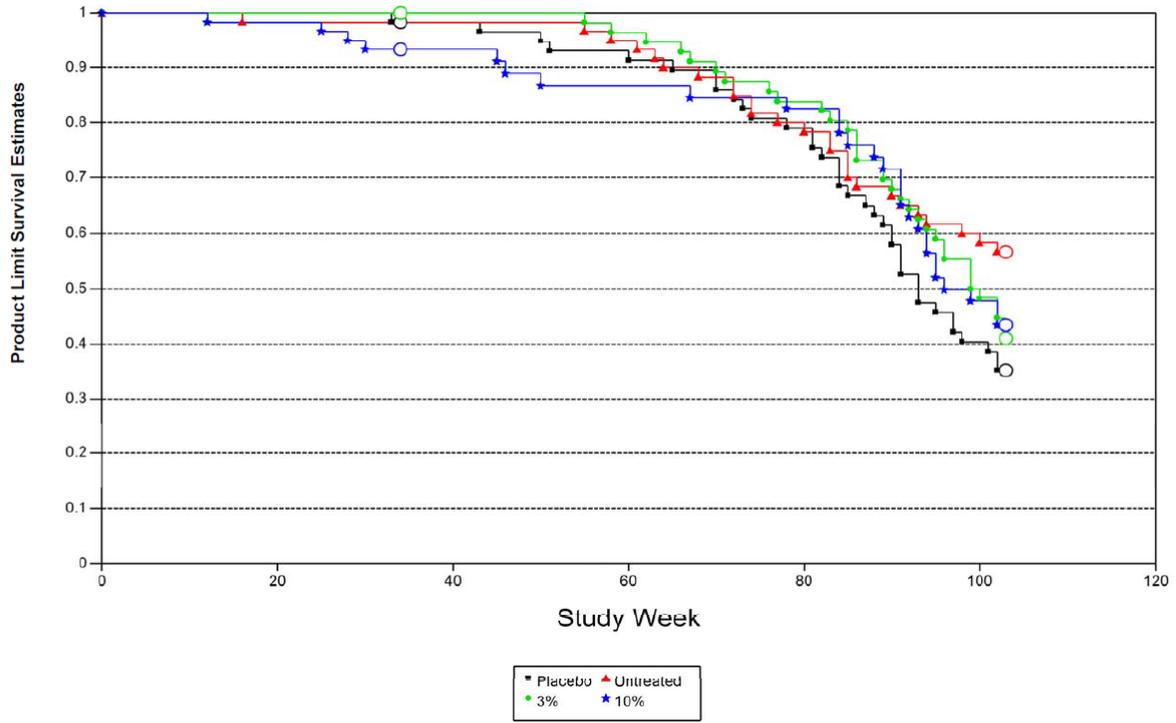
The quarterly survival of each group during the study is given in the table below.

Survival (Weeks)									
Males	-1	13	26	39	52	65	78	91	102*
Placebo	60	60	60	56	53	51	45	30	20
Untreated	60	60	59	59	59	54	48	39	34
3%	60	60	60	56	56	53	47	37	25
10%	60	59	58	43	40	40	39	30	20
* All male groups were terminated in Week 102 when the total survivors in the control group reached 20.									

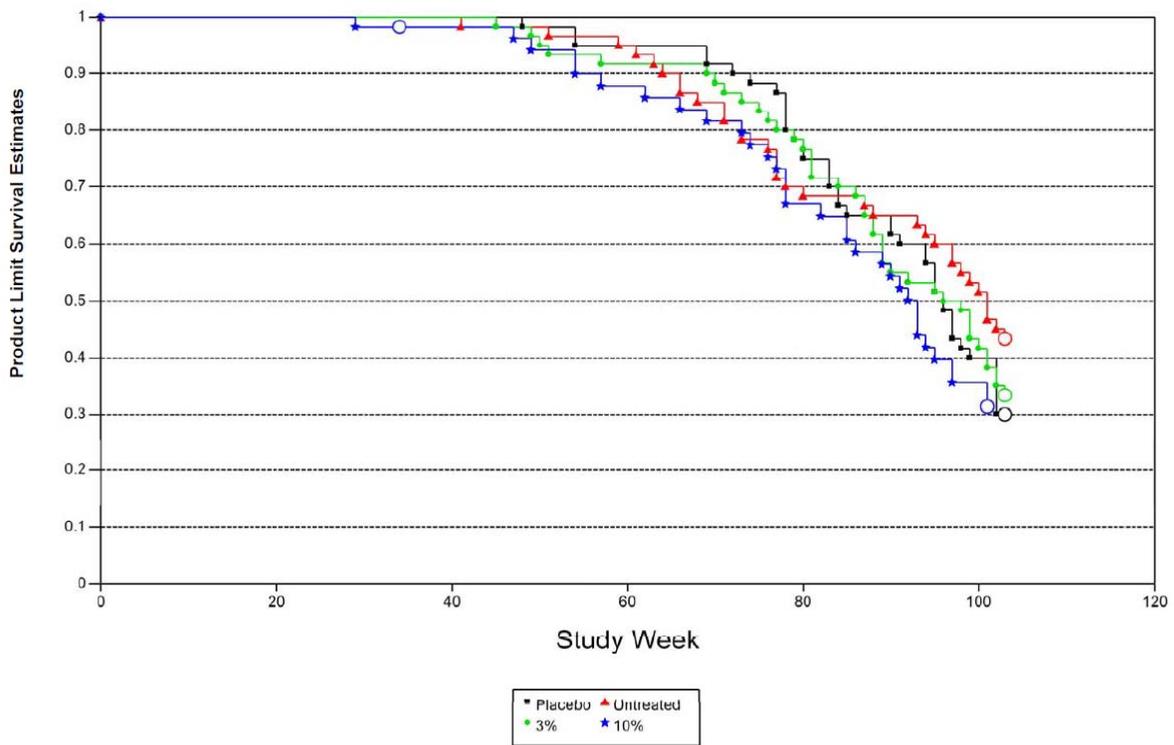
Survival (Weeks)									
Females	-1	13	26	39	52	65	78	91	102
Placebo	60	60	60	60	59	57	48	36	18
Untreated	60	60	60	60	58	54	42	39	27
3%	60	60	60	60	56	55	48	33	21
10%	60	60	60	47	45	41	32	25	17**
**All females at 10% were terminated in Week 100 and the remaining groups were terminated in Week 102.									

The placebo referred to in the survival tables above is the vehicle control.

Summary of Survival Estimates - MALE



Summary of Survival Estimates - FEMALE



There were no treatment-related effects of IDP-108 on survival.

Clinical Signs

Clinical examinations of all animals were performed weekly.

Beginning at Week 20 some animals in the low and mid dose groups had abrasions, scabbing, and swelling at the cervical region. Dorsal application of the test article to the upper back close to the cervical region and application of the higher strengths of test article appeared to exacerbate the incidence of skin lesions. By study Week 24, approximately 30% of the mice in the mid dose group and 55% of the mice in the high dose group exhibited severe scabbing compared to 5% of the animals in the vehicle control group. Scabbing and abrasions with lesser severity were also observed in the untreated control group and the low dose group. There were no other test article-related clinical findings. The other clinical findings noted were common to laboratory mice.

Body Weights

Body weights of all animals were measured and recorded weekly.

At the end of the study the body weights of males in the vehicle control group were 4.2% higher than the body weights of males in the untreated control group. The body weights of males in the mid dose group were lower (-4.5%) than the body weights of males in the vehicle control group. These changes in male mean body weights are not considered biologically significant changes. The body weights of males and females in the low and mid dose groups were comparable to both the vehicle and the untreated control groups.

Feed Consumption

Feed consumption of all animals were measured and recorded weekly. Mean feed consumption for the entire study for treated males and females was comparable to the vehicle control group.

Gross Pathology

At Week 34, test article-related macroscopic findings consisted of abrasion/scab in the treated skin and ears in males at all dose levels. High dose males were terminated due to excessive skin effects and tissues from the high dose group were not analyzed.

Benign follicular cell adenomas were present in the thyroid glands (2/47, 4.3%) of mid dose males. This incident is higher than those recorded in historical control data [up to 1.7%, (b) (4) CD-1 Mouse, (b) (4) 2 Year Studies 10/99 to 10/09]. Although the incidence of benign follicular adenomas in this study is higher (4.3%) than the historical control (1.7%), the incidence of benign follicular adenomas in this study is not statistically significant at $P < 0.01$, which is CDER's recommended level of statistical significant for common tumors.

The National Cancer Institute has determined that the incidence of mouse lymphomas should be combined and analyzed across all sites. Thus, statistical analysis of lymphomas at separate sites is not appropriate. Lymphomas are common tumors in mice and the P value must be less than 0.01 for CDER to consider a common tumor to be statistically significant. The incidence of multicentric lymphomas in treated groups compared to the vehicle control group (low dose group; $P < 0.44$; mid dose group; $P < 0.98$) is not statistically significant. In addition, the incidence of multicentric lymphomas in treated groups compared to the untreated control group (low dose group; $P < 0.26$; mid dose group; $P < 0.94$) is not statistically significant. Similarly, the increased incidence of benign follicular adenomas in the mid dose group compared to the vehicle control group ($P < 0.08$) in this study is not statistically significant and there is no positive trend ($P < 0.21$).

There were no significant test-article-related findings.

Non Neoplastic

Beginning at Week 20 some animals in the mid and high dose groups had abrasions, scabbing, and swelling at the cervical region. Dorsal application of the test article to the upper back close to the cervical region and application of the higher strengths of test article appeared to exacerbate the incidence of skin lesions. By study Week 24, approximately 30% of the mice in the mid dose group and 55% of the mice in the high dose group exhibited severe scabbing compared to 5% of the animals in the vehicle control group. Scabbing and abrasions with lesser severity were also observed in the untreated control group and the low dose group. At the end of the study, skin irritation was observed at the treatment site at all doses. This skin irritation may be related to vehicle.

The treated skin of animals that were euthanized at Week 34 was examined microscopically. Treatment-related findings consistent with severe irritation were observed at the treatment site during Week 34. These treatment related skin effects were exacerbated by the application of IDP-108 solution to irritated and abraded skin.

