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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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:	204427
Supporting document/s:	1
Applicant's letter date:	July 26, 2013
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Product:	KERYDIN (tavaborole) Solution
Indication:	Onychomycosis
Applicant:	Anacor Pharmaceuticals Inc.
Review Division:	Dermatologic and Dental Products
Reviewer/Supervisor:	Barbara Hill, PhD
Division Director:	Susan Walker, MD
Project Manager:	Cristina Attinello

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1 Executive Summary

1.1 Introduction

The sponsor has submitted a 505(b)(1) NDA application for tavaborole solution, 5%. Tavaborole is an oxaborole anti-fungal agent and is a new molecular entity. Tavaborole solution is being developed for the topical treatment of onychomycosis.

1.2 Brief Discussion of Nonclinical Findings

Repeat dose oral toxicity studies up to 6 months in rats have been conducted with tavaborole and repeat dose dermal toxicity studies up to 9 months in minipigs have been conducted with tavaborole solution. The target organ of toxicity identified in oral rat toxicity studies was the nonglandular stomach which exhibited as epithelial hyperplasia and hyperkeratosis. The nonglandular stomach is absent in humans. Therefore, the clinical significance of this finding is unclear. The target organ of toxicity identified in the dermal minipig toxicity studies was the skin at the site of application which exhibited a dose dependent increase in the incidence and severity of dermal irritation. Both the treatment related effects on the nonglandular stomach in rats and at the treatment site in minipigs were reversible after stopping treatment.

Tavaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

An oral carcinogenicity study in rats was conducted with tavaborole and a dermal carcinogenicity study in mice was conducted with tavaborole solution. No drug related increase in the incidence of neoplasms was noted in either carcinogenicity study.

The potential reproductive toxicity of tavaborole was evaluated in an oral fertility study in rats, oral embryofetal development studies in rats and rabbits, a dermal embryofetal development study in rabbits and an oral pre- and post-natal development study in rats.

No treatment related effects on fertility were noted in rats at oral doses up to 300 mg/kg/day tavaborole. In the oral embryofetal development study in rats, a treatment related increase in embryofetal resorption and/or embryofetal death was noted at an oral dose of 300 mg/kg/day tavaborole which correlated with maternal toxicity (significant body weight decrease). Drug related skeletal malformations and variations suggestive of delayed development were noted in fetuses at the 300 mg/kg/day tavaborole dose in rats. This delay in ossification may be related to the lower fetal body weights noted at the 300 mg/kg/day tavaborole dose.

A dose dependent increase in dermal irritation was noted in the 5% and 10% tavaborole solution dose groups in the dermal embryofetal development study in rabbits. No treatment related effects on fetal evaluations (external, visceral, and skeletal) were noted in this study. However, a decrease in fetal body weight (decrease of 7 – 10%)

was noted in the 10% tavaborole solution group compared to the control group. No drug related malformations was noted in this study. The NOAEL for drug related malformations was 10% AN2690 solution. The NOAEL for maternal and fetal developmental toxicity was 5% AN2690 solution.

An increase in mortality and significant body weight loss was noted at 150 mg/kg/day tavaborole in the oral embryofetal development study in rabbits. There was a treatment related increase in post implantation loss at 150 mg/kg/day tavaborole which was mainly due to an increased incidence in early resorptions. A significant decrease in live fetuses was noted at 150 mg/kg/day tavaborole. No treatment related effects on fetal external malformations or variations, fetal visceral malformations or variations or fetal skeletal malformations or variations were noted in this study. The NOAEL for drug related malformations was 150 mg/kg/day. The NOAEL for maternal toxicity and embryofetal toxicity was 50 mg/kg/day.

No treatment related effects on pre- and post-natal development were noted in rats at doses up to 100 mg/kg/day tavaborole.

Tavaborole solution was slightly irritating to intact rabbit skin after a single 24 hour topical application under occlusion and was an ocular irritant in rabbits. Tavaborole solution was classified as a non-sensitizer in guinea pigs. The need for a nonclinical photoirritation study was waived for tavaborole solution since no absorption was noted from 225 nm – 700 nm.

The toxicity profile of tavaborole solution has been well characterized by the nonclinical studies conducted by the sponsor. There is no significant safety concern for tavaborole solution at the proposed clinical dose. No nonclinical postmarketing requirement is recommended for this NDA.

1.3 Recommendations

1.3.1 Approvability

NDA 204407 for tavaborole solution is approvable from a Pharmacology/Toxicology perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the tavaborole solution label.

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 tavaborole solution label reproduced below. The pharmacologic class designation for tavaborole for the treatment of onychomycosis is oxaborole antifungal. A clean copy of the suggested wording for the nonclinical sections of the label is provided in Appendix 1.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Tavaborole is an oxaborole antifungal indicated for the topical treatment of onychomycosis [redacted].

8.1 Pregnancy

[redacted]: Pregnancy Category C. [redacted]

There are [redacted] no adequate and well-controlled studies with KERYDIN [redacted] in pregnant women. KERYDIN [redacted] should be used during pregnancy only if [redacted] the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits [redacted] In an oral embryofetal development study in rats, oral doses of 30, 100 and 300 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and drug related skeletal malformations and variations suggestive of delayed development (i.e., a delay in ossification) were noted in fetuses at 300 mg/kg/day tavaborole [570 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No developmental toxicity was noted in rats at 100 mg/kg/day tavaborole (26 times the MRHD based on AUC comparisons).

In an oral embryofetal development study in rabbits, oral doses of 15, 50 and 150 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 7-19) to pregnant female rabbits. In the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 150 mg/kg/day tavaborole. No drug related malformations were noted in rabbits at 150 mg/kg/day tavaborole (155 times the MRHD based on AUC comparisons). No embryofetal mortality was noted in rabbits at 50 mg/kg/day tavaborole (16 times the MRHD based on AUC comparisons].

In a dermal embryofetal development study in rabbits, topical doses of 1, 5 and 10% tavaborole solution were administered during the period of organogenesis (gestational days 6-28) to pregnant female rabbits. A dose dependent increase in dermal irritation at the treatment site was noted at 5 and 10% tavaborole solution. A decrease in fetal bodyweight was noted at 10% tavaborole solution. No drug related malformations were noted in rabbits at 10% tavaborole solution (36 times the MRHD based on AUC

comparisons). No embryofetal toxicity was noted in rabbits at 5% tavaborole solution (26 times the MRHD based on AUC comparisons).

Nonteratogenic effects:

In an oral pre- and post-natal development study in rats, oral doses of 15, 60 and 100 mg/kg/day tavaborole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development were noted at 100 mg/kg/day (29 times the MRHD based on AUC comparisons).

12.1 Mechanism of Action

(b) (4) KERYDIN (b) (4) antifungal (b) (4)

Clinica (b) (4) *Pharmacology* (b) (4) *-12.4)*].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an (b) (4) oral carcinogenicity study in Sprague-Dawley rats, oral doses of 12.5, 25 and 50 mg/kg/day tavaborole were administered to rats once daily for 104 weeks. No drug related neoplastic findings were noted at oral doses up to 50 mg/kg/day tavaborole (14 times the MRHD based on AUC comparisons). (b) (4)

In a (b) (4) dermal carcinogenicity study in CD-1 mice, topical doses of 5, 10 and 15% tavaborole solution were administered to mice once daily for 104 weeks. No drug related neoplastic findings were noted at topical doses up to 15% tavaborole solution (89 times the MRHD based on AUC comparisons). (b) (4)

(b) (4)

Tavaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

(b) (4)

(b) (4)

No effects on fertility were observed in male and female rats that were administered oral doses up to 300 mg/kg/day tavaborole (107 times the MRHD based on AUC comparisons) prior to and during early pregnancy.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number

174671-46-6

Generic Name

Tavaborole

Code Name

AN2690, SCH900340

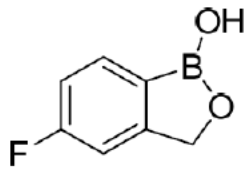
Chemical Name

5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

Molecular Formula/Molecular Weight

$C_7H_6BFO_2$ / 151.93

Structure or Biochemical Description



Pharmacologic Class

Oxaborole antifungal

Reviewer' comments: The pharmacologic class designation was based on information provided in the submission concerning the chemical class for this antifungal drug substance. Concurrence for the pharmacologic class designation for tavaborole was obtained from the Clinical Reviewer, Dr. Melina Lolic, and the ODE Associate Pharmacology/Toxicology Director, Dr. Paul Brown.

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 71206 (AN2690 solution, onychomycosis, Anacor Pharmaceuticals, DDDP)

2.3 Drug Formulation

The composition of tavaborole topical solution is provided in the following table (copied from NDA submission).

Components	Quality Standard	Function	Concentration (% w/w)
Tavaborole	In-house	Active	5.00
Alcohol	USP		(b) (4)
Propylene Glycol	USP		
Edetate Calcium Disodium	USP		

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

The three nonclinical studies conducted by the sponsor to support the safety of impurities in the drug substance are provided below.

1) Bacterial mutagenicity study of SCH 900340 – Impurity qualification assessment (Study No. 002-NCL TX-075-01)
2) Chromosome aberration study of SCH 900340 (AN2690) in human peripheral blood lymphocytes – Impurity qualification assessment (002-NCL TX-076-01)
3) One month oral (gavage) qualification study of SCH 900340 in rats (Study No. 002-NCL TX-077-01)

The genotoxicity of tavaborole spiked with four impurities [redacted] as assessed in an Ames test. DMSO was the vehicle used in this assay. Tavaborole spiked with the four impurities at doses up to [redacted] µg/plate was negative in the Ames test.

The genotoxicity of tavaborole spiked with four impurities [redacted] was assessed in a Human lymphocyte chromosomal aberration assay. DMSO was the vehicle used in this assay. Tavaborole spiked with the four impurities at concentrations up to [redacted] was negative in this assay.

The toxicity profile for tavaborole and tavaborole spiked with four impurities was similar at a dose of [redacted] of oral administration to rats. The impurities that were included in the tavaborole spiked with impurities sample included: [redacted] The vehicle used in this study was [redacted]. The primary treatment related microscopic findings were noted in the nonglandular stomach in both treatment groups which has been previously identified as a target organ of toxicity for tavaborole.

The impurities specifications for tavaborole solution are the following.