At the end of the study, test article-related microscopic non-neoplastic findings were present in the treated skin and liver in males and females in the low and mid dose groups. The following microscopic changes in treated skin were increased in incidence or severity in males and females in the low and mid dose groups compared to the vehicle control group: epidermal hyperplasia, hyperkeratosis, serocellular crust, subacute/chronic inflammation in the dermis, mast cell aggregates in the dermis. These

changes were considered secondary to a mild irritant effect of the test article and did not progress to erosion/ulcers. No dose response between the low and mid dose groups was observed.

Test Article-related Microscopic Observations - Terminal								
Dose level	Placebo		Untreated		3%		10%	
Sex	M	F	M	F	M	F	M	F
Number Examined	57	60	60	60	56	60	47	48
Skin, treated								
Aggregates, mast cell	0	33	0	0	14	47	9	31
-minimal	0	33	0	0	13	41	9	22
-mild	0	0	0	0	1	5	0	9
-moderate	0	0	0	0	0	1	0	0
Crust, serocellular	1	1	1	0	4	3	2	7
-minimal	1	1	0	0	3	2	2	4
-mild	0	0	0	0	1	0	0	3
-moderate	0	0	0	0	0	1	0	0
-severe	0	0	1	0	0	0	0	0
Hyperkeratosis	17	25	1	0	30	47	29	28
-minimal	14	16	1	0	18	23	15	9
-mild	3	8	0	0	11	22	11	10
-moderate	0	1	0	0	1	2	3	9
Hyperplasia, epidermal	46	44	1	0	51	56	43	29
-minimal	20	17	1	0	8	8	8	6
-mild	26	27	0	0	43	47	29	19
-moderate	0	0	0	0	0	1	6	4
Inflammation, subacute/chronic	2	1	0	1	8	20	5	18
-minimal	2	1	0	1	8	18	4	12
-mild	0	0	0	0	0	2	1	6
M - Male F - Female								

Toxicokinetics

N/A

Dosing Solution Analysis

All dosing solutions were evaluated and were found within the appropriate target concentrations.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study 1

Preliminary study of fertility and early embryo development to implantation in rats treated subcutaneously with KP-103. Study No. ST950305.

KP-103 was dissolved in propylene glycol (vehicle) and administered subcutaneously to non-pregnant adult rats once daily for 14 days at a dose of 0.4, 2.0, 10 and 50 mg/kg. Skin thickening in the injection site was observed in animals at the dose of 50 mg/kg/day. Therefore, the highest dose for the pivotal fertility and early embryofetal development study was set at 25 mg/kg/day, and the mid and low dose levels were set at 5 and 1 mg/kg/day, respectively, using a common ratio of 5. The dose volume was set at 2.0 ml/kg.

Study 2

Study title: Study of fertility and early embryonic development to implantation in rats treated subcutaneously with KP-103.

Study no.: Study No. ST031

Study report location: SDN 1

Conducting laboratory and location:

(b) (4)

Date of study initiation: 12/26/1995

GLP compliance: Yes.

QA statement: Provided but not signed.

Drug, lot #, and % purity: KP-103, Lot # 94Z22, 99.5%

Propylene glycol, Lot # ESG5942, 99.1%

Key Study Findings

Skin thickening at the injection site was observed in KP-103 treatment groups, and a subcutaneous nodule in the injection site was histopathologically found in vehicle control and each KP-103 treatment group. In the high dose group, there was an increase in spleen weight of males. Micro-vacuolation of peripheral hepatocytes was observed in the mid and high dose groups, and slight extramedullary hematopoiesis was observed in the high dose group.

A tendency to slightly prolong the estrous cycle in females was observed in the high dose group, but the copulation index was 100% in all the groups. There was no alteration in the fertility index and/or the insemination index as a result of KP-103 administration. No significant differences between the vehicle control group and the KP-

103 treatment groups were observed in the number of sperm, sperm motility and the percentage of abnormal sperm. There were no KP-103 related effects on the number of corpora lutea, the number of implantations and the number of live embryos in pregnant animals.

Based on the above findings, the no observed adverse effect level (NOAEL) of KP-103 was 5 mg/kg/day for maternal toxicity, and 25 mg/kg/day for fertility and early embryonic development.

Methods

Doses:	0 (Untreated control), 0 (Vehicle control), 1, 5, and 25 mg/kg/day
Frequency of dosing:	Once daily, 7 days per week
Dose volume:	2 ml/kg
Route of administration:	Subcutaneous injection into the clipped dorsal back
Formulation/Vehicle:	Propylene glycol, neat
Species/Strain:	Crj:CD(SPF) rats
Number/Sex/Group:	16/sex/group
Satellite groups:	NA
Study design:	Males were dosed from 28 days before the start of mating through the mating period until Day 20, the day before necropsy. Females were dosed from 14 days before the start of mating through the mating period until day 7 of gestation.
Deviation from study protocol:	Yes, but the deviations did not affect the integrity of the study or the interpretation of the study results.

Observations and Results

Mortality

All animals were observed twice daily for signs of morbidity and mortality.

No animals died during the study.

Clinical Signs

Clinical signs were observed 3 times daily during the dosing period, and once daily after the dosing period. The injection sites were observed once daily during the pre-mating / dosing period and during pregnancy.

There were no test article-related changes in clinical signs.

Skin thickening at the injection site was observed in KP-103 treatment groups,

Body Weight

Body weight was measured twice a week in males, and every other day during the pre-mating / dosing period and during pregnancy in females.

There were no test article-related changes in body weight.

Feed Consumption

Daily feed consumption was calculated from the differences between the amount of feed supplied and the amount of feed left twice a week during the pre-mating / dosing period in males, and every other day during pre-mating / dosing period and during pregnancy in females.

There were no test article-related changes in feed consumption.

Toxicokinetics

NA

Dosing Solution Analysis

All dosing solutions were analyzed and were found between 99.5% and 100.6% of target concentrations.

Necropsy

The ovaries and uterus of all females were fixed in 20% neutral buffered formalin solution, hematoxylin and eosin stained specimens were prepared and examined histopathologically.

After the end of the terminal examination (cesarean section and necropsy) on females, all males were sacrificed by exsanguinations via the abdominal aorta under ether anesthesia and major organs/tissues in the thoracic and abdominal cavities were examined macroscopically.

The liver, spleen, kidneys, adrenal glands, prostate, testis seminal vesicle and epididymis were removed, and weighed. The organs/tissues in which abnormalities were observed were fixed in 20% neutral buffered formalin solution and the testis and epididymis of all males in Bouin's solution. The liver, spleen and skin of 4 males out of each group were fixed in 20% neutral buffered formalin solution, hematoxylin and eosin stained specimens were prepared and examined histopathologically.

Subcutaneous nodule in the injection site was histopathologically evaluated in the vehicle-control and each KP-103 treatment group.

In the high dose group, there was an increase in spleen weight of males. Micro-vacuolation of peripheral hepatocytes was observed in the mid and high dose animals, and slight extramedullary hematopoiesis was observed in the high dose animals.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Sperm was collected from the left cauda epididymis of all males, and the number of sperm was counted and the sperm motility was calculated. After preparation of sperm smears, its morphological observation was evaluated.

No significant differences between the vehicle control group and the KP-103 treatment groups were observed in the number of sperm, sperm motility and the percentage of abnormal sperm.

For all females, vaginal smears were taken every day during the pre-mating / dosing period and the mating period. After the end of the pre-mating / dosing period, males and females from the same group were housed together overnight on a one-to-one basis with a cohabitation period of up to 14 days. If the presence of vaginal plugs or sperm in vaginal smears were found, it was considered that copulation had occurred. The day of copulation was designated as day 0 of gestation.

A tendency to slightly prolong the estrous cycle in females was observed in the high dose group, but the copulation index was 100% in all the groups. A table that summarizes these effects is provided below.

SOT031 Fertility and Early Embryonic Development of KP-103 in Rats

96/11/15 13:19

Table 12 Estrous cycle before and during mating in animals(F0)

Generation : F0					
Group	Intact Control	Vehicle Control	KP-103	KP-103	KP-103
Dose (mg/kg/day)	0	0	1	5	25
Number of Animals	16	16	16	16	16
Regular Cycle (%)	16 (100.0)	16 (100.0)	16 (100.0)	15 (93.8)	10 (62.5)
Irregular Cycle (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	6 (37.5)
1 : Conti.-Es (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 : Conti.-Di (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)
3 : Conti.-Me (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 : 5 day (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	2 (12.5)
5 : 6 day (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 : 7 day (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Conti.-Es: Continuous estrus

Conti.-Di: Continuous diestrus

Conti.-Me: Continuous metaestrus

There was no alteration in the fertility index and/or the insemination index as a result of KP-103 administration.

Females with successful copulation were sacrificed on day 14 of gestation by exsanguination via the abdominal aorta under ether anesthesia and major organs/tissues in the thoracic and abdominal cavities were examined macroscopically. The ovaries and uterus were removed to macroscopically examine for implantation. For females in which implantations were observed, the number of dead embryos, live embryos and corpora lutea were counted.

There were no KP-103-related effects on the number of corpora lutea, the number of implantations and the number of live embryos in pregnant animals. A table that summarizes these effects is provided below.

Group	Intact Control	Vehicle Control	1 mg/kg	5 mg/kg	25 mg/kg
Number of Dams	15	14	13	16	15
Corpora Lutea					
Total	254	228	210	257	247
Mean \pm SD	16.9 \pm 1.2	16.3 \pm 1.4	16.2 \pm 2.3	16.1 \pm 1.4	16.5 \pm 1.5
Implantations					
Total (%)	240 (94.8)	221 (97.1)	200 (95.8)	256 (99.6)	233 (94.8)
Mean \pm SD	16.0 \pm 1.6	15.8 \pm 1.3	15.4 \pm 1.7	16.0 \pm 1.4	15.5 \pm 2.2
Pre-implantation Loss					
Total (%)	14 (5.2)	7 (2.9)	10 (4.2)	1 (0.4)	14 (5.2)
Post-implantation Loss					
Total (%)	25 (10.6)	10 (4.5)	6 (3.0)	13 (4.9)	20 (8.6)
Early Total (%)	25 (10.6)	10 (4.5)	6 (3.0)	13 (4.9)	20 (8.6)
Late Total (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Live Fetus					
Total (%)	215 (89.4)	211 (95.5)	194 (97.0)	243 (95.1)	213 (91.4)
Mean \pm SD	14.3 \pm 3.7	15.1 \pm 1.6	14.9 \pm 1.8	15.2 \pm 1.3	14.2 \pm 2.2

Implantations(%) = No. of implantations / No. of Corpora Lutea x 100

Live Fetus(%) = No. of Live Embryos / No. of Implantations x 100

Early Total = No. of Implantations sites + No. of Resorptions

Late Total = No. of Dead fetuses

9.2 Embryonic Fetal Development

Study 3

Preliminary study of the effects on embryofetal development in rats treated subcutaneously with KP-103. Study No. ST960307.