- [redacted] – NMT [redacted] % LS
- Individual unspecified – NMT [redacted] % LS
- Total – NMT [redacted] % LS

The nonclinical toxicology studies conducted with the potential impurities of tavaborole support the safety of the specifications proposed by the sponsor for tavaborole solution. However, there would typically be very minimal concern for toxicity associated with impurities in a topical drug formulation being used for the treatment of toenail onychomycosis due to very limited systemic exposure after topical administration to all toenails.

2.6 Proposed Clinical Population and Dosing Regimen

Apply tavaborole solution to affected toenails with onychomycosis once daily for 48 weeks.

2.7 Regulatory Background

Several meetings were conducted with the sponsor during the clinical development of tavaborole solution under IND 71206. The type of meeting and corresponding meeting dates are provided below.

1) Guidance meeting; July 11, 2007
2) Guidance meeting; August 13, 2008

3) End of Phase 2 meeting; October 28, 2009
4) Guidance meeting; November 14, 2012
5) Pre-NDA meeting; May 29, 2013

Reviewer's comments: The original IND was submitted by Anacor Pharmaceuticals. The code name for tavaborole was designated as AN2690 by Anacor Pharmaceuticals. Schering Plough was also involved with part of the clinical development of tavaborole solution. The code name for tavaborole was designated as SCH 900340 by Schering Plough. Therefore, reference is made to both code names during the clinical development of tavaborole.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

1) Inhibition of aminoacyl-tRNA synthetase by trapping tRNA in the editing site via an oxaborole-adenosine adduct (Study No. 002-NCL PP-011-01)
2) Mechanism of action of AN2690 resistance in *C. Alibcans* ATCC90028 (Study No. 002-NCL PP-016-2)
3) Evaluation of the in vivo efficacy of AN2690 against systemic *Candida albicans* infection in mice (Study No. 002-NCL PP-012-01)
4) Efficacy of AN2690 against systemic murine candidiasis (Study No. 002-NCL PP-013-01)

Secondary Pharmacology

1) Effect of AN2690 on the inhibition of cytokine release from THP-1 cells stimulated with lipopolysaccharide (Study No. 002-NCL PP-006-01)
2) (b) (4) pharmacology data report on compounds ACL-115, AN2690 for Anacor Pharmaceuticals, Inc. (Study No. 002-NCL PP-007-01)
3) In vitro pharmacology and ADME-Tox: ExpresSProfile + CYP450 + HERG (Study No. 002-NCL SP-001-01)

Safety Pharmacology

1) AN2690: A cardiovascular safety pharmacology study using radiotelemetry in conscious male beagle dogs following a single oral gavage administration (Study No. 002-NCL SP-002-01)
2) AN2690: A safety pharmacology study of the central nervous system of male Sprague-Dawley rats, employing a functional observational battery (FOB) following single oral gavage administration (Study No. 002-NCL SP-004-01)

Pharmacokinetics

1) Compound AN2690: A single dose oral, subcutaneous, and intravenous pharmacokinetics study in male Sprague-Dawley rats (Study No. 002-NCL-PK-002-01)
2) A pharmacokinetic study of AN2690 when administered by subcutaneous injection and oral gavage to Sprague-Dawley rats for 1 or 14 days (Study No. 002-NCL PK-010-01)
3) A pharmacokinetic study of AN2690 when administered by dermal application to Gottingen minipigs (Study No. 002-NCL PK-014-01)
4) Pharmacokinetics of AN2690 following oral administration to non-naïve male beagle dogs (Study No. 002-NCL PK-015-01)
5) SCH 900340: Pharmacokinetics, excretion and metabolism of ^{14}C-SCH 900340 following a single oral administration of ^{14}C-SCH 900340 to male and female rats (Study No. CM27575)
6) Plasma binding assay of AN2690 by equilibrium dialysis: Sample analysis by LC/MC/MC and calculation of protein binding (Study No. 002-NCL PK-006-01)
7) Protein binding of AN2690 in human, minipig, dog and rat plasma (Study No. 002-NCL PK-034-01)
8) SCH 900340 (AN2690): Tissue distribution and excretion pattern of [^{14}C]-SCH-900340-derived radiocarbon after a single dermal dose to male and female pigmented mice (Study No. 002-NCL PK-044-01)
9) SCH 900340: In vitro binding of SCH 900340 to mouse, rat, rabbit, minipig, dog and human plasma proteins using ultrafiltration (Study No. DM27860)
10) SCH 900340: In vivo stability of radiolabel after administration of a single oral dose of ^{14}C-SCH 900340 suspension to male rats (Study No. DM27567)
11) Evaluation of the in vitro metabolism of AN2690 in mouse, rat, minipig and human liver fractions (Study No. 002-NCL PK-003-01)
12) SCH 900340 (AN2690): Excretion and metabolism of [^{14}C]-SCH 900340 following a single dermal administration of a 5% [^{14}C]-SCH 900340 solution to male and female mice (Study No. 002-NCL PK-045-01)
13) SCH 900340: Identification of human cytochrome P450 enzyme(s) responsible for the metabolism of SCH 900340
14) In vitro evaluation of SCH 900340 as an inducer of cytochrome P450 expression in cultured human hepatocytes (Study No. 002-NCL PK-046-01)
15) In vitro assessment of human liver cytochrome P450 inhibition potential of SCH 900340 (AN2690) (Study No. 002-NCL PK-053-01)

Repeat dose toxicology

1) A 3-month dose range finding study of AN2690 administered topically to CD-1 mice (Study No. 002-NCL TX-041-01)
2) Evaluation of in vivo toxicity of AN2690 in male Sprague-Dawley rats following oral administration for 28 days (Study No. 002-NCL TX-002-01)
3) AN2690: A 28-day oral toxicity study in rats (Study No. 002-NCL TX-026-01)

4) A 6-month toxicity study of AN2690 administered by the oral (gavage) route to rats with a 28-day recovery period (Study No. 002-NCL TX-007-01)
5) AN2690: A 28-day dermal toxicity study in Gottingen minipigs (Study No. 002-NCL TX-030-01)
6) A 3-month toxicity study of AN2690 solution administered by the dermal route to minipigs (Study No. 002-NCL TX-016-01)
7) A 6-month toxicity study of AN2690 solution administered by the dermal route to minipigs with a 1-month recovery period (Study No. 002-NCL TX-022-01)
8) A nine-month toxicity study of AN2690 solution administered by the dermal route to Gottingen minipigs with a one-month recovery period (Study No. 002-NCL TX-072-01)

Genotoxicity

1) Bacterial reverse mutation assay (Study No. 022-NCL TX-034-01)
2) In vitro mammalian chromosome aberration test (Study No. 022-NCL TX-036-01)
3) Mammalian erythrocyte micronucleus test (Study No. 022-NCL TX-038-01)

Carcinogenicity

1) AN2690: A 104-week oral carcinogenicity study in Sprague-Dawley rats (Study No. 002-NCL TX-071-01)
2) A 104 week dermal oncogenicity study of AN2690 in mice (Study No. 002-NCL-TX-073-01)

Reproductive and Developmental Toxicology

1) Study of fertility and early embryonic development to implantation in rats following oral administration of AN2690 (Study No. 002-NCL TX-068-01)
2) An oral range-finding prenatal developmental toxicity study of AN2690 in rats (Study No. 002-NCL TX-064-01)
3) An oral prenatal developmental toxicity study of AN2690 in rats (Study No. 002-NCL TX-069-01)
4) A range-finding dermal prenatal developmental toxicity study of AN2690 in New Zealand White rabbits (Study No. 002-NCL TX-065-01)
5) A dermal prenatal developmental toxicity study of AN2690 in New Zealand White rabbits (Study No. 002-NCL TX-067-01)
6) A pilot embryo-fetal developmental toxicity and toxicokinetic study of SCH 900340 administered orally by gavage in rabbits (Study No. 002-NCL TX-079-01)
7) Embryo-fetal developmental toxicity and toxicokinetic study of SCH 900340 administered orally by gavage in rabbits (Study No. 002-NCL TX-080-01)
8) Prenatal and postnatal developmental toxicity and maternal function study of SCH 900340 (AN2690) administered orally by gavage in rats (Study No. 002-NCL TX-074-01)

Special Toxicology

1) Primary eye irritation of 10% AN2690 solution and AN2690 vehicle (Study No. 002-NCL TX-040-01)
2) FHSA primary skin irritation (Study No. 002-NCL TX-042-05)
3) Acute dermal irritation of 10% AN2690 solution and AN2690 vehicle (Study No. 002-NCL TX-043-01)
4) Dermal sensitization in Guinea pigs – Magnusson Kligman (ISO) method (Study No. 002-NCL TX-044-01)

Toxicology studies conducted with impurities

1) Bacterial mutagenicity study of SCH 900340 – Impurity qualification assessment (Study No. 002-NCL TX-075-01)
2) Chromosome aberration study of SCH 900340 (AN2690) in human peripheral blood lymphocytes – Impurity qualification assessment (002-NCL TX-076-01)
3) One month oral (gavage) qualification study of SCH 900340 in rats (Study No. 002-NCL TX-077-01)

3.2 Studies Not Reviewed

Pharmacokinetics

The method validation reports for measurement of AN2690 in minipig, dog, mouse, rabbit and rat plasma have not been formally reviewed.

Repeat dose toxicity

The following study was not reviewed because it was a preliminary study and longer term repeat dose dermal toxicity studies conducted in minipigs have been reviewed.

A 2-month dermal irritation study of AN2690 in male Gottingen minipigs (Study No. 002-NCL TX-054-01)

3.3 Previous Reviews Referenced

Pharmacology/Toxicology reviews under IND 71206

4 Pharmacology

4.1 Primary Pharmacology

Tavaborole is an oxaborole antifungal agent and represents a new molecular entity. Tavaborole is being developed for the topical treatment of onychomycosis.

In vitro assays show that tavaborole is active against a broad range of fungal pathogens. Tavaborole exhibits fungicidal activity against *T. rubrum* and *T. mentagrophyte*, both of which are directly implicated in onychomycosis. In vitro assays

conducted in *S. cerevisiae* provide preliminary information that indicates that tavaborole may have a unique mechanism of inhibition by targeting the CDC60 gene sequence (the cytoplasmic leucyl-tRNA synthetase) as a target for antifungal activity.

4.2 Secondary Pharmacology

AN2690 (10 µM) did not significantly inhibit release of TNF-α, IL-1β, IL-6 or IL-8 (proinflammatory cytokines) from THP-1 cells challenged with liposaccharide. The THP-1 cell line (TIB-202, ATCC) was derived from a patient with acute monocytic leukemia.

AN2690 (10 µM) was tested against a panel of 50 transmembrane and soluble receptors, ion channels and mono-amine transporters. All assays were performed using competition against radioligands. The percent inhibition of control specific radioligand binding was considered significant only for values greater than 50% inhibition. AN2690 did not significantly inhibit any of the receptors tested in this study.

AN2690 was tested against a panel of 5 human recombinant CYP450 isoforms including: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The percent of inhibition of control values was considered significant only for values greater than 30% inhibition. AN2690 did not significantly inhibit any of the CYP450 isoforms tested in this study.

4.3 Safety Pharmacology

Neurological effects

The effects of AN2690 on behavior and on the central autonomic and somatic nervous systems were investigated in rats. Single oral doses of 0, 30, 100 or 200 mg/kg AN2690 (in 1% carboxymethylcellulose; 5 ml/kg) or 20 mg/kg diazepam were administered to male Sprague-Dawley rats (6/group). A functional observational battery of observations that included behavioral, neurological (sensimotor)/neuromuscular and autonomic evaluations was recorded for each rat prior to dosing and at 0.25, 1, 2 and 3 hours post dose. No treatment related effects on any of the functional observational battery of observations were noted in this study. The positive control generated an appropriate response in this study.

Cardiovascular effects

The effects of AN2690 on the cardiovascular system were evaluated in an in vitro HERG assay and in an in vivo cardiovascular safety pharmacology study conducted in Beagle dogs.

AN2690 (1 µM) was tested for HERG-channel inhibition. The mean percent inhibition of tail current amplitude was 22.6%. The potency ranking used for this study used the following criteria: high potency is greater than 50% inhibition, medium potency is 25 – 50% inhibition and low potency is less than 25% inhibition. AN2690 was classified as a

low-potency HERG-channel blocker based on its HERG tail current inhibition in this study.

Four adult naïve male Beagle dogs (8.1 – 8.9 kg) were used in the in vivo cardiovascular safety pharmacology study. Single oral doses of 0, 30, 100 or 200 mg/kg AN2690 (in 1% carboxymethylcellulose; 5 ml/kg) or 5 mg/kg isoproterenol hydrochloride (positive control) were administered in a latin-square design. Approximately 48 hours was allowed as a washout period between successive doses. The positive control was administered as the last dose in each animal. Telemetry recordings were continuously collected on each treatment day for all the evaluated parameters (systolic, diastolic and mean arterial blood pressure and pulse rate) for at least 1.5 hours before dosing and for at least 24 hours post dose. Electrocardiograms were obtained from subcutaneous biopotential leads and from the telemetry transmitter in a Lead II configuration. Average values for heart rate, PR, QT and QTc intervals and QRS duration, locomotor activity and body temperature were reported every 15 min.

No treatment related effects on blood pressure, electrocardiograms, body temperature, locomotor activity, pulse rate or heart rate were noted at 30 mg/kg. No treatment related effects on the pattern of the P-QRS-T complexes, PR, QT and QTc intervals and the duration of the QRS complex were noted at doses up to 200 mg/kg. A dose related increased, reversible, mild to marked hypotension was noted from the 100 mg/kg to 200 mg/kg doses. In parallel, variable, transient increases in heart and pulse rates were noted shortly after administration of the 100 and 200 mg/kg doses. Treatment related clinical findings noted at the 100 and 200 mg/kg doses included evidence of discharge and liquid feces. The positive control generated an appropriate response on blood pressure and heart rate in this study.

Summary

AN2690 did not elicit any neurological effects at doses up to 200 mg/kg in rats. AN2690 did not elicit any cardiovascular effects in dogs at the 30 mg/kg dose (NOEL). AN2690 caused a dose-related, reversible, mild to marked hypotension and variable, transient increase in heart and pulse rates at doses of 100 and 200 mg/kg in dogs.

It is not anticipated that the cardiovascular effects noted in the safety pharmacology study conducted in dogs would be of concern for the clinical use of the tavaborole solution due to a much lower extent of systemic exposure under conditions of clinical use (topical application to toenails for the treatment of onychomycosis).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Methods of Analysis

Bioanalytical methods were developed to measure tavaborole in mouse, rat, rabbit, dog, and minipig plasma. Liquid chromatographic-tandem mass spectrometric methods with

atmospheric pressure ionization (LC-API/MS/MS) with a lower limit of quantitation (LLOQ) of 25 ng/mL or 100 ng/mL were developed and validated for determination of rat tavaborole plasma concentrations in studies performed under GLP regulations. An LC-API/MS/MS method with a LLOQ of 100 ng/mL was developed and validated for determination of tavaborole plasma concentrations in minipigs. Because it was determined that acidification stabilizes tavaborole in plasma samples, LC-MS/MS methods with LLOQs of 25 ng/mL or 100 ng/mL were developed and validated for determination of tavaborole concentrations in acidified rat and rabbit plasma, respectively.

Absorption

Tavaborole absorption was assessed in the rat (after oral [PO], subcutaneous [SC], and intravenous [IV] administration of single and multiple dosing in both fasted and fed conditions); in the dog (following PO administration); and in the minipig and mouse (following topical administration). Tavaborole was found to be rapidly absorbed and excreted in rats and dogs following oral administration. However, systemic exposure was found to be low, and in some cases below the level of quantitation, following SC and topical tavaborole administration to rats and minipigs.

The in vitro plasma protein binding of [^{3}H]-tavaborole was determined in mice, rats, rabbits, dogs, minipig and humans using ultrafiltration. The range of plasma protein binding in all species ranged between 26.9% to 80.2%, which suggests that the extent of tavaborole protein binding is low to moderate. The range of [^{3}H]-tavaborole plasma protein binding in human plasma (45.8 – 76.9%) was generally similar to that observed in mice (26.9 – 48.7%), rats (40.7 – 59.3%), rabbits (46.4% - 62.3%) and dogs (38.7 – 66.3%), but minipig (55.0 – 80.2%) was slightly higher compared to humans.

Distribution

To determine the extent of distribution of tavaborole in tissues, a tissue distribution study of [^{14}C]-tavaborole was conducted in pigmented mice. After a single dermal dose, [^{14}C]-tavaborole was rapidly and incompletely absorbed, then widely distributed to tissues. Concentrations of [^{14}C]-tavaborole were below quantifiable limits in all tissues by 168 hours (7 days) post-dose.

Metabolism

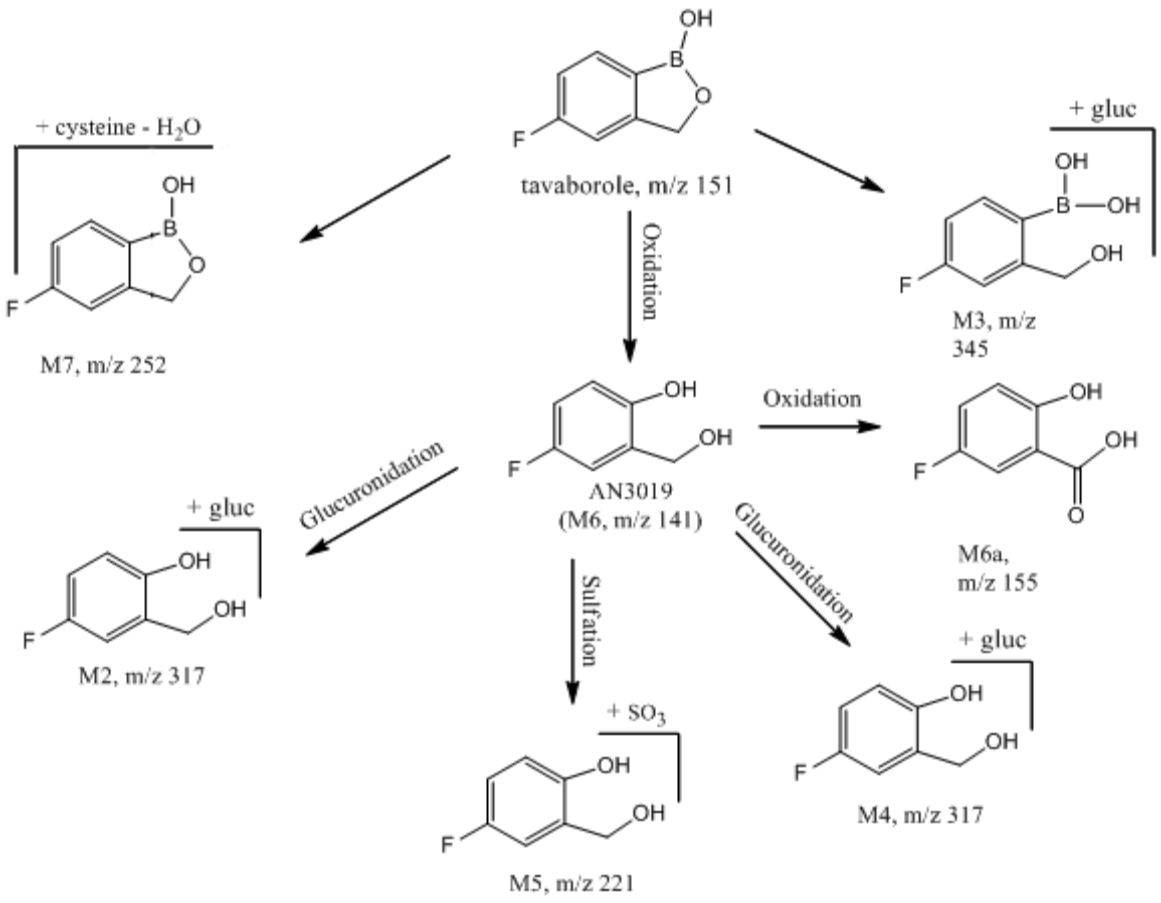
The metabolism of tavaborole was studied both in vitro and in vivo. In vitro, the human cytochrome P450 enzymes mainly responsible for the metabolism of tavaborole were CYP3A5 and CYP2C18. CYP2C19 and CYP3A4 had a minor role in the formation of the major metabolite, M6 (AN3019). Flavinmonooxygenases (FMO3 and FMO5) are involved in the formation of the intermediate metabolite M6. In a separate study evaluating the in vitro metabolism of tavaborole in mouse, rat, minipig, and human liver fractions, no significant metabolism of tavaborole was observed by cytochrome P450,

glucuronidation, or sulfation. Tavaborole was metabolically stable under the tested conditions.