A preliminary study of the effects of KP-103 on embryofetal development in pregnant rats was conducted with subcutaneous doses of 0 (vehicle; propylene glycol), 2, 10, or 50 mg/kg/day KP-103 administered from Day 6-16 of gestation. There were no effects on body weight and feed consumption at the high dose. Skin thickening and induration at the injection site and an increase in placental weight were observed in high dose animals. There were no adverse effects on the pregnant female and development of the embryo and fetus in the low and mid dose groups. Based on these results, 50 mg/kg/day was chosen as the high dose for the pivotal rat embryofetal development study. Then 10 and 2 mg/kg/day were chosen as the mid and low doses, respectively, according to a ratio of 5. The dose volume was set at 2 ml/kg.

Study 4

Study title: Effects of subcutaneous KP-103 treatment on embryofetal development.

Study no.: Study No. SPT018.
Study report location: SDN 1
Conducting laboratory and location:  (b) (4)
Date of study initiation: 10/18/1996
GLP compliance: Yes.
QA statement: Yes.
Drug, lot #, and % purity: KP-103, Lot # 94Z22, 100.6%
Propylene glycol, Lot # DLJ5354, 99.3%

Key Study FindingsEffects on pregnant rats

Skin thickening at the injection site, reduced body weight gain from Day 16 of gestation and reduced feed consumption from Day 15 of gestation was observed at the high dose. In addition, macroscopic examination found subcutaneous nodule at the injection site and swelling of the spleen at the high dose. Subcutaneous nodule at the injection site was observed in 2 animals at the mid dose.

Effects on the placenta

In the histopathological examination of placenta, vacuolar degeneration of decidua cells and fibrinoid necrosis of decidua basalis were observed at the mid dose or higher. In addition, dilatation, fibrinoid deposit and hemorrhage of intervillous space were observed at the high dose. The effects noted in the placenta in the high dose dams may be related to the increased embryofetal deaths and decreased number of live fetuses noted in the high dose group. There were no treatment-related abnormalities at the low dose.

Effects on fetuses

An increase in the number of embryofetal deaths and decrease in the number of live fetuses were noted at the high dose. Increases in the number of lumbar ribs and increases in the number of fetuses having skeletal variations were found at the high dose. In the visceral examination, there were no treatment-related abnormalities in any of the groups.

Based on the skin thickening and subcutaneous nodule at injection site and the effects on the placenta, the maternal NOAEL for KP-103 is 2 mg/kg/day. The developmental NOAEL is 10 mg/kg/day based on the increase in the number of embryofetal deaths and decrease in the number of live fetuses. The increases in the number of lumbar ribs and increases in the number of fetuses having skeletal variations noted in the high dose

group is considered treatment related but not of biological concern. The NOAEL for treatment related malformations is 50 mg/kg/day.

Methods

Doses: 0 (Untreated control), 0 (Vehicle control), 2, 10 and 50 mg/kg/day
Frequency of dosing: Once daily 7 days per week
Dose volume: 2ml/kg
Route of administration: Subcutaneous injection into the clipped dorsal back
Formulation/Vehicle: Propylene glycol, neat
Species/Strain: Crj:CD(SPF) rats
Number/Sex/Group: 20 Females/group
Satellite groups: NA
Study design: Pregnant females are dosed from Day 6 to 16 of gestation and necropsied on gestation Day 19.
Deviation from study protocol: Yes, but the deviations did not affect the integrity of the study or the interpretation of the study results.

Observations and Results

Mortality

The pregnant animals were observed for morbidity and mortality at least once daily and twice daily during the dosing period.

No animals died during the study.

Clinical Signs

Clinical signs were observed at least once daily and twice daily during the dosing period. The injection sites were observed once daily during the dosing period and on Day 20 of gestation.

There were no test article-related changes in clinical signs.

Skin thickening was observed in several high dose animals from the second day of administration and in all high dose animals from Day 13 of gestation, but it was attenuated on Day 20 of gestation. Skin thickening was observed in only one mid dose animal from Day 16 of gestation. No skin thickening was observed in low dose or vehicle control animals. Scab formation was observed in several animals in the vehicle control group and all KP-103 treated groups.

Body Weight

The weight of each female was recorded on Days 0, 3, 6-18 and 20 of gestation.

An 11% reduction in body weight gain was noted from Day 16 of gestation in high dose animals, compared to the vehicle control.

Feed Consumption

Daily feed consumption was calculated from the differences between the amount of feed supplied and the amount of feed left on Days 0, 3, 6, 9, 12, 15, 18 and 20 of gestation.

A 6% reduction in feed consumption was noted from Day 15 of gestation in high dose animals, compared to the vehicle control.

Toxicokinetics

NA

Dosing Solution Analysis

All dosing solutions were analyzed and were found between 99.3% and 100.6% of target concentrations.

Necropsy

The dams were sacrificed by exsanguination from the posterior vena cava and abdominal aorta under ether anesthesia in the afternoon on Day 20 of gestation. Evidence of pregnancy was examined and major organs/tissues in the thoracic and abdominal cavities were examined macroscopically. The injection sites of 3 animals in each group and regions showing macroscopic abnormality were fixed in 20% neutral buffered formalin solution, hematoxylin and eosin stained specimens were prepared and examined histopathologically.

In the untreated and the vehicle control groups, 2 and 1 animal, respectively, were found to be non-pregnant. Subcutaneous nodule at the injection site was noted in 16 dams in the high dose group and 2 dams in the mid dose group. Swelling of the spleen was noted in 10 dams in the high dose group. These findings are treatment-related.

At the injection site, subcutaneous hemorrhage, edema, proliferation of fibroblast, fibrosis, regeneration of muscle-fiber, vascularization, infiltration of inflammatory cell, foreign body and appearance of giant cell were observed in the vehicle control group and all KP-103 treated groups. An increased degree of fibroblast proliferation, fibrosis, regeneration of muscle-fiber and vascularization was noted in the high dose group compared with the vehicle control.

Extramedullary hematopoiesis and proliferation of megakaryocyte in the spleen and nephroblastoma in the kidney were observed at 50 mg/kg/day. Dilatation of renal pelvis in kidney was observed in the vehicle control group.

The following effects were noted in the placenta of mid and high dose animals. Vacuolar degeneration of decidua cells was noted in 4 high dose dams. Fibrinoid necrosis of decidua basalis, dilatation of intervillous space and fibrinoid deposit in intervillous space was noted in all high dose dams. Hemorrhage in intervillous space was noted in 2 high dose dams. Vacuolar degeneration of decidua cells was noted in 4 mid dose dams. Fibrinoid necrosis of decidua basalis was noted in 1 mid dose dam. There were no abnormalities in the decidua basalis and the intervillous space of the placenta in untreated control, vehicle control and low dose groups.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

For each pregnant animal, the number of corpora lutea in each ovary, the number of implantation sites and live and dead fetuses was counted, and the implantation index and embryofetal mortality were calculated.

The number of corpora lutea, the number and percent of implantations, sex ratio and live fetal bodyweights, in any of KP-103 treated groups were comparable to the vehicle control. On the other hand, an increase in the number of dead fetuses, a reduction in the number of live fetuses and increase in placental weight and diameter were found in the high dose group compared to the vehicle control.

Resorption of all embryos was observed in 2 dams in the high dose group. External abnormalities noted in this study included craniorachischisis and omphalocele in 1 fetus in the untreated group, agnathia in 1 fetus in the low dose group and generalized edema in 1 fetus in the high dose group. Although the sponsor did not provide historical control data for this study, these effects are noted in only a few embryos and are not observed in a dose-dependent manner. Therefore, these effects are not considered as treatment related effects.

Offspring (Malformations, Variations, etc.)

The live fetuses were examined for external abnormalities including those in the oral cavity, sexed and weighed. Each placenta was weighed and its diameter was measured using a caliper. The placentas of 5 dams/group were histopathologically examined. About half of the fetuses of each dam were examined for visceral abnormalities and the remaining fetuses were examined for skeletal abnormalities. The fetuses for visceral examination were fixed in Bouin solution. The head and abdominal organs and thoracic organs were observed for abnormalities and variations according to Wilson method and to microdissection method, respectively. The fetuses for skeletal examination were fixed in 99% ethanol and prepared into transparent skeletal specimens with alizarin red staining and observed to examine progress of ossification as well as abnormalities and variations.

Visceral abnormalities noted in this study included ventricular septal defect in the untreated control group, the vehicle control group, the low dose group, the mid dose group and the high dose group. Dilatation of lateral ventricle (external abnormality; agnathia) was observed in the mid dose group. These effects are not considered treatment related due to the low incidence of these findings noted across treatment groups and no dose response.

The table below contains the visceral anomalies noted during this study.

Reviewer's comment: The "Intact Control" group referred to in the tables below is the "Untreated control" group.

SPT018 Study for effects on embryo-fetal development of KP-103 in rats
Table 10 Visceral anomalies of fetuses(F1) at cesarean section

Group	Intact Control	Vehicle Control	2mg/kg	10mg/kg	50mg/kg
Dose (mg/kg/day)	0	0	2	10	50
No. of Dams	18	19	20	20	18
No. of Dams with Anomalies (%)	4 (22.2)	1 (5.3)	2 (10.0)	2 (10.0)	1 (5.6)
No. of Examined	184	142	143	142	111
No. of Anomalies (%)	4 (2.7)	1 (0.7)	2 (1.3)	4 (2.6)	1 (0.7)
Lateral Ventricle Dilatation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Ventricular Septal Defect	4 (2.7)	1 (0.7)	1 (0.7)	4 (2.6)	1 (0.7)

Visceral variations noted in this study included thymic remnant in the neck and dilatation of renal pelvis in each dose group including the control groups. These visceral variations are commonly observed in rats and are not considered to be treatment related.

The table below contains the visceral variations noted during this study.

SPT018 Study for effects on embryo-fetal development of KP-103 in rats

Table 11 Visceral variations of fetuses(F1) at cesarean section

Group	Intact Control	Vehicle Control	2mg/kg	10mg/kg	50mg/kg
Dose (mg/kg/day)	0	0	2	10	50
No. of Dams	18	19	20	20	18
No. of Dams with Variations (%)	6 (33.3)	4 (21.1)	6 (30.0)	4 (20.0)	3 (16.7)
No. of Examined	134	142	143	142	111
No. of Variations (%)	8 (5.9)	4 (2.8)	11 (7.3)	4 (2.8)	6 (4.5)
Thymus Remnant in neck	3 (2.0)	3 (2.1)	4 (2.7)	1 (0.6)	2 (1.5)
Renal Pelvis Dilatation	5 (3.9)	1 (0.8)	7 (4.6)	3 (2.2)	4 (3.0)

Skeletal abnormalities noted in this study included wavy rib in one dam in the vehicle control group and one dam in the high dose group.

The table below contains the skeletal anomalies noted during this study.

SPT018 Study for effects on embryo-fetal development of KP-103 in rats

Table 12 Skeletal anomalies of fetuses(P1) at cesarean section

Group	Intact Control	Vehicle Control	2mg/kg	10mg/kg	50mg/kg
Dose (mg/kg/day)	0	0	2	10	50
No. of Dams	18	19	19	20	18
No. of Dams with Anomalies (%)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.6)
No. of Examined	129	131	130	131	103
No. of Anomalies (%)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	2 (1.9)
Rib Wavy	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	2 (1.9)

Skeletal variations noted in this study included an increase in the number of fetuses with lumbar rib (bilateral, unilateral + bilateral) in the high dose group compared to the vehicle control. Unilateral cervical rib, splitting of thoracic vertebral body, dumbbell shape of lumbar vertebral body, short 13th rib, splitting and asymmetry of sternbrae were also noted in the high dose group. Refer to the table below for a summary of these findings.

SPT018 Study for effects on embryo-fetal development of KP-103 in rats

Table 13 Skeletal variations of fetuses(F1) at cesarean section

Group	Intact Control	Vehicle Control	2mg/kg	10mg/kg	50mg/kg
Dose (mg/kg/day)	0	0	2	10	50
No. of Dams	18	19	19	20	18
No. of Dams with Variations (%)	13 (72.2)	11 (57.9)	16 (84.2)	12 (60.0)	17 (94.4)*
No. of Examined	123	131	130	131	103
No. of Variations (%)	36 (29.4)	21 (15.5)	37 (30.5)	20 (15.0)	52 (49.6)**,#
Thoracic Vertebral Body Splitting	1 (0.7)	1 (0.8)	6 (4.7)	1 (0.7)	1 (0.8)
Dumbbell shape	15 (12.9)	13 (9.7)	21 (17.1)	5 (4.2)	22 (22.7)
Rib 13th Short	1 (0.8)	1 (0.7)	1 (0.8)	0 (0.0)	0 (0.0)
Sternebrae Splitting	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (2.6)
Asymmetry	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (3.0)
Lumbar Vertebral Body Dumbbell shape	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Lumbar Rib Unilateral	8 (5.9)	5 (3.7)	12 (10.2)	6 (4.4)	13 (10.8)
Bilateral	14 (11.4)	0 (0.0)	3 (2.4)	6 (4.3)	18 (16.4)**
Unilateral+ Bilateral	22 (17.9)	5 (3.7)	15 (12.6)	12 (8.7)	31 (27.2)**
Cervical Rib Unilateral	0 (0.0)	0 (0.0)	2 (1.5)	2 (1.4)	2 (1.7)

Significantly different from Vehicle Control-Group, *P<0.05, **P<0.01
 Significantly different from Intact Control-Group, #P<0.05

The small increase in bilateral lumbar rib variation and unilateral + bilateral lumbar rib variation in the high dose compared to the untreated control is not considered biologically relevant. No significant increase in drug related malformations was noted in this rat embryofetal development study.

Study 5

A subcutaneous injection dose-range finding study of the effects of IDP-108 on embryofetal development in rabbits. Study No. DSIN-7001-A6HP-18-08.

In a preliminary study, IDP-108 was dissolved in the vehicle, propylene glycol (neat), and administered via subcutaneous injection to 3 groups of 6 time-mated female New Zealand White rabbits once daily from gestation days 6 through 19. Dosage levels were 0.5, 5 and 50 mg/kg/day and the dose volume was 2 ml/kg. A concurrent control group composed of 6 time-mated females received the vehicle (propylene glycol) on a comparable regimen. The high dose group was terminated on gestation day 8 due to severe local irritation at the injection sites. On gestation day 11, the 0.5 mg/kg/day group was divided into 2 groups of 3 females each. One group continued to be administered 0.5 mg/kg/day, and the other group was administered 10 mg/kg/day. The females were approximately 6 months of age at the initiation of dose administration. All animals were observed twice daily for mortality and moribundity. Clinical and injection site observations, body weights and feed consumption were recorded at appropriate intervals. On gestation day 29, a laparohysterectomy was performed on each surviving female. The uteri, placentas and ovaries were examined; placental weights and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed and examined for external malformations and developmental variations.

All females in the highest dose group were euthanized in extremis on gestation day 8 (following administration of the first dose) due to severe localized effects of the test article in combination with the vehicle at the injection sites. These findings consisted of erythema (very slight to moderate), very slight edema, blanching and brown discoloration. No test article-related effects on body weight or feed consumption parameters were noted in this group prior to euthanasia.

One female in the mid dose group was also euthanized in extremis on gestation day 20 due to an open lesion at the injection site. There was no dose-related trend observed for the injection site findings, therefore the localized effects observed at the injection site are due to the vehicle, not the test article.

All other females survived to the scheduled necropsy. No test article-related clinical findings were noted at any dosage level. However, irritation at the injection sites was noted in all groups, including the vehicle control group. There were no dose-related trends in the onset of occurrence or severity in these findings, which included erythema and edema (very slight to severe), fissuring, desquamation, eschar, exfoliation, blanching, subcutaneous hemorrhage, brown discoloration and coriaceousness. Therefore these findings are attributed to localized effects of the vehicle.

At necropsy, 2 vehicle control group animals were determined to be nongravid. All other study females were gravid. Therefore, for statistical comparison, the number of animals

for which data were analyzed in each group was 4, 3, 6, and 3 in the vehicle control group, low dose, mid dose, and high dose groups, respectively. A lower (67%) mean body weight gain was noted in the high dose group during the treatment period (gestation days 6-19). Mean body weight gain recovered to control group levels in the high dose group after dosing ended (gestation days 21-29). No change in mean body weights or mean body weight gains was noted in the low and mid dose groups. Gravid uterine weights in the low, mid and high dose groups were unaffected by test article administration. Intrauterine growth and survival and placental weights were unaffected by test article administration at the low, mid and high dose groups. No external fetal malformations or developmental variations were noted in any fetuses in any dose group in this study.

A dose of 10/mg/kg/day induced maternal toxicity manifested as lower (67%) mean body weight gain over the entire treatment period (gestation days 6-19). Mean body weight gain recovered to the control group levels after dosing ended (gestation days 21-29). No systemic toxicity was induced in the low or mid dose groups. No effects on teratogenic endpoints were elicited at any dose in this study. Based on these findings, the high-dose level in the definitive rabbit embryofetal developmental toxicity study was set at 10 mg/kg/day.

Study 6

Study title: A subcutaneous and toxicokinetic study of the effects of IDP-108 on embryofetal development in rabbits.

Study no.:	DSIN-7001-A6HP-20-08
Study report location:	SDN 1
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	6/30/2008
GLP compliance:	Yes.
QA statement:	Yes.
Drug, lot #, and % purity:	IDP-108, lot # 26114, 100.25% Propylene glycol, lot # 080676 and 08139, 99.7%

Key Study Findings

Maternal toxicity was observed in the high group. Lower mean body weight gains (35% lower) with corresponding decreased feed consumption were noted in the high dose group over the treatment period when compared to the control group. The decreases in mean body weights and feed consumption correlated to an increase of soft stool in the high dose group. Although maternal toxicity was evident in the high dose group, there were no indications of test article related effects on embryofetal development. Intrauterine growth and fetal morphology was not affected by test article administration at any dose level.

Based on the decreased mean body weight gains and decreased feed consumption in the high dose group, a dose level of 5 mg/kg/day is the NOAEL for maternal toxicity. Based on the absence of an effect on embryofetal development and malformations, a dose level of 10 mg/kg/day, the highest dose level evaluated, is the NOAEL for embryofetal development and malformations when IDP-108 is administered in propylene glycol via subcutaneous injection to pregnant New Zealand White rabbits.

Methods

Doses:	0 (Vehicle control), 1, 5, and, 10 mg/kg/day
Frequency of dosing:	Daily 7 days per week
Dose volume:	1ml/kg
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	Propylene glycol, neat
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	23 females/group
Satellite groups:	3 females/group-toxicokinetic
Study design:	Time-mated females were dosed during gestation Days 6-19. Laparohysterectomies were performed on gestation Day 29. TK animals euthanized on gestation Day 21.
Deviation from study protocol:	Yes, but the deviations did not affect the integrity of the study or the interpretation of the study results.

Observations and Results

Mortality

All rabbits were observed twice daily, once in the morning and once in the afternoon, for moribundity and mortality.

Three and 2 females in the vehicle control and high dose groups, respectively, were euthanized in extremis between gestation days 15 and 22 due to severe localized effects at the injection sites that included desquamation, erythema (very slight to severe), edema (very slight to moderate), eschar, blanching and brown discoloration 1-3

days prior to and on the day of euthanasia. In the surviving females in the low, mid and high dose groups, additional injection site observations included desquamation and subcutaneous hemorrhage. These findings are due to the irritating properties of the vehicle (propylene glycol).

All females in the toxicokinetic phase survived to the scheduled euthanasia on gestation Day 21.

Clinical Signs

Clinical signs were evaluated daily. The dermis surrounding the injection sites was scored daily (prior to and approximately 3 hours following dose administration) during and following the treatment period for erythema and edema in accordance with the Draize 4-step grading system.