In vivo metabolic studies of [^{14}C]-tavaborole administered to mice and rats revealed similar metabolic profiles in both species. Biotransformation of tavaborole after dermal administration to mice involves oxidative oxaborole ring cleavage followed by sulfation or glucuronidation. In male and female mice dosed with a dermal application of radiolabeled tavaborole, the prominent circulating drug-derived components in plasma were the parent drug, a sulfate-conjugate (M5), a glucuronide-conjugate (M2), a benzyl alcohol metabolite (M6), and a benzoic acid metabolite (M6a). The [^{14}C]-tavaborole-derived radioactivity was primarily excreted in the urine as the sulfate-conjugate (M5), representing 31% to 35% of the dose.

Similarly, in rats receiving a single oral [^{14}C]-tavaborole dose, the major drug-related components in plasma were a sulfate-conjugate (M5) and a benzoic acid metabolite (M6a). The sulfate-conjugate (M5), representing ~62% of the dose in rats, was the major rat metabolite. In addition to the parent drug, other prominent circulating metabolites included a benzyl alcohol metabolite (M6) and its glucuronide-conjugate (M2), a boronic acid-glucuronide metabolite (M3) and a cysteine-conjugate metabolite (M7), while M6-glucuronide (M4) was minor. Approximately 80% of the dose was excreted in 0- to 24-hour rat urine. The parent drug was not detected in rat urine. The remainder of the radioactive dose was excreted in the form of glucuronides (M2, M3, and M4), the benzoic acid metabolite (M6a) and the cysteine-conjugate metabolite (M7). Approximately 3% of the dose was excreted in rat feces, with no single metabolite greater than 1% of the dose within a 0- to 48-hour period.

The proposed biotransformation pathways of tavaborole are provided below (copied from NDA submission).



Excretion

The excretion pattern of [^{14}C]-tavaborole-derived radiocarbon was found to be similar in mice and rats. The most important route of elimination of absorbed radiocarbon was via the urine with lesser amounts excreted in feces in both species. In mice administered a dermal dose of tavaborole, the most prominent route of elimination was via the urine (≥ 33.5%), with minimal excreted in the feces (≤ 1.71%). Renal excretion was also the most prominent route of elimination in the rat (≥ 81.2% of the radioactive dose) with fecal excretion representing a minor route of elimination (≤ 2.87% of the radioactive dose).

Effects of tavaborole on CYP enzymes

Tavaborole (up to 12.6 µM) was not an inducer of any of the evaluated CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5). There was evidence of time-dependent and partial NADPH-dependent inhibition of CYP2A6 activity

at a concentration of tavaborole > 30 µM. However, there was insufficient inhibition across the range of tavaborole concentrations examined to calculate an IC_{50} value. Tavaborole caused direct inhibition of CYP2E1, but at an IC_{50} value of >100 µM. Therefore, it is unlikely that tavaborole would have any effects on the induction or inhibition of CYP enzymes under conditions of clinical use due to low systemic exposure after topical administration of tavaborole to toenails.

5.2 Toxicokinetics

Refer to Section 6.2 Repeat Dose Toxicity for description of toxicokinetic information.

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose toxicology studies were not conducted with tavaborole.

6.2 Repeat-Dose Toxicity

Study 1

A 3-month dose range finding study of AN2690 administered topically to CD-1 mice (GLP; Study No. 002-NCL TX-041-01)

This study was conducted as a dose range finding study for a dermal mouse carcinogenicity study. Dermal doses of 0 (vehicle), 17 (1.7%), 33 (3.3%), 50 (5.0%), 100 (10%) and 150 (15%) mg/kg/day AN2690 were administered daily to CD-1 mice for 3 months. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v).

Treatment related findings noted in this study were minimal and restricted to the treated skin site only. A yellowish white to white residue (presumably residual drug) was present at the application site at the 1 hour post dose observation time in mice treated with 10% and 15% AN2690 solution. This finding suggested that the 10% and 15% AN2690 solutions were achieving the maximum topical exposure levels in this clinical formulation.

Very slight erythema was present sporadically in females in all AN2690 treatment groups. Increased signs of erythema (very slight to moderate) were noted in males in the 3.3%, 5%, 10% and 15% AN2690 treatment groups sporadically throughout each dose group and throughout the study. No dose dependent relationship was noted for this finding. Treatment related histopathological findings were limited to the skin of male animals only and were very minimal. Minimal acanthosis was noted in all treated male groups including vehicle control at a low incidence rate (1/5 for all groups). No treatment related effects on microscopic parameters were noted in female animals in this study. The NOAEL was identified as 150 mg/kg/day AN2690 (15% AN2690 solution) in mice after topical administration for 3 months, under the conditions of this study.

Study 2

Evaluation of in vivo toxicity of AN2690 in male Sprague-Dawley rats following oral administration for 28 days (non-GLP; Study No. 002-NCL TX-002-01)

Oral (gavage) doses of 0, 100, 200, 500 or 1000 mg/kg/day AN2690 were administered to Sprague-Dawley rats (5 males/group) for 28 days. The vehicle used in this study was 1% carboxymethyl cellulose.

One hundred percent mortality was noted in the 1000 mg/kg/day group with the first deaths noted on day 2. Body weight and body temperatures started decreasing after the first dose and continued until death. No blood or tissues samples could be obtained from this dose group. Sixty percent mortality was noted in the 500 mg/kg/day group with the first deaths noted at day 6. Body weight gain was decreased in this group and body temperatures were routinely 2-3 ºC lower than the control group. Serum cholesterol was significantly decreased in this group.

No treatment related effects on body weight, body temperatures, clinical signs, body weights, macroscopic findings or organ weights were noted in the 100 and 200 mg/kg/day dose groups. A significant decrease in serum cholesterol was noted in the 200 mg/kg/day dose group. Microscopic evaluation was not performed in this study. The NOEL was identified as 100 mg/kg/day in this study.

Study 3

AN2690: A 28-day oral toxicity study in rats (GLP; Study No. 002-NCL TX-026-01)

Oral (gavage) doses of 0, 30, 50, 100 and 200 mg/kg/day AN2690 were administered to Sprague-Dawley rats for 28 days. The vehicle used in this study was 1% carboxymethyl cellulose. A NOAEL could not be determined in this study. Treatment related microscopic findings were noted in the nonglandular stomach in all dose groups. Microscopic findings were more prominent in males than females which correlated with the increased systemic exposure. No other treatment related findings were noted in this study.

A summary of the mean pharmacokinetic parameters for AN2690 measured in this study is provided in the following table.

Dose (mg/kg/day)	T_{max} (hr)		C_{max} (µg/ml)		$AUC_{0\text{-}4\ hr}$ (µg·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
30	0.25	0.25	1.23	0.61	0.41	0.19
50	0.25	0.25	2.84	2.67	1.15	1.04
100	0.25	0.25	9.91	9.93	4.99	3.92
200	0.25	0.25	23.4	18.0	17.2	11.6
Day 28						
30	0.25	0.25	0.71	0.18	0.33	0.17
50	0.25	0.25	0.69	0.4	0.51	0.20
100	0.25	0.25	1.61	0.85	1.03	0.45
200	0.5	0.25	4.33	2.48	3.83	1.97

A greater than dose proportional increase in systemic exposure was noted in males and females on day 1. A close to dose proportional increase in systemic exposure was noted in males and females on day 28. Males exhibited a greater systemic exposure to AN2690 at each dose level compared to females. Significantly less systemic exposure was noted on day 28 compared to day 1 at all dose levels and in male and female animals.

Study 4

Study title: A 6-month toxicity study of AN2690 administered by the oral (gavage) route to rats with a 28-day recovery period

Study no.:	002-NCL TX-007-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6-29-05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690; Lot# MCLS 1144-150-1, MCLS 1161-028-1, MCLS 1161-043-1, MCLS 1161-064-1, MCLS 1208-005-1, MCLS 1161-132-1; 99.2%

Key Study Findings

A treatment related decrease in body weight was noted in high dose animals (males: ↓12%; females: ↓5%) compared to vehicle control animals. Treatment related microscopic findings (epithelial hyperplasia and hyperkeratosis) were noted in the nonglandular stomach in mid-low, mid-high and high dose groups. A dose dependent increase in severity and incidence was noted for the epithelial hyperplasia and hyperkertaosis findings in the nonglandular stomach. The treatment related findings in the nonglandular stomach were not noted in recovery animals. Very minimal treatment related histopathological effects were noted in the nonglandular stomach in low dose animals. The NOAEL was identified as 30 mg/kg/day AN2690 ($AUC_{0\text{-}3\ hr}$ = 0.21 and

0.24 µg·hr/ml in males and females, respectively) in rats after administration for 6 months, under the conditions of this study.

Methods

Doses:	0, 30, 50, 100 and 200 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral (gavage)
Dose volume:	10 ml/kg
Formulation/Vehicle:	1% carboxymethyl cellulose
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10/sex/group
Age:	7 weeks
Weight:	Males: 203-238 g; Females: 153-181 g
Satellite groups:	TK: 14/sex/group excluding vehicle control group Recovery: 5/sex/group for vehicle control and high dose
Unique study design:	N/A
Deviation from study protocol:	None of significance

Observations and Results

Mortality

Mortality was evaluated daily. Three vehicle control animals (2 males; 1 female), one mid-low dose male and two high dose females died during the study. No treatment related effects on mortality were noted in this study.

Clinical Signs

Clinical signs were evaluated daily. Treatment related effects on clinical signs (sporadic salivation, transient decreased activity and wobbly gait) were noted in this study. The treatment related effects were primarily noted in high dose animals with a few observations noted in mid-high dose animals. No treatment related effects on clinical signs were noted in the recovery animals.

Body Weights

Body weights were evaluated weekly. A treatment related effect on body weight was noted in high dose animals (males: ↓12%; females: ↓5%) compared to vehicle control animals in this study. No treatment related effects on body weight were noted in the recovery animals.

Feed Consumption

Food consumption was evaluated weekly. No treatment related effects on food consumption were noted in this study.

Ophthalmoscopy

Ophthalmology was evaluated prior to treatment and at the end of treatment. No treatment related effects on ophthalmologic parameters were noted in this study.

ECG

N/A

Hematology

Hematology was evaluated at the end of treatment and end of recovery. No treatment related effects on hematologic parameters were noted in this study.

Clinical Chemistry

Clinical chemistry was evaluated at the end of treatment and end of recovery. No treatment related effects on clinical chemistry parameters were noted in this study.

Urinalysis

Urinalysis was evaluated at the end of treatment and end of recovery. No treatment related effects on urinalysis parameters were noted in this study.

Gross Pathology

A necropsy was performed at the end of treatment and at the end of recovery. No treatment related effects on macroscopic parameters were noted in this study.

Organ Weights

The following organ weights were obtained: adrenals, brain, epididymis, heart, kidneys, liver, lung, ovaries, pituitary, prostate, salivary gland, seminal vesicles, spleen, testes, thymus, thyroid, uterus. No treatment related effects on organ weights were noted in this study.

Histopathology

The following organs were preserved from all animals in all treatment groups: adrenals, aorta, bone (femur, sternum), bone marrow (sternum), brain, cecum, cervix, colon, duodenum, epididymis, esophagus, eyes with optic nerve, harderian gland, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mandibular, mesenteric), mammary gland, ovaries, pancreas, pituitary gland, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin (mammary), spinal cord, spleen, stomach, testes, thymus, thyroid with parathyroid, tongue, trachea, urinary bladder, uterus, vagina and gross lesions/masses

Histological examination was performed for all preserved tissues for control and high dose animals only. Histological examination was also performed for all preserved tissues for animals found dead or euthanized moribund. Histological examination was performed for gross lesions in low and mid dose animals. The stomach was identified as a target tissue and underwent histological examination in low and mid dose animals.

Adequate Battery
Yes

Peer Review
Yes

Histological Findings

Treatment related findings were limited to the nonglandular stomach and included epithelial hyperplasia and hyperkeratosis findings noted in mid-low, mid-high and high dose animals (refer to table below copied from the study report). A dose dependent increase in severity and incidence was noted for the epithelial hyperplasia and hyperkeratosis findings in the nonglandular stomach. The treatment related findings in the nonglandular stomach were not noted in recovery animals. Very minimal treatment related histopathological effects were noted in the nonglandular stomach in low dose animals.

Table 5 – Test Article-related Histopathology Findings in Non-Glandular Stomach

	Males					Females				
Dose (mg/kg)	**0**	**30**	**50**	**100**	**200**	**0**	**30**	**50**	**100**	**200**
3-Month Euthanasia										
# Ex	10	10	10	10	10	9	10	10	10	10
Stomach, Non-glandular										
Hyperplasia	(0)	(0)	(6)	(10)	(10)	(1)	(2)	(5)	(10)	(10)
Minimal	0	0	2	0	0	1	2	1	1	0
Mild	0	0	4	10	4	0	0	4	4	4
Moderate	0	0	0	0	4	0	0	0	5	5
Marked	0	0	0	0	2	0	0	0	0	1
Hyperkeratosis	(0)	(0)	(5)	(10)	(9)	(0)	(0)	(6)	(10)	(9)
Minimal	0	0	0	1	4	0	0	2	1	0
Mild	0	0	5	9	4	0	0	4	4	5
Moderate	0	0	0	0	1	0	0	0	5	4
3-Month Recovery										
# Ex	5	0	0	0	5	5	0	0	0	5
Stomach, Non-glandular										
Hyperplasia	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Hyperkeratosis	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
6-Month Euthanasia										
# Ex	10	10	9	10	10	10	10	10	10	10
Stomach, Non-glandular										
Hyperplasia	(0)	(1)	(7)	(10)	(9)	(0)	(0)	(4)	(8)	(9)
Minimal	0	0	1	1	1	0	0	2	0	3
Mild	0	1	5	3	2	0	0	2	7	2
Moderate	0	0	1	5	3	0	0	0	1	2
Marked	0	0	0	1	3	0	0	0	0	2
Hyperkeratosis	(0)	(2)	(8)	(10)	(8)	(0)	(0)	(6)	(8)	(8)
Minimal	0	1	3	1	1	0	0	2	1	1
Mild	0	1	4	6	3	0	0	4	6	4
Moderate	0	0	1	3	4	0	0	0	1	3
Marked	0	0	0	0	0	0	0	0	0	0
6-Month Recovery										
# Ex	3	0	0	0	5	5	0	0	0	3
Stomach, Non-glandular										
Hyperplasia	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Hyperkeratosis	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Special Evaluation

N/A

Toxicokinetics

Blood samples were obtained on days 1, 90 and 181 from TK animals. Blood was taken at 0, 0.25, 0.5, 1, 2 and 3 hours post dose (4/sex/timepoint). A summary of the mean pharmacokinetic parameters for AN2690 measured in this study is provided in the following table.

Dose (mg/kg/day)	T_{max} (hr)		C_{max} (µg/ml)		$AUC_{0-3\ hr}$ (µg·hr/ml)	
	Males	Females	Males	Females	Males	Females
Day 1						
30	0.25	0.25	1.77	1.74	0.93	1.03
50	0.25	0.25	2.17	3.3.4	0.89	1.06
100	0.25	0.25	9.58	11.1	5.76	6.10
200	0.5	0.5	23.8	28.5	24.1	59.5
Day 90						
30	0.5	0.25	0.37	0.39	0.29	0.26
50	0.25	0.5	0.74	2.56	0.67	1.23
100	0.25	0.25	2.96	1.23	1.43	0.73
200	0.25	0.25	18.4	9.96	6.31	4.46
Day 181						
30	0.5	0.25	0.26	0.36	0.21	0.24
50	0.5	0.25	1.03	0.78	0.89	0.68
100	0.25	0.25	2.15	1.73	1.63	1.92
200	0.25	0.5	7.83	5.63	5.56	7.09

A greater than dose proportional increase in systemic exposure was noted in males and females on day 1. A close to dose proportional increase in systemic exposure was noted in males and females on day 90 and 181, except for high dose animals. No apparent difference in systemic exposure was noted based on sex. Significantly less systemic exposure was noted on days 90 and 181 compared to day 1 at all dose levels and in male and female animals. The extent of systemic exposure was similar on days 90 and 181 across the dose groups.

Dosing Solution Analysis

The percent AN2690 in the formulation ranged from 89.8 – 99.1%. The dosing solutions were acceptable for this study.

Study 5

AN2690: A 28-day dermal toxicity study in Gottingen minipigs (Study No. 002-NCL TX-030-01)

Dermal doses of 0 (vehicle), 0.9 (1%), 6.4 (7%), 9.2 (10%) and 13.8 (15%) mg/kg/day AN2690 were administered daily to Gottingen minipigs (4/sex/dose) for 28 days. Test article was administered to 5% total body surface area at a dose volume of 5 µl/cm^2. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v).

The only treatment related toxicity that was noted in this study was a dose dependent increase in dermal irritation at the treatment site. The systemic NOAEL for AN2690 solution was 15% AN2690 solution and the dermal NOAEL for the AN2690 solution was 1% AN2690. Limited systemic exposure was noted after dermal administration of AN2690 solution to minipigs.

Study 6

A 3-month toxicity study of AN2690 solution administered by the dermal route to minipigs (Study No. 002-NCL TX-016-01)

Dermal doses of 0 (vehicle), 1.0 (1%), 2.8 (3%), 4.7 (5%) and 9.6 (10%) mg/kg/day AN2690 were administered daily to Gottingen minipigs (4/sex/dose) for 3 months. Test article was administered to 5% total body surface area at a dose volume of 5 µl/cm^2. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v).

The only treatment related toxicity that was noted in this study was a dose dependent increase in dermal irritation at the treatment site. The systemic NOAEL for AN2690 solution was 10% AN2690 solution and the dermal NOAEL for the AN2690 solution was 1% AN2690. Limited systemic exposure was noted after dermal administration of AN2690 solution to minipigs.

Study 7

A 6-month toxicity study of AN2690 solution administered by the dermal route to minipigs with a 1-month recovery period (Study No. 002-NCL TX-022-01)

Dermal doses of 0 (vehicle), 0.9 (1%), 2.8 (3%), 4.7 (5%) and 9.2 (10%) mg/kg/day AN2690 were administered daily to Gottingen minipigs (4/sex/dose) for 6 months. Test article was administered to 5% total body surface area at a dose volume of 5 µl/cm^2. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v).

The only treatment related toxicity that was noted in this study was a dose dependent increase in dermal irritation at the treatment sight. The extent of dermal irritation noted in high dose animals was severe enough that all of the high dose animals were euthanized prior to the end of the study. The systemic NOAEL for AN2690 solution was 10% AN2690 solution and the dermal NOAEL for the AN2690 solution was 1% AN2690. Limited systemic exposure was noted after dermal administration of AN2690 solution to minipigs.

It appears that 10% AN2690 is greater than the maximum tolerated dose in minipigs after 6 months of daily topical administration based on the extent of dermal irritation noted in this study.

Study 8

Study title: A nine-month toxicity study of AN2690 solution administered by the dermal route to Gottingen minipigs with a one-month recovery period

Study no.:	002-NCL TX-072-01
Study report location:	Electronic, SND 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 30, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690 solution vehicle, Lot# LB-07001 0.3% AN2690 solution, Lot# LB-07002 1% AN2690 solution, Lot# LB-07003 3% AN2690 solution, Lot# LB-07004 3% AN2690 solution + degradants, Lot# LB-07005

Key Study Findings

The only treatment related toxicity that was noted in this study was a dose dependent increase in the incidence and severity of dermal effects at the treatment sight. There were no differences in the dermal findings between the 3% AN2690 group with and without degradants. The systemic NOAEL for AN2690 solution was 3% AN2690 solution ($AUC_{0\text{-}8\ hr}$ = 753 ng·hr/ml). A dermal NOAEL for the AN2690 solution was not established in this study. Limited systemic exposure was noted after dermal administration of AN2690 solution to minipigs. Systemic exposure was only noted in the high dose group, 3% AN2690 solution, in this study.