Single occurrences of vocalization upon dosing and upon return to the cage in 2, 1, 6 and 4 females in the vehicle control, low, mid and high dose groups.

Erythema (very slight to severe) and edema (very slight to moderate), desquamation, eschar, blanching, exfoliation, subcutaneous hemorrhage and brown discoloration were observed at the injection sites of animals in all groups.

Body Weight

Individual maternal body weights were recorded on gestation days 0, 4, 7-21 (daily), 24 and 29 for the embryofetal development phase and on gestation days 0, 4 and 6-19 (daily) for the toxicokinetic phase.

A decrease in mean body weight gain (35% lower) with corresponding decrease in feed consumption was noted in the high dose group during treatment (Days 6-19). No treatment related decrease in body weight gain was noted in the low and mid dose groups.

Feed Consumption

Individual feed consumption was recorded on gestation days 4-29 (daily).

Mean feed consumption in the high dose group was 17% lower than the vehicle control group. The reduced feed consumption observed in the high dose group corresponds to the lower mean body weight gains noted during the treatment period. Feed consumption in the low and mid dose groups was unaffected by test article administration.

Toxicokinetics

Blood samples (approximately 1 ml each) for toxicokinetics were collected from all animals on gestation days 6 and 19 at 0 (pre-dose), 1, 4, 6, 8 and 24 hours after dose administration.

A summary of the toxicokinetic parameters for IDP-108 and the H3 metabolite obtained on gestation Days 7 (which is actually gestation day 6) and 20 (which is actually gestation day 19) in this study are provided in the table below.

Text Table 3. Pharmacokinetic Parameters for IDP-108 and Metabolite H3 in Female Rabbits

IDP-108 Dosage (mg/kg/day)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)	t _{1/2} (h)
IDP-108					
<u>GD 7</u>					
1	18.6±5.4	2.0±1.7	181±38	181±38	10.7±1.5
5	164±106	1.0±0	1242±346	1242±346	9.26±2.34
10	193±80	3.7±2.5	2355±521	2355±521	9.31±2.06
<u>GD 20</u>					
1	51.0±4.0	1.0±0	384±63	384±63	5.61±0.78
5	284±109	2.0±1.7	2311±461	2311±461	6.45±1.02
10	334±89	2.0±1.7	3881±804	3881±804	9.07±1.87
H3					
<u>GD 7</u>					
1	0	NA	0	0	NA
5	2.26±1.10	3.0±1.7	12.6±6.2	20.5±11.9	6.28 ^a
10	3.10±0.81	5.0±3.6	44.2±28.7	48.2±22.8	14.5 ^a
<u>GD 20</u>					
1	0	NA	0	0	NA
5	3.34±0.60	3.0±1.7	29.7±21.5	37.6±15.6	7.46±5.88
10	4.02±0.58	4.0±0	59.4±14.5	59.4±14.5	29.6 ^a

Note: N was 3 except as noted

Standard deviation values were not calculated when all values were 0 or when n<3.

NA = not applicable

^a = N was 2

Peak exposure to IDP-108, as measured by C_{max}, and total daily exposure, as measured by AUC₀₋₂₄, increased with increasing dose on both sampling days. At both

gestation day 7 and gestation day 20, the increases were approximately linear from 1 to 10 mg/kg/day for AUC_{0-24} . At gestation day 7, the increases in C_{max} were greater than dose-proportional from 1 to 5 mg/kg/day and less than dose-proportional from 5 to 10 mg/kg/day, while at gestation day 20, the increases in C_{max} were dose-proportional from 1 to 5 mg/kg/day and less than dose-proportional from 5 to 10 mg/kg/day. IDP-108 accumulated in pregnant rabbits with repeated exposure. The individual values for T_{max} ranged from 1 to 6 hours, and the mean values for the dose groups ranged from 1 to 3.7 hours. The mean values for $t_{1/2}$ ranged from 5.6 to 10.7 hours, and there was no clear indication of dependence on dose. The plasma concentrations of Metabolite H3 were substantially lower than the plasma concentrations of IDP-108, and there were no measurable concentrations of H3 on either sampling day for the animals receiving 1 mg/kg/day. For rabbits receiving 5 or 10 mg/kg/day, peak exposure to Metabolite H3, as measured by C_{max} , and total exposure, measured by AUC_{0-t} , increased with increasing dose on both sampling days. For the dose increase from 5 to 10 mg/kg/day, the increases in C_{max} were less than dose-proportional (gestation Day 7 and 20) and the increases in AUC_{0-t} were dose-proportional (gestation day 20) or somewhat more than dose-proportional (gestation day 7). Between gestation day 7 and gestation day 20, there were increases in C_{max} and AUC_{0-t} values for H3 for the mid and high dose groups, indicating day-to-day carryover. The values for T_{max} were generally longer for Metabolite H3 than for IDP-108. The individual values ranged from 1 to 8 hours, and the mean values ranged from 3.0 to 5.0 hours. No firm conclusions could be drawn regarding the half-life values for H3.

Dosing Solution Analysis

All dosing solutions were analyzed and were within acceptable range.

Necropsy

Three and 2 females in the vehicle control and the high dose groups, respectively, were euthanized in extremis due to severe localized effects at the injection sites. All of these females were gravid with normally developing implantation sites or fetuses. There were no test article-related internal findings noted for these females.

At the scheduled necropsy on gestation day 29, evidence of irritation at the injection sites was observed in all groups, including the vehicle control group. Therefore, the localized effects noted at the injection sites are due to the vehicle. Findings at the injection site consisted of dark red area(s), open sore(s), scabbing and thickening of the injection site. Masses were noted at the injection site of 3 females in each of the vehicle control, low, mid and high dose groups

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Gravid uterine weight was collected and net body weight and net body weight change were calculated at the scheduled laparohysterectomy. The number of corpora lutea on each ovary was recorded. The trimmed uterus was weighed and opened, and the

number and location of all fetuses, early and late resorptions and the total number of implantation sites were recorded. The placentas were also examined and weighed.

Intrauterine growth and survival were unaffected by test article administration at any dose in this study.

Offspring (Malformations, Variations, etc.)

The detailed external examination of each fetus included examination of the eyes, palate and external orifices, and each finding was recorded. Crown-rump measurements and degrees of autolysis were recorded for late resorptions. Each viable fetus was subjected to a visceral examination to include the heart and major blood vessels. The sex of each fetus was determined by internal examination. Heads from all fetuses were examined by a mid-coronal slice. Skeletal findings were recorded as skeletal variations or malformations.

External malformations were noted in 0(0), 1(1), 1(1) and 0(0) [numbers of fetuses (number of litters)] in the vehicle control, low, mid and high dose groups, respectively. Microphthalmia was noted in one low dose fetus and one mid dose fetus. However, microphthalmia was not observed in the high dose group. These effects were within the (b) (4) historical control data ranges. Therefore, these external malformations are not test article related. No external developmental variations were observed in fetuses in this study.

Visceral malformations were noted in 1(1), 4(4), 1(1) and 2(2) in the vehicle control, low, mid and high dose groups, respectively. Hydrocephaly was noted in one high dose fetus. Another high dose fetus had a malpositioned kidney. However, these findings occurred in single fetuses and the mean litter proportions of hydrocephaly (0.8% per litter) and malpositioned kidney (0.5% per litter) are within the ranges of the (b) (4) historical control data (0.0% to 0.9% and 0.0% to 1.1% per litter, respectively). Therefore, these effects are not test article related. One mid dose fetus had a diaphragmatic hernia. One low dose fetus had persistent truncus arteriosus and two low dose fetuses had enlarged hearts. One vehicle control fetus had lobular agenesis. These effects did not occur in a dose related manner. Therefore, these effects are not test article related.

Skeletal malformations were noted in 0(0), 1(1), 4(4) and 0(0) in the vehicle control, low, mid and high dose groups, respectively. Fused ribs were noted in three mid dose fetuses. Another mid dose fetus had an extra rib with no articulating head. Fused sternbrae were noted in one low dose fetus. These skeletal malformations did not occur in a dose related manner and were within the range of the (b) (4) historical control data. Therefore these skeletal malformations are not test article related.

The numbers of fetuses (litters) available for morphological evaluation were 164(19), 194(22), 204(23) and 173(20) in the vehicle control, low, mid and high dose groups, respectively. Malformations were observed in 1(1), 4(4), 5(4) and 2(2) fetuses (litters) in the same respective groups. However, these fetal malformations and developmental

variations occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose related manner and/or were within the (b) (4) historical control data ranges. Based on these data, no fetal malformations or developmental variations were attributed to the test article.

9.3 Prenatal and Postnatal Development

Study 7

Study title: Subcutaneous developmental and perinatal-postnatal reproduction toxicity study in rats.

Study no.:	DSIN-7001-A6HP-26-09
Study report location:	SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7/22/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	IDP-108, lot # DFP-002, 101.9-105.6% Propylene glycol, lot # G08001335, 99.7%

Key Study Findings

Injection site reactions occurred throughout the study in all groups including the vehicle control group. Injection site swelling and masses near the injection sites occurred in increased numbers of high dose rats late in the dosing period. No treatment related effect on body weight gain was noted in this study. The F₀ maternal NOAEL for IDP-108 is 5 mg/kg/day based on the increased injection site reactions noted in the high dose group.

There were no toxicologically significant effects on duration of gestation or the ability of dams to deliver litters. The reproductive NOAEL in the F₀ dams is 25 mg/kg/day, the highest dose tested.

The NOAEL for viability and growth in the F₁ offspring is 5 mg/kg/day based on the increased perinatal pup mortality, reduced live litter sizes, and increased pup mortality on lactation Days 1 through 4 in the high dose group.

No treatment related effects on postnatal development of F₁ offspring was noted in this study. The NOAEL for postnatal development of F₁ offspring is 25 mg/kg/day, the highest dose tested.