Methods

Doses:	0 (untreated control), 0 (vehicle control), 0.3%, 1%, 3% and 3% (+ degradants) AN2690 solution [Degradants were (b) (4)]
Frequency of dosing:	Once daily
Route of administration:	Topical
Dose volume:	5 µl/cm^2
Formulation/Vehicle:	Propylene glycol/ethanol (20/80, v/v)
Species/Strain:	Gottingen minipig
Number/Sex/Group:	Refer to table below
Age:	3 – 5 months
Weight:	Males: 8 – 13 kg; Females: 9 – 14 kg
Satellite groups:	Refer to table below
Unique study design:	Test article was applied topically to a hair clipped, unoccluded treatment site that was equal to 10% total body surface area.
Deviation from study protocol:	None of significance

Group Number	Number of Animals[a]		Test Article	Dose Concentration of AN2690 (v/v)	Dose Volume (µL/cm^2)
	Males	Females			
1	3	3	Untreated Control	0	0
2	6	6	Vehicle Control	0	5
3	6	6	Test Article 1: AN2690	0.3%	5
4	6	6	Test Article 2: AN2690	1.0%	5
5	6	6	Test Article 3: AN2690	3.0%	5
6	6	6	Test Article 4: AN2690 + degradants[b]	(b) (4)	

[a]Up to four animals/sex/group in Groups 2-6 were necropsied after nine months of treatment. The remaining two animals/sex/group in Groups 2-6 were necropsied following a one-month recovery period. Group 1 animals were not necropsied, but were euthanized and discarded at the end of the recovery period.

[b]The test article for Group 6 contained 3.0% AN2690, (b) (4) (b) (4)

Observations and Results

Mortality

Mortality was evaluated twice daily. One group 5 female died on day 38 from multi-organ hemorrhage that was not considered treatment related. One group 6 male was euthanized in moribund conduction on day 80 due to dermatitis at the treated site that was considered to be treatment related.

Clinical Signs

Clinical signs were evaluated once daily. Treatment related clinical signs noted in group 4 – 6 animals that were related to dermal irritation included: carriage low, sensitivity/hypersensitivity to touch, abnormal vocalization, excessive scratching, abnormal surface material, discharge, abrasion, fissuring, raised areas, scabbed areas, scaling, red skin discoloration, dry skin, thickened skin, and ulceration. These clinical signs were first noted during the first month of treatment and continued through the treatment period. Clinical signs related to dermal irritation (scaling, dry skin, abrasion, brown or red skin discoloration and scabbed areas) persisted though the recovery period but with lower incidences which suggests partial recovery.

Due to the adverse dermal effects, dosing holidays were prescribed by the veterinarian as needed during the study. The following table summarizes the total number of days that the affected animals were not dosed during the 273 day treatment period.

Summary of Missed Doses

Group and Sex	Animal Number	Total Number of Missed Doses
Group 2 male	5217	1
Group 2 male	5227	18
Group 2 female	5218	1
Group 2 female	5220	1
Group 2 female	5224	3
Group 3 male	5231	9
Group 3 male	5233	1

Summary of Missed Doses (Continued)

Group and Sex	Animal Number	Total Number of Missed Doses
Group 3 female	5230	1
Group 3 female	5234	18
Group 3 female	5240	1
Group 4 male	5241	10
Group 4 male	5249	15
Group 4 female	5242	31
Group 4 female	5244	5
Group 4 female	5248	14
Group 4 female	5252	22
Group 5 male	5253	9
Group 5 male	5255	31
Group 5 male	5257	45
Group 5 male	5261	4
Group 5 male	5263	37
Group 5 female	5254	50
Group 5 female	5256	9
Group 5 female	5260	36
Group 5 female	5262	35
Group 5 female	5264	2
Group 6 male	5265	39
Group 6 male	5269	27
Group 6 male	5271	8
Group 6 male	5273	10
Group 6 male	5275	4
Group 6 female	5266	1
Group 6 female	5268	20
Group 6 female	5270	20
Group 6 female	5272	30
Group 6 female	5274	32
Group 6 female	5276	26

Dermal Irritation

Dermal irritation was evaluated once weekly. There was a dose related increase in incidence and severity of dermal irritation noted during the treatment period. There did not appear to be a difference in the extent of dermal irritation noted between group 5 and 6. During the recovery period, desquamation and/or scabbing were frequently noted for all test article treatment groups.

Body Weights

Body weights were evaluated once weekly. No treatment related effects on body weights were noted in this study.

Feed Consumption

N/A

Ophthalmoscopy

Ophthalmology was evaluated prior to treatment and at during week 39. No treatment related effects on ophthalmologic parameters were noted in this study.

ECG

ECGs were obtained prior to treatment and during week 39. No treatment related effects on ECGs were noted in this study.

Hematology

Hematology was evaluated prior to treatment, during week 39 and 43. No treatment related effects on hematologic parameters were noted in this study.

Clinical Chemistry

Clinical chemistry was evaluated prior to treatment, during week 39 and 43. No treatment related effects on clinical chemistry parameters were noted in this study.

Urinalysis

N/A

Gross Pathology

A necropsy was performed at the end of treatment and at the end of recovery. The only treatment related effects on macroscopic parameters was crust formation at the treatment site.

Organ Weights

The following organ weights were obtained: adrenals, brain, heart, kidneys, liver, lung, ovaries, pituitary, prostate, spleen, testes. No treatment related effects on organ weights were noted in this study.

Histopathology

The following organs were preserved from all animals in Groups 2 - 6: adrenal gland, administration site (treated skin, dorsal), aorta, bone (femur), bone (sternum), bone marrow (sternum), brain (brain stem, cerebellum, cerebrum), cervix, epididymis, esophagus, eye, gall bladder, gross lesions, heart, intestine (cecum, colon, rectum, duodenum, ileum [with Peyer's patch], jejunum), kidney, lacrimal gland, liver, lung, lymph node (mandibular, mesenteric), mammary gland, nerve (optic, sciatic), ovary, pancreas, pituitary gland, prostate gland, salivary gland (mandibular), seminal vesicle, skeletal muscle, skin (untreated, abdominal and dorsal adjacent to dose site), spinal

cord (cervical, lumbar, thoracic), spleen, stomach (cardiac, fundic, pyloric), testis, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, and vagina.

Adequate Battery
Yes

Peer Review
Yes

Histological Findings

The only treatment related effects on microscopic parameters were noted at the treatment site. Treatment related findings at the treatment site were still noted after the one month recovery period in group 4 – 6 animals. Treatment related histopathology findings are summarized in the following tables (copied from the study report).

Summary of Test Article-Related Histologic Findings in Study Day 274 Animals

	Males					Females				
Group	2	3	4	5	6	2	3	4	5	6
Finding (Number of Animals)	(4)	(4)	(4)	(4)	(3*)	(4)	(4)	(4)	(3*)	(4)
Administration Site (Treated Skin, Dorsal)	N=4	N=4	N=4	N=4	N=3*	N=4	N=4	N=4	N=3*	N=4
Pustule, epidermal										
Minimal	1	0	0	1	0	0	0	0	0	0
Mild	0	0	1	0	0	0	0	0	0	2
Moderate	0	0	1	2	2	0	0	2	2	1
Marked	0	0	0	1	1	0	0	0	0	1
Hyperkeratosis, epidermal										
Minimal	1	1	2	1	0	2	0	1	1	0
Mild	1	0	1	1	1	0	0	1	1	2
Moderate	0	0	1	2	2	0	0	1	1	2
Hyperplasia, epidermal										
Minimal	0	1	0	0	0	0	0	0	1	1
Mild	0	0	2	2	1	0	1	1	0	1
Moderate	0	0	0	1	2	0	0	2	2	2
Edema, dermal										
Minimal	0	0	1	3	3	0	0	2	2	4

N= Number examined
*Only three Group 5 females and three Group 6 males were necropsied on Study Day 274 due to the early deaths of a Group 5 female (#5264) and a Group 6 male (#5269).

Summary of Test Article-Related Histologic Findings in Study Day 302 Animals

Finding / Group (Number of Animals)	Males					Females				
	2 (2)	3 (2)	4 (2)	5 (2)	6 (2)	2 (2)	3 (2)	4 (2)	5 (2)	6 (2)
Administration Site (Treated Skin, Dorsal)	N=2	N=2	N=2	N=2	N=2	N=2	N=2	N=2	N=2	N=2
Pustule, epidermal										
Minimal	2	0	1	0	0	0	0	1	0	0
Mild	0	1*	1	0	0	0	0	0	1	1
Moderate	0	0	0	1	1	0	0	0	0	0
Hyperkeratosis, epidermal										
Minimal	2	1	1	1	1	1	2	0	1	0
Mild	0	1*	1	0	0	0	0	1	1	1
Moderate	0	0	0	1	1	0	0	0	0	0
Hyperplasia, epidermal										
Minimal	0	0	1	1	0	0	0	0	0	1
Mild	0	1*	0	0	1	0	0	0	1	0

*In a Group 3 male (#5239), the pustules, hyperkeratosis, and hyperplasia were associated with an area of ulceration. Ulceration was not present in the other Study Day 302 animals. Based upon the association of the pustules, hyperkeratosis, and hyperplasia with the area of ulceration in this Study Day 302 Group 3 animal, the lack of ulceration in Study Day 302 Group 4, 5, and 6 animals, and the lack of microscopic findings at the administration site that were considered to be related to test article 1 in Study Day 274 Group 3 animals, these findings were not considered to be related to test article 1 in this Study Day 302 Group 3 male.

Special Evaluation

N/A

Toxicokinetics

Blood samples were obtained from animals in Groups 2 – 6 at 0.25, 1, 2, 3, 5 and 8 hours post dose on day 1 and at 0, 0.25, 1, 2, 3, 5 and 8 hours post dose on day 273. The mean toxicokinetic parameters are provided in the tables below (copied from the study report).

Table 1. Mean (±SD) Toxicokinetic Parameters of AN2690 in Mini-pigs Following Daily Dermal Administration of 0.3%, 1% and 3% AN2690 for Study Day 1

Dose (%AN2690)	Dose Group	Gender		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-8 hr}}$ (ng·hr/mL)
0.3%	3	M	Mean[1]	NC[2]	NC	NC	NC
			±SD	NC	NC	NC	NC
0.3%	3	F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	M	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
3%	5	M	Mean	180	1.5	305	413
			±SD	±55.1	±0.55	±140	±184
3%	5	F	Mean	74.7	2.0	144	207
			±SD	±84.4	±0	±171	±240
3%[3]	6	M	Mean	164	2.0	256	355
			±SD	±46.7	±0	±180	±221
3%[3]	6	F	Mean	67.3	2.0	91.6	140
			±SD	±74.5	±0	±127	±181
0.3%	3	M+F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	M+F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
3%	5	M+F	Mean	127	1.7	224	310
			±SD	±87.4	±0.50	±171	±231
3%[3]	6	M+F	Mean	116	2.0	174	247
			±SD	±77.8	±0	±171	±223

Table 2. Mean (±SD) Toxicokinetic Parameters of AN2690 in Mini-pigs Following Daily Dermal Administration of 0.3%, 1% and 3% AN2690 for Study Day 273

Dose (%AN2690)	Dose Group	Gender		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-8 hr}}$ (ng·hr/mL)
0.3%	3	M	Mean[1]	NC[2]	NC	NC	NC
			±SD	NC	NC	NC	NC
0.3%	3	F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	M	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
3%	5	M	Mean	297	1.3	703	871
			±SD	±77.6	±0.52	±267	±289
3%	5	F	Mean	243	1.2	480	611
			±SD	±60.5	±0.45	±192	±227
3%[3]	6	M	Mean	422	0.85	944	1100
			±SD	±94.7	±0.34	±541	±606
3%[3]	6	F	Mean	231	0.85	354	434
			±SD	±186	±0.34	±288	±334
0.3%	3	M+F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
1%	4	M+F	Mean	NC	NC	NC	NC
			±SD	NC	NC	NC	NC
3%	5	M+F	Mean	273	1.3	602	753
			±SD	±72.7	±0.47	±253	±284
3%[3]	6	M+F	Mean	318	0.85	622	737
			±SD	±176	±0.32	±504	±570

No assessment of AUC could be conducted in groups 3 and 4 due to the lack of measurable plasma concentrations in these animals. Systemic exposure was apparent in groups 5 and 6 and increased from day 1 to day 273. Males appeared to have higher systemic exposure compared to females. The presence of degradants in group 6 did not appear to affect systemic exposure compared to group 5.

Dosing Solution Analysis

Dosing solutions analyzed on days 1, 126, 182 and 273 were all within the protocol specifications of 90 – 110% of the theoretical concentrations.

7 Genetic Toxicology

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

Study title: Bacterial reverse mutation assay

Study no.:	022-NCL TX-034-01
Study report location:	Electronic , SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-25-05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# MCLS1161-028-1, 98.3%

Key Study Findings

AN2690 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 *uvr*A
Concentrations in definitive study:	0.5, 1.5, 5.0, 15, 50 and 150 µg/plate for tester strains TA98 and TA1537 (± S9; S9 derived from Aroclor 1254 induced rat liver homogenate) and TA1535 – S9; 1.5, 5.0, 15, 50, 150 and 500 µg/plate were tested for all other possible test conditions; 2 plates/dose
Basis of concentration selection:	Dose range finding study performed with dose levels of 0.15, 0.50, 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate in all tester strains. No precipitate was noted but toxicity was noted starting at 50 or 150 µg/plate. Based on the findings noted in the dose range finding study, the maximum doses plated in the definitive study were 150 µg/plate for TA98 and TA1537 ± S9 and for TA1535 – S9. The remaining test conditions tested up to 500 µg/plate.
Negative control:	DMSO
Positive control:	Refer to table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Plates were incubated at 37 ± 2ºC for 2 days (*S. typhimurinum*) or 3 days (*E. coli*) after treatment. Plates were counted for colony formation by hand after completion of the incubation period.

Test strain	S9 mix	Positive control	Dose (µg/plate)
TA 98	+	2-aminoanthracene	1.0
TA 98	–	2-nitrofluorene	1.0
TA 100	+	2-aminoanthracene	1.0
TA 100	–	Sodium azide	1.0
TA 1535	+	2-aminoanthracene	1.0
TA 1535	–	Sodium azide	1.0
TA 1537	+	2-aminoanthracene	1.0
TA 1537	–	9-aminoacridine	75
WP2*uvr*A	+	2-aminoanthracene	10
WP2*uvr*A	–	Methyl methanesulfonate	1000

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*uvr*A 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 more 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 of the 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

Study title: In vitro mammalian chromosome aberration test

Study no.:	022-NCL TX-036-01
Study report location:	Electronic , SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-20-05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# MCLS1161-028-1, 98.3%

Key Study Findings

AN2690 was negative in the human blood peripheral lymphocyte assay with and without S9 activation, under the conditions of this assay.

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	Concentrations of 1.25, 2.5, 5, 10, 15, 20, 25 µg/ml AN2690 were used for the 3 sets of incubation conditions
Basis of concentration selection:	The test compound was evaluated by testing 9 concentrations of AN2690 ranging from 0.151 µg/ml – 1510 µg/ml in the absence and presence of S9 for 4 hours or in the absence of S9 for 20 hours. Substantial toxicity (at least 50% reduction in the mitotic index relative to the solvent

	control) was noted at concentrations ≥15.1 µg/ml. Doses selected for the definitive study were based on the extent of toxicity noted in the dose range finding study.
Negative control:	DMSO
Positive control:	Mitomycin C (-S9): 0.6 µg/ml for 4 hour exposure, 0.3 µg/ml for 20 hour exposure Cyclophosphamide (+S9): 20 µg/ml for 4 hour exposure
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cell cultures were incubated with test article ± S9 for 4 hours and harvested 20 hours after treatment initiation. Cell cultures were incubated with test article –S9 for 20 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.

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)

Study title: Mammalian Erythrocyte micronucleus test

Study no:	022-NCL TX-038-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-25-05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# MCLS1161-028-1, 98.3%

Key Study Findings

AN2690 was negative in the in vivo rat micronucleus assay, under the conditions of this experiment.

Methods

Doses in definitive study:	0, 250, 500 and 1000 mg/kg AN2690
Frequency of dosing:	Once
Route of administration:	Oral (gavage)
Dose volume:	20 ml/kg
Formulation/Vehicle:	1% carboxymethylcellulose
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	5/sex/group/timepoint
Satellite groups:	N/A
Basis of dose selection:	Preliminary toxicity study was conducted with oral (gavage) doses of 1 (2 males), 10 (2 males), 100 (2 males), 500 (3/sex), 1000 (3/sex), 1200 (5/sex), 1400 (5/sex), 1600 (5/sex), 1800 (5/sex) and 2000 mg/kg (5/sex) AN2690 (20 ml/kg). Mortality was noted at doses ≥ 1200 mg/kg. No mortality was noted at 1000 mg/kg, which was set as the high dose in the definitive study.
Negative control:	1% carboxymethylcellulose
Positive control:	Cyclophosphamide (40 mg/kg), oral (gavage)
Sampling times:	Single oral (gavage) doses of AN2690 or cyclophosphamide were administered to rats. Bone marrow for analysis of nucleated cells was obtained from control and AN2690 treated rats at 24 and 48 hours (5/sex/group/timepoint) after dose administration and at 24 hr after dose administration in positive control animals (5/sex). Stained bone marrow slides were scored for micronucleus and the PCE (polychromatic erythrocytes) to NCE (normal chromatic erythrocytes) cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined by scoring the number of PCEs and NCEs observed while scoring at least 500 erythrocytes per animal.

Study Validity

A test article was considered to be positive if a statistically significant increase in micronucleated PCEs was noted for at least one dose level, and a statistically significant dose-related response were observed.

Solvent control mutant frequencies fell within established ranges. Positive control results were appropriate. Dose range selected for the definitive study was appropriate according to ICH guidelines.

Results

AN2690 did not induce any statistically significant increases in micronucleated PCEs at any of the doses tested in this study.

7.4 Other Genetic Toxicity Studies

N/A

8 Carcinogenicity

Study 1

Study title: AN2690: A 104-week oral carcinogenicity study in Sprague-Dawley rats

Study no.:	002-NCL TX-071-01
Study report location:	SDN 1, electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 24, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, lot # S508S2-06-001, 98.5%
CAC concurrence:	Yes, 6-13-06

Key Study Findings

No treatment related neoplastic findings were noted in this study. A treatment related increased incidence of hyperplasia of the non-glandular stomach was noted in high dose animals. However, the clinical significance of this finding is unclear since the nonglandular stomach is absent in humans.

Adequacy of Carcinogenicity Study

The two year oral rat carcinogenicity study appears to be adequate.

Appropriateness of Test Models

Conduct of an oral rat carcinogenicity study is appropriate for this drug product to evaluate possible systemic tumors if adequate systemic exposure is achieved after topical administration.

Evaluation of Tumor Findings

No treatment related tumors were noted in this study.

Methods

Doses:	0 (vehicle), 12.5, 25 and 50 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg/day
Route of administration:	Oral (gavage)
Formulation/Vehicle:	1% carboxymethylcellulose
Basis of dose selection:	MTD based on hyperplasia and hyperkeratotis in the nonglandular stomach noted in a 6 month rat toxicity study
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	65/sex/group
Age:	6 – 7 weeks; Males: 151 – 273 grams; Females: 124 – 196 grams
Animal housing:	Single animal housing
Paradigm for dietary restriction:	N/A
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	TK: 12/sex/group
Deviation from study protocol:	None of significance

Observations and Results

Mortality

Mortality was assessed twice daily. No treatment related effects on mortality were noted in this study. The survival data is provided in the following table (copied from NDA submission).