Methods

Doses: 0 (vehicle control), 1, 5, or 25 mg/kg/day
Frequency of dosing: Once daily 7 days per week
Dose volume: 1 ml/kg
Route of administration: Subcutaneous injection (sc)
Formulation/Vehicle: Propylene glycol
Species/Strain: Sprague-Dawley rat/Crj:CD(SP)
Number/Sex/Group: 25 Pregnant females/group
Satellite groups: 9 Pregnant females/group–Toxicokinetic
Study design: Test article or vehicle were administered via subcutaneous injection once daily to F₀ rats from Gestation Day (GD) 6 through Lactation Day (LD) 20 for rats that delivered a litter, or Gestation Day (GD) 24 for rats that did not deliver a litter. F₁ pups did not receive test article administration. After completion of the 21 day postpartum period, F₀ female rats were sacrificed on postpartum day 21. F₀ rats that did not deliver a litter were sacrificed on GD 25. On LD 21, all pups not selected for continued evaluation were sacrificed. After completion of the cohabitation period, all surviving F₁ male rats were sacrificed. All F₁ generation female rats were sacrificed on GD 21.

Deviation from study protocol: Yes, but the deviations did not affect the integrity of the study or the interpretation of the study results.

Observations and Results

F₀ Dams

Survival: Mortality was evaluated daily. There were no test article related deaths in the F₀ generation rats. One high dose female was found dead on GD 20. There was no obvious cause of death for this rat. This death was within the range observed historically at the testing facility and therefore was not treatment related. All other F₀ generation rats survived until scheduled sacrifice.

- Clinical signs: Clinical signs were evaluated daily. There were no dose-dependent increases in adverse clinical observations in the F₀ generation female rats during the gestation period. Discoloration, scabs, and erythema occurred at injection sites in comparable numbers of rats in all dose groups. During the lactation period, swelling at the injection site (a transient observation) and masses on the back (a persistent sign) occurred in increased numbers of rats in the high dose group.
- Body weight: Body weights were evaluated on gestation days 0, 6, 9, 12, 15, 17, and 21 and lactation days 1, 4, 7, 14, and 21. Body weights and body weight gains during the gestation period were comparable among all dose groups including the vehicle control group. LD 1 body weight was reduced (5% below control) in the high dose group. Maternal body weight gain increased in the high dose group on LDs 2 to 4. Body weight gains were then comparable among all dose groups including the vehicle control group for the remainder of the lactation period.
- Feed consumption: Feed consumption was evaluated on gestation days 0, 6, 12, 17, and 20 and lactation days 1, 4, 7, 14, and 20. No treatment related effects on feed consumption was noted in this study.
- Uterine content: Perinatal pup mortality was slightly increased at the high dose. Liveborn litter size was reduced at the high dose (16% less than vehicle control). No other treatment related effects on litter observations were noted in this study.
- Necropsy observation: Adhesions of abdominal organs or tissues (i.e., liver, kidneys, intestines, stomach, spleen, uterus, diaphragm adipose tissue and /or abdominal wall) occurred in increased numbers (5 or 6) of rats in the mid and high dose groups, and also occurred in 3 rats in each of the vehicle control and low dose groups. This reviewer agrees with the sponsor's suggestion that these adhesions are related to the spread of inflammation, swelling and/or masses at the injection site, from the subcutaneous administration of the propylene glycol vehicle and exacerbated by the test article.

Toxicokinetics: Blood samples for toxicokinetic analysis were collected on GD 7, GD 17 and LD 20 at 0, 0.5, 1, 4, 8 and 24 hours post dose. Milk samples were collected from five rats that delivered a litter per dose group on LD 14 at 4 hours post dose. Systemic exposure to IDP-108 increased with increasing dose. The overall increase in C_{max} was less than dose proportional. The overall increase in AUC_{0-24} was close to dose proportional on GD 17 and LD 20. See the Table below for a summary of the toxicokinetic parameters.

IDP-108 was excreted in milk. The milk concentrations of IDP-108 were 54.1 ng/ml, 1536 ng/ml and 2157 ng/ml in the low, mid and high dose groups, respectively. The milk concentrations of IDP-108 were higher than the corresponding plasma concentrations of IDP-108.

Toxicokinetic Parameters for Female Rats for IDP-108

Dose (mg/kg/ day)	Day	C_{max} (ng/mL)	Day-to-Day Change for C_{max}	T_{max} (hr)	AUC_{0-24} (ng·hr/mL)	Day-to-Day Change for AUC_{0-24}	r^2	$t_{1/2}$ (hr)
1	DG 7	7.11		4	54.9		0.9582	3.86
	DG 17	14.5	104%	4	120	118%	0.8920	5.58
	DL 20	9.15	-37%	4	85.8	-28%	0.9778	5.57
5	DG 7	38.1		0.5	364		1.0000	5.52
	DG 17	46.4	22%	4	552	52%	0.9690	8.01
	DL 20	29.1	-37%	4	422	-24%	0.9805	6.58
25	DG 7	57.7		8	1,033		nc	nc
	DG 17	189	228%	4	3,363	225%	0.9989	21.1 ^a
	DL 20	128	-32%	1	2,253	-33%	0.9999	1

r^2 = correlation coefficient

nc = could not be calculated

a. Values not considered reliable since the apparent $t_{1/2}$ is based on a time span less than the $t_{1/2}$ value.

Dosing Solution Analysis All dosing solutions were analyzed and were within the acceptable range.

F₁ Generation

- Survival:** Mortality was evaluated daily. There were no test article related deaths in the F₁ generation male and female rats after weaning. One male rat in the vehicle control group was sacrificed due to a snout injury and one male rat in the mid dose group was found dead on the day after weaning. All other F₁ generation rats survived to scheduled sacrifice.
- Clinical signs:** Clinical signs were evaluated daily. No treatment related effects on clinical signs were noted in F₁ male and female rats.
- Body weight:** Body weights were evaluated on lactation days 1, 4, 7, 14, and 21 in female F₁ rats; weekly during cohabitation for male and female F₁ rats; on gestation days 0, 6, 9, 12, 15, 17, and 21, and lactation days 1, 4, and 7 in female F₁ rats. No treatment related effects on body weights or body weight gains were noted during the postweaning, precohabitation and/or gestation periods.
- Feed consumption:** Feed consumption was evaluated weekly during the postweaning period and cohabitation for male and female F₁ rats; on gestation days 0, 6, 12, 17, and 20, and lactation days 1, 4, and 7 in female F₁ rats. No treatment related effects on feed consumption were noted during the postweaning, precohabitation and/or gestation periods.
- Physical development:** Vaginal patency was evaluated in female rats daily from postnatal Day 28. Preputial separation was evaluated in male rats daily from postnatal Day 39. No treatment related effects on sexual maturation were noted in F₁ rats.
- Neurological assessment:** Neurological assessment was evaluated in one male rat and one female rat from each litter by performance in the passive avoidance test conducted beginning on postnatal Day 24 and one week later and the watermaze test beginning on postnatal day 70 and one week later. No treatment related effects on performance in a passive avoidance test or a watermaze test were noted in F₁ rats.
- Reproduction:** Mating performance was assessed in one male F₁ rat and one female F₁ rat (age 92 -97 days) from each dose group. There were no treatment related effects on the mating and fertility parameters evaluated in the F₁ generation male and female rats.

F₂ Generation

- Survival: There were no treatment related effects on F₂ pup viability based on 23 (92.0%), 22 (88.0%), 19 (79.2%) and 21 (80.8%) pregnant rats with one or more live fetuses.
- Body weight: There were no treatment related effects on F₂ pup body weights in this study.
- External evaluation: There were no treatment related effects on F₂ external fetal malformations.
- Male/Female ratio: IDP-108 had no effect on the percent live male fetuses compared to the vehicle control group.

10 Special Toxicology Studies

Efinaconazole

A nonclinical photoirritation/photosensitization study was conducted in guinea pigs with topical KP-103. Primary dermal irritation and ocular irritation studies were conducted in rabbits with topical KP-103 and IDP-108 formulations. Cumulative skin irritation studies (14 days) were conducted in rabbits with topical KP-103.

1. Photosensitization and phototoxicity of KP-103 in the skin of guinea pigs. Study No, ST960206.

A skin phototoxicity study of KP-103 was conducted in male Std:Hartley guinea pigs. Two 1.5 x 1.5 cm areas were shaved on the left and right flanks under ether anesthesia the day before challenge. The test substance solution was openly applied to symmetrical sites, 0.02 ml per site. These areas were exposed to about 10 J/cm² of UV-A for 60 minutes. The positive control substance was 8-methoxypsoralen (8-MOP), and acetone was the negative control substance. The photosensitization portion of this study is not reviewed since CDER does not ask for nonclinical photosensitization studies because they are not predictive of human response.

KP-103 did not elicit a photoirritation response in guinea pigs, under the conditions of this study.

2. Primary dermal irritation study in rabbits with IDP-108. Study No. DSIN-7001-A6HP-02-07.

The test article, IDP-108, 10% solution, was applied to two sites (one intact and one abraded) on the clipped dorsal trunk of three male New Zealand White rabbits. The exposure period was 24 hours (1 day), and both sites were covered with semi-occlusive wrapping. Observations for dermal irritation were recorded for each site

immediately after patch removal (Day 2), at 24, 48 and 72 hours after unwrap (Days 3-5), and on Days 6 through 10. Scores returned to normal on Day 10 and the in-life portion was terminated. Grading of irritation was according to the method of Draize.

IDP-108 (10%) was a non-irritant on intact rabbit skin and a mild irritant on abraded rabbit skin.

3. Cumulative skin irritation study of KP-103CR in rabbits. Study No. SQT021.

Three groups, 6 male rabbits per group, were administered 0 (vehicle control), 1 or 2 % KP-103 for 14 days to intact and abraded dorsal skin. The test substance 0.5 g, equivalent to 0.5 ml, was applied to 2.5 x 2.5 cm² application site and covered with occlusive wrap film. The period of exposure was 6 hours per day. After exposure to the test substance, the application sites were gently wiped with warm water to remove any residual test substance.

KP-103 (1% or 2%) was a minimal dermal irritant on intact and abraded (tape-stripped) rabbit skin after 14 days of treatment (6 hours/day).

4. Primary ocular irritation study of KP-103 in rabbits. Study No. SQT019.

Three groups, 6 male rabbits per group, were administered 0 (vehicle control), 1 or 2 % KP-103. The test substances were administered to left eyes. The right eyes were untreated and served as a control. Left lower eyelids were pulled gently, and the test article 0.1 g, equivalent to 0.1 ml, was instilled into conjunctival sac. The eye was closed for about 1 second to contain the spill. In all animals in the test groups, cornea, iris and corneal conjunctiva were observed at 1, 3, 6 and 24 hours, and 2, 3 and 6 days post-dosing.

KP-103 (1% or 2%) was a mild ocular irritant in rabbits.

5. Primary eye irritation study in rabbits with IDP-108. Study No. DSIN-7001-A6HP-03-07.

The test article, IDP-108 10% solution, was instilled directly into the right eye of three male New Zealand White rabbit at a volume of 0.1 ml/eye. Upon instillation, the eye was held closed for ~1 second to prevent loss of material. The left eye was untreated and served as the control. Both eyes of all animals were examined and scored for ocular irritation prior to dosing, 1 hour after dosing, and at 24, 48 and 72 hours post-dosing.

IDP-108 (10%) was a mild ocular irritant in rabbits.

Alkyl Lactate

Reviewer's Comments: Alkyl lactate is widely used in cosmetics and has been identified as a skin and eye irritant in humans, depending on the concentration. However, alkyl lactate is not included in the CDER inactive ingredients database. Therefore the sponsor provided the following studies to qualify C12-C15 alkyl lactate for use at the 10% level in this topical drug product.

Primary dermal irritation and ocular irritation studies were conducted in rabbits with topical C12-C15 alkyl lactate solution.

1. Primary dermal irritation study in rabbits with C12-C15 alkyl lactate. Study No. S11T003.

C12-C15 Alkyl Lactate (neat solution), saline (negative control) and 3 w/v% sodium lauryl sulfate (SLS; positive control) were applied (occluded for 24 hours) to intact and abraded dorsal skin of 6 male New Zealand White rabbits (Kbl:NZW). The dose volume was 0.2 ml. Skin reactions were assessed and scored according to Draize method.

C12-C15 alkyl lactate was a non-irritant on intact rabbit skin and a mild irritant on abraded rabbit skin.

2. Primary eye irritation study in rabbits with C12-C15 alkyl lactate. Study No. S11T004.

A volume of 0.1 ml of saline, as a negative control article, or C12-C15 Alkyl Lactate was instilled into right eyes (6 animals/group) of New Zealand white rabbits. The cornea, iris, and conjunctiva were examined before instillation and 1, 24, 48, 72 hours, 4 and 7 days after instillation.

C12-C15 alkyl lactate was not an ocular irritant in rabbits.

11 Integrated Summary and Safety Evaluation

Repeat-dose systemic rodent toxicity and developmental and reproductive toxicity studies were conducted with subcutaneous administration of efinaconazole dissolved in propylene glycol. Efinaconazole appeared well tolerated but subcutaneous administration of propylene glycol was not well tolerated and resulted in significant injection site toxicity.

Efinaconazole was evaluated in rats with repeated daily subcutaneous doses of up to 30 (males) and 40 (females) mg/kg/day for up to 6 months. No systemic target organ toxicity was noted at the high dose. An increased frequency of severe injection site toxicity plus 17% lower body weight in high dose males precluded testing higher doses.

Repeated subcutaneous administration of the propylene glycol vehicle at 2 ml/kg was not well tolerated in rats dosed for 6 months. Vehicle related effects included severe dermal injection site reactions and gross and microscopic pathology findings at the injection sites. Mortality (7/15) was noted in the high dose males. The cause of the increased mortality in high dose males was unknown.

The vehicle used in the 6 month rat subcutaneous toxicity study was not acceptable for repeat dose subcutaneous administration due to the injection site reactions noted in all treatment groups. However, systemic exposure following dermal administration is minimal under conditions of maximal clinical use. Therefore, it is not necessary to repeat this 6 month subcutaneous rat study with another vehicle that would be better tolerated after repeat dose subcutaneous administration.

Efinaconazole solution was administered to minipigs with repeated daily dermal administration of up to 30% efinaconazole solution for up to 9 months. The efinaconazole solution used in the chronic dermal minipig study was similar to the to-be-marketed formulation. The minor differences in a few excipients in the formulation were determined to not be of toxicological significance. No significant efinaconazole related dermal toxicity was evident in this study. The vehicle and efinaconazole solution produced mild skin irritation. Dermal effects noted in this study included slight microscopic hyperkeratosis, acanthosis, and localized inflammation observed in skin at the application site of all dose groups. No systemic toxicity was identified at the high dose, the maximal feasible dose. The high dose (30% efinaconazole solution) was the dermal and systemic NOAEL in this study.

Efinaconazole was not mutagenic or clastogenic in a standard ICH battery of genotoxicity tests including an in vitro test for gene mutation in bacteria (Ames), an in vitro test with cytogenetic evaluation for chromosomal damage in mammalian cells (chromosome aberration in CHL cells), and an in vivo test for chromosomal damage in rodent hematopoietic cells (mouse micronucleus assay with IP injection).

A dermal mouse carcinogenicity was conducted with the to-be-marketed efinaconazole solution. Daily dermal doses of 0% (vehicle), 3%, 10% and 30% efinaconazole solution were evaluated in this study. Severe irritation was noted at the treatment site in all dose groups which was probably due to the vehicle. The high dose group was terminated at week 34 due to severe skin effects. Termination of the high dose group received ECAC concurrence. It appeared that adequate numbers of animals in the low and mid dose groups survived to the end of the study. The mid dose was equal to the clinical concentration of the drug product. No treatment related increase in the incidence of neoplasms was observed in this study. However, the skin effects of the propylene glycol vehicle confounded assessment of any skin effects due to efinaconazole. The ECAC concluded that the study was suboptimal due to the mice being very sensitive to the severe dermal effects elicited by the vehicle. However, the ECAC did not recommend repeating the dermal mouse carcinogenicity study since no preneoplastic lesions were noted in the 9 month dermal minipig study conducted with a high dose of 30%

efinazonale solution.

Reproductive and developmental toxicology studies have been conducted with efinaconazole in rats and rabbits.

A subcutaneous rat fertility study was conducted with doses of 0 (untreated control), 0 (vehicle control), 1, 5 and 25 mg/kg/day efinaconazole. The vehicle was propylene glycol and the dose volume was 2 ml/kg. Males were dosed for 28 days prior to mating and through the mating period. Females were dosed from 14 days prior to mating, through the mating period and until gestation day 7. Skin thickening at the injection site was noted in all efinaconazole treated groups and the vehicle control group. A tendency to slightly prolong the estrous cycle was noted in high dose females but the copulation index was 100% in all dose groups. No treatment related effects on male or female fertility parameters were noted in this study. The NOAEL for maternal toxicity was 5 mg/kg/day and the NOAEL for effects on fertility and early embryonic development was 25 mg/kg/day.

A subcutaneous rat embryofetal and development study was conducted with doses of 0 (untreated control), 0 (vehicle control), 2, 10 and 50 mg/kg/day efinaconazole. The vehicle was propylene glycol and the dose volume was 2 ml/kg. Pregnant female rats were dosed from gestation Day 6 to 16 and necropsied on gestation Day 19. Skin thickening at the treatment site was noted in most high dose animals and one mid dose animal. An 11% decrease in body weight gain was noted in high dose dams after gestation day 16. Resorption of all embryos was noted in 2 high dose dams. An increased incidence of embryofetal deaths was noted in the high dose group. An increased incidence of lumbar ribs and minor skeletal variations was noted in the high dose group. The maternal NOAEL is 10 mg/kg/day based on the skin thickening noted in the high dose group. The developmental NOAEL is 10 mg/kg/day based on the increased incidence of embryofetal deaths noted in the high dose group. The NOAEL for treatment related effects on embryofetal malformations is 50 mg/kg/day since the increased incidence of fetuses having skeletal variations noted in the high dose group, although treatment related, is not of biological concern.

A subcutaneous rabbit embryofetal development study was conducted with doses of 0 (vehicle control), 1, 5, and 10 mg/kg/day efinaconazole. The vehicle was propylene glycol and the dose volume was 1 ml/kg. Time-mated female rabbits were dosed from gestation Day 6 to 19. Laparohysterectomies were performed on gestation Day 29. Desquamation, erythema (very slight to severe), edema (very slight to moderate), eschar, and brown discoloration at the injection site were noted in two high dose animals and three vehicle control animals. These animals were euthanized in extremis due the severe localized effects. Injection site observations in surviving females from all dose groups including the vehicle control group included dark red areas, open sores, scabbing and thickening at the injection site. Masses were noted at the injection site of three females in each of the vehicle control, low mid and high dose groups. A 35% decrease in body weight gain with a corresponding decrease in feed consumption was noted in high dose animals during treatment Days 6-19. There were no indications of

test article-related effects on embryofetal development. Intrauterine growth and fetal morphology were not affected by test article administration at any dose level. The maternal NOAEL is 5 mg/kg/day based on the decreased body weight gain and decreased feed consumption noted in the high dose group. The developmental NOAEL is 10 mg/kg/day, the highest dose tested, based on the absence of an effect on embryofetal development. The NOAEL for teratogenic effects is 10 mg/kg/day, the highest dose tested, based on the absence of adverse fetal morphology.

A subcutaneous rat pre- and postnatal development study was conducted with doses of 0 (vehicle control), 1, 5 and 25 mg/kg/day efinaconazole. The vehicle was propylene glycol and the dose volume was 1 ml/kg. Pregnant female rats were dosed from gestation Day 6 to lactation Day 20 and necropsied on lactation Day 21, or gestation Day 24 for rats that did not deliver a litter. Injection site reactions occurred throughout the study in all groups, including the vehicle control group. Injection site swelling and masses near the injection sites occurred in increased numbers of rats in the high dose group late in the lactation dosing period. Body weight gain was slightly reduced (5%) compared to F₀ control dams on lactation Day 1 but recovered to F₀ control levels by lactation day 4. Perinatal pup mortality was increased at the high dose. Liveborn litter size was reduced at the high dose, and the numbers of pups found dead on lactation Days 1 through 4 were increased in this group. There were no toxicologically significant effects on duration of gestation or the ability of dams to deliver litters. The NOAEL for viability and growth in the offspring is 5 mg/kg/day based on the increased perinatal pup mortality at the high dose, reduced live litter sizes, and increased pup mortality on lactation Days 1 through 4. No treatment related effects on postnatal development of F₁ offspring was noted in this study. The NOAEL for postnatal development of F₁ offspring is 25 mg/kg/day, the highest dose tested.