Group Number	Group Designation	Sex	Mean Survival (Days)	Cumulative Survival (%)	
				Week 53	Week 104
1	Control	♂	693	100	71
		♀	682	100	54
2	Low Dose	♂	681	97	69
		♀	686	97	52
3	Mid Dose	♂	686	98	66
		♀	652	97	45
4	High Dose	♂	697	98	77
		♀	642	97	52

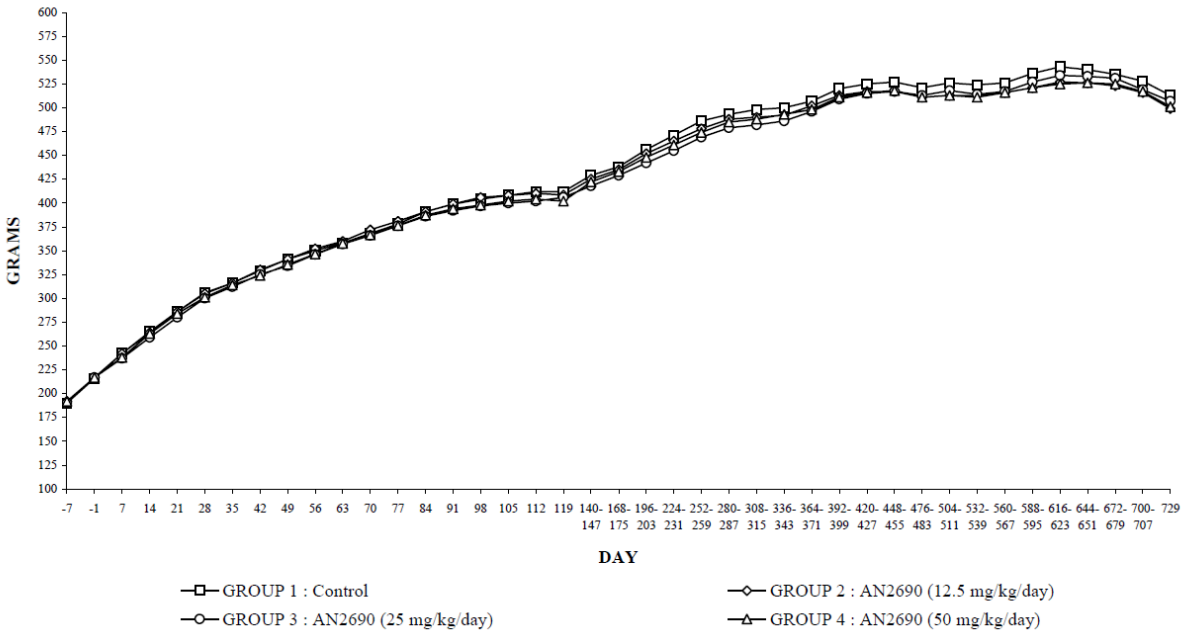
Clinical Signs

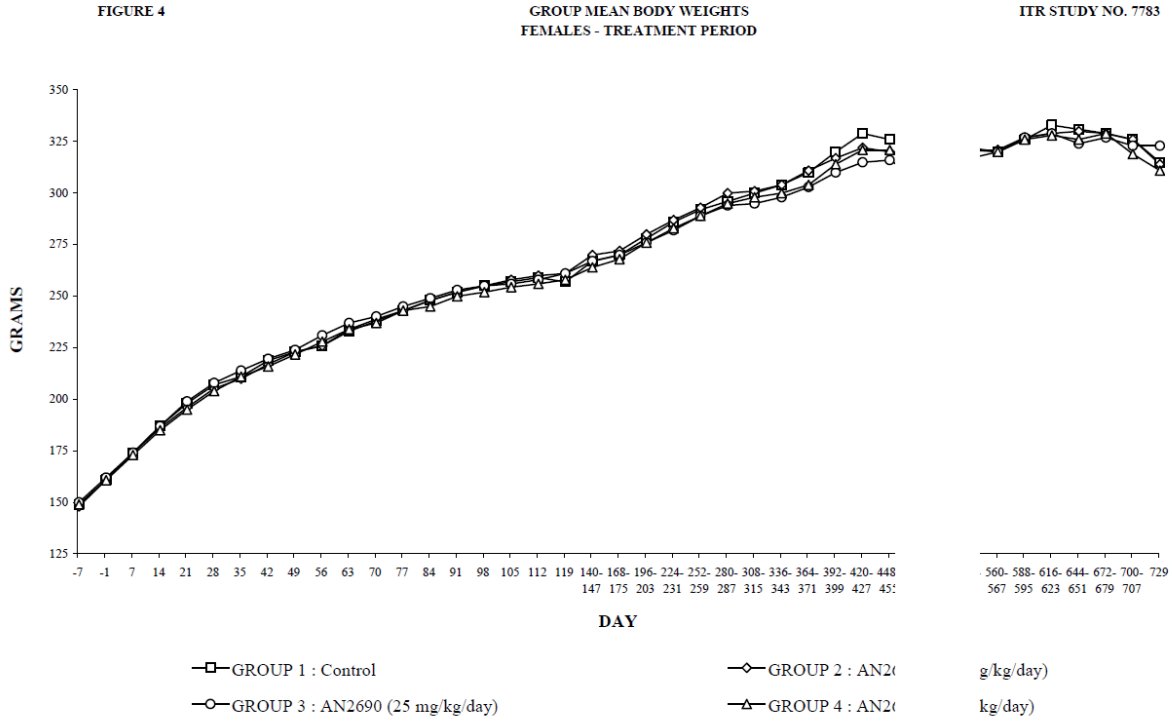
Clinical signs were assessed once daily. No treatment related effects on clinical signs were noted in this study.

Body Weights

Body weights were assessed weekly for the first 14 weeks and once every four weeks thereafter. No treatment related effects on body weight was noted in this study. Male and female body weight curves are provided below (copied from NDA submission).

FIGURE 3 GROUP MEAN BODY WEIGHTS MALES - TREATMENT PERIOD ITR STUDY NO. 7783





Feed Consumption

Food consumption was assessed weekly for the first 14 weeks and once every four weeks thereafter. No treatment related effects on food consumption was noted in this study.

Gross Pathology

A complete gross necropsy with collection of tissues was performed for each animal at the end of treatment. No treatment related effects on macroscopic parameters were noted in this study.

Histopathology

The following tissues were collected for histopathological evaluation: adrenal gland, aorta, bone (femur, sternum), bone marrow (sternum), brain, cervix, epididymis, esophagus, eyes, harderian gland, heart, intestine (cecum, colon, duodenum, ileum, jejunum, rectum), kidneys, liver, lung, lymph node (mandibular, mesenteric), mammary gland, nerve (optic, sciatic), ovaries, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicles, skeletal muscle (thigh), skin (mammary), spinal cord, spleen, stomach (nonglandular and glandular), testes, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, vagina and gross lesions/masses.
Histopathological evaluation of all collected tissues was performed for all animals in all dose groups in this study.

Peer Review
Yes

Neoplastic

The CDER statistical reviewer, Dr. Steven Thomson, generated the following table in his review that lists the potentially statistically significant results for organ-tumor combinations in rats.

Table 5. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats

Organ/ Tumor	Overall Results Veh	Low	Med	High	ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Rats								
PITUITARY GLAND								
# Evaluated	65	65	65	65				
Adj. # at Risk	55.7	54.1	54.3	57.0				
PARS INTERMEDIA ADENOMA [B].	0	0	4	1	.2107	.5045	.0568	.
Systemic								
# Evaluated	65	65	65	65				
Adj. # at Risk	55.7	54.1	54.2	57.9				
Malignant Fibrous Histiocytoma	0	0	0	2	.0663	.2568	.	.
TESTES								
# Evaluated	65	65	65	65				
Adj. # at Risk	55.7	54.4	55.0	57.7				
INTERSTITIAL CELL ADENOMA [B].	1	1	4	7	.0059	.0341	.1760	.7477
THYROID GLAND								
# Evaluated	64	63	64	65				
Adj. # at Risk	54.8	52.9	53.2	57.0				
C-CELL ADENOMA [B].	1	5	2	3	.4251	.3298	.4929	.0942
Female Rats								
MAMMARY GLANDS								
# Evaluated	64	65	63	65				
Adj. # at Risk	53.6	53.8	50.2	52.1				
FIBROADENOMA [B].	11	22	15	13	.5939	.3877	.1970	.0176
OVARIES								
# Evaluated	65	65	65	65				
Adj. # at Risk	52.8	51.0	48.7	50.8				
TUBULOSTROMAL ADENOMA [B].	0	0	0	3	.0149	.1142	.	.
PANCREAS								
# Evaluated	64	65	65	65				
Adj. # at Risk	51.8	51.0	48.7	49.7				
ISLET CELL A DENOMA [B].	0	2	1	3	.0821	.1139	.4848	.2426
UTERUS								
# Evaluated	65	65	65	64				
Adj. # at Risk	53.9	52.5	51.6	50.8				
ENDOMETRIAL STROMAL POLYP [B].	4	6	11	8	.0968	.1518	.0386	.3585

The tumors identified by Dr. Thomson in the previous table are considered common tumors. The CDER Executive Carcinogenicity Assessment Committee (eCAC) criteria for considering a common tumor as treatment related is if both the trend and pairwise comparison for high dose versus vehicle have a p-value less than 0.01. None of the tumors listed in the previous table meet this criteria. The closest tumor that might be considered treatment related is the interstitial cell adeoma of the testis noted in male

rats with a trend p value of 0.0059 and a pairwise comparison of high dose versus vehicle p-value of 0.0341. Even though the trend p-value for this tumor is less than 0.01, the pairwise comparison of high dose versus vehicle p-value is greater than 0.01. In addition, the increased incidence of interstitial cell adenoma of the testis in the mid does group (4/65, 6.2%) and high dose group (7/65, 10.8%) was within the published historical control range (0 – 25%) for this strain of rat. Therefore, this is not a treatment related tumor.

In conclusion, no treatment related tumors were noted in this study.

Non Neoplastic

A treatment related increased incidence of hyperplasia of the non-glandular stomach was noted in high dose animals (refer to the table below copied from the NDA submission).

Principal Non-Neoplastic Findings: Male and Female Rats, All Fates

	Male				Female			
Dose (mg/kg/day):	0	12.5	25	50	0	12.5	25	50
Organ/Finding/Severity	Incidence[a]							
Stomach	(64)[b]	(65)	(65)	(65)	(65)	(65)	(65)	(65)
- hyperplasia, nonglandular stomach	1	0	1	19*	0	2	2	12*
minimal	0	0	0	8	0	0	0	5
mild	0	0	0	11	0	2	2	7
moderate	1	0	1	0	0	0	0	0

* = Test article-related
a: Incidence = Number affected.
b: ( ) = Number examined.

This treatment related finding was not associated with any additional proliferative or neoplastic findings in the stomach. This treatment related finding was also noted in the 6 month oral rat toxicity study used to determine the MTD for the oral rat carcinogenicity study. The nonglandular stomach is absent in humans. Therefore, the clinical significance of this finding is unclear.

Toxicokinetics

Blood samples for toxicokinetic assessment were collected from 3 animals/sex/group/timepoint on day 1 and week 26 at 0 (pre-dose