Single dermal application of up to 10% efinaconazole solution to rabbits did not elicit dermal irritation in intact skin but was a mild irritant to abraded skin. Efinaconazole solution, 10%, was a mild ocular irritant in rabbit eyes. Efinaconazole solution did not elicit a photoirritation response in guinea pigs.

The multiples of human exposures (MHE) were calculated based on Area Under the Curve (AUC) comparisons for the Maximum Recommended Human Dose (MRHD) for efinaconazole and the NOAELs identified in the pivotal nonclinical studies. The AUC values for the NOAELs are the average of male and female AUC values for the longest duration of exposure available, unless otherwise specified. The MHE values are provided in the following table.

Toxicity	Species	NOAEL (mg/kg)	NOAEL AUC (ng·hr/ml)	MHE Based on AUC*
6 Month subcutaneous toxicity	Rat	10	1776	70
9 Month dermal toxicity	Minipig	30% IDP-108 solution	5255	208
2 Year dermal carcinogenicity	Mouse	10% efinaconazole solution	6252	248
Fertility and early embryonic development	Rat	5 ^a 25 ^b	1411 7052	56 279
Embryofetal development	Rat	2 ^c 10 ^d 50 ^e	564 2821 14105	22 112 559
Embryofetal Development	Rabbit	5 ^f 10 ^g	2311 3881	92 154
Pre- and postnatal development	Rat	5 ^h 25 ⁱ	422 2253	17 89

*Maximum AUC in humans based on the results of the maximal use clinical pharmacokinetic study is 25.25 ng·hr/ml.

a – based on maternal toxicity

b – based on effects on fertility

c – based on maternal toxicity

d – based on embryofetal toxicity

e – based on malformations

f – based on maternal toxicity

g - based on embryofetal toxicity and malformations

h – based on F₀ and F₁ maternal toxicity

i – based on F₀ reproductive effects and F₁ postnatal development effects

Extrapolated AUC values were used for the mouse dermal carcinogenicity, rat fertility and early embryonic development, and rat embryofetal development studies. These calculations assumed linear PK within the extrapolated dose range.

To extrapolate the AUC at the NOAEL (10% efinaconazole solution) for the mouse dermal carcinogenicity study, the 13 week dose range finding study AUC using the 10% efinaconazole solution was divided by 2 (12503 ng·hr/ml ÷ 2 = 6252 ng·hr/ml). The AUC was reduced because of the dose volume reduction from 100 µL to 50 µL that occurred on Week 42 of the dermal carcinogenicity study.

To extrapolate the AUC for the maternal toxicity NOAEL (i.e. 5 mg/kg/day) for the rat fertility and early embryonic development study, the 6 month repeat dose toxicity study AUC for females at 10 mg/kg/day on Day 90 was adjusted by the dose multiple 0.5 ($2821 \text{ ng}\cdot\text{hr}/\text{ml} \times 0.5 = 1411 \text{ ng}\cdot\text{hr}/\text{ml}$).

To extrapolate the AUC for the NOAEL for effects on fertility (i.e., 25 mg/kg/day) for the rat fertility and early embryonic development study, the 6 month repeat dose toxicity study AUC for females at 10 mg/kg/day on Day 90 was adjusted by the dose multiple of 2.5 ($2821 \text{ ng}\cdot\text{hr}/\text{ml} \times 2.5 = 7052 \text{ ng}\cdot\text{hr}/\text{ml}$).

To extrapolate the AUC for the maternal toxicity NOAEL (i.e. 2 mg/kg) for the rat embryofetal development study, the 6 month repeat dose toxicity study AUC for females at 10 mg/kg on Day 90 was adjusted by the dose multiple 0.2 ($2821 \text{ ng}\cdot\text{hr}/\text{ml} \times 0.2 = 564 \text{ ng}\cdot\text{hr}/\text{ml}$).

The AUC for the embryofetal toxicity NOAEL for the rat embryofetal development study was the 6 month repeat dose toxicity study AUC for females at 10 mg/kg/day on Day 90 ($2821 \text{ ng}\cdot\text{hr}/\text{ml}$).

To extrapolate the AUC for the treatment related malformations NOAEL (i.e., 50 mg/kg/day) for the rat embryofetal development study, the 6 month repeat dose toxicity study AUC for females at 10 mg/kg/day on Day 90 was adjusted by the dose multiple of 5 ($2821 \text{ ng}\cdot\text{hr}/\text{ml} \times 5 = 14105 \text{ ng}\cdot\text{hr}/\text{ml}$).

The sponsor provided data to support the use of the novel excipient, alkyl lactate, in the efinaconazole solution. Alkyl lactate has not been used in previously approved drug products. However, alkyl lactate has been used extensively in cosmetics. The repeat dose dermal toxicity of alkyl lactate was evaluated in the 9 month dermal minipig study by inclusion of 10% alkyl lactate in the efinaconazole solution used in this study. Alkyl lactate was negative in a standard battery of genotoxicity studies (i.e., Ames assay, an in vitro chromosomal aberration assay and an in vivo mouse micronucleus assay). The dermal carcinogenic potential of alkyl lactate was evaluated in the dermal mouse carcinogenicity by inclusion of 10% alkyl lactate in the efinaconazole solution used in this study. Alkyl lactate was non-irritating to intact rabbit skin and a mild irritant on abraded rabbit skin. Alkyl lactate was not an ocular irritant in rabbit eyes. The sponsor did not evaluate the reproductive toxicity associated with alkyl lactate. However, it is anticipated that very minimal systemic exposure to alkyl lactate would occur under clinical maximal use conditions. Therefore, reproductive toxicity studies for alkyl lactate are not needed to support the use of this excipient in efinaconazole solution for the treatment of onychomycosis. Adequate nonclinical data is available to support the use of 10% alkyl lactate in the efinaconazole solution for the treatment of onychomycosis.

The provided nonclinical data support approval for efinaconazole solution from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

[ECAC meeting minutes from November 27, 2012 meeting for the dermal mouse carcinogenicity study](#)

Executive CAC

Date of Meeting: November 27, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lynnda Reid, Ph.D., DRUP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Linda Pellicore, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Linda Pellicore, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 203567
Drug Name: Efinaconazole Topical Solution, 10%
Sponsor: Dow Pharmaceutical Sciences

Background:

Efinaconazole Topical Solution, 10% is a triazole antifungal agent being developed for the topical treatment of onychomycosis in adults 18 years of age and older. Dose selection for the dermal mouse carcinogenicity study was based on a 13 week dose range finding study. However, the 13 week dose range finding study was not conducted with the to-be-marketed formulation. Therefore, the Executive CAC recommended that another dose range finding study be conducted with the to-be-marketed formulation to support dose selection for the dermal mouse carcinogenicity study. However, the sponsor decided to conduct the dermal mouse carcinogenicity study with the to-be-marketed formulation without conducting another dose range finding study.

Dermal Mouse Carcinogenicity Study

CD-1 mice (60 mice/sex/group) were treated with 0% (untreated control), 0% (vehicle control), 3%, 10%, or 30% efinaconazole solution. The initial dose volume was 100 μ L of test article applied to an unoccluded treatment site (2 x 3cm²). Test article was to be applied once daily, 7 days per week for up to 104 weeks. The clinical vehicle contained cyclomethicone, NF (b) (4), diisopropyl adipate (b) (4), C12-C15 alkyl lactate, (b) (4), purified water (b) (4), butylated hydroxytoluene, NF (b) (4), citric acid, USP (b) (4), edetate disodium (b) (4), (b) (4) alcohol, USP (b) (4).

Severe irritation was noted at the treatment site beginning at week 20 in vehicle, low-, mid- and high-dose groups. The irritation noted at the treatment site appeared to be related to the vehicle and did increase in severity in the high-dose group. All animals were placed on a dosing holiday from week 25 to week 31 due to skin irritation and scabbing in all treatment groups. At week 31, the dose volume was decreased from 100 μ L to 50 μ L and the high dose group was terminated at week 34 due to severe skin effects. These modifications in the study received Executive CAC concurrence. It appeared that adequate numbers of mid- and low-dose animals survived to the end of the study.

Executive CAC Recommendations and Conclusions:

Dermal Mouse:

- The Committee concluded that the study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. However, the Committee did not recommend repeating the dermal mouse carcinogenicity study. The Executive CAC noted the results of the chronic dermal minipig study

conducted with once daily application of up to 30% efinaconazole solution for 9 months. No preneoplastic lesions were observed in that study and the high-dose of 30% efinaconazole was the no-observed-adverse-effect level (NOAEL) for dermal and systemic toxicity in the minipig.

- The Committee concurred that there were no drug-related neoplasms in the dermal mouse carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

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/s/

LINDA S PELLICORE
03/04/2013

BARBARA A HILL
03/05/2013

Comments on NDA 203567 Efinaconzazole

From A. Jacobs, AD

March 1, 2013

1. I concur that there are no pharm-tox issues for approval of this NDA .
2. I concur with the proposed pregnancy category.
3. I have conveyed my other content and editorial comments to the reviewer and supervisor, and they will address them as appropriate.

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/s/

ABIGAIL C JACOBS
03/01/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203567

Applicant: Dow Pharmaceutical
Sciences, Petaluma, CA

Stamp Date: 07/26/2012

Drug Name: (b) (4)
(efinconazole) Topical Solution,
10%

NDA Type: Original-NME

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		The sponsor made slight changes in the formulation to improve absorption characteristics. These minor changes are not considered significant to the toxicity profile. The pivotal dermal mouse carcinogenicity study was conducted with the to-be-marketed formulation. No additional toxicity study is recommended.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The sponsor provided the chemical structure and origin of each of the known drug-related impurities. Detailed information can be found in DMF No. 21870. A letter authorizing the Agency to refer to this file was provided in DMF 21870.
11	Has the applicant addressed any abuse potential issues in the submission?			It is not applicable to this NDA submission.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This NDA submission is not to support a Rx to OTC switch.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

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

N/A.

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

None.

Linda Pellicore See sign-off date

 Reviewing Pharmacologist Date

Barbara Hill See sign-off date

 Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

LINDA S PELLICORE
09/11/2012

BARBARA A HILL
09/11/2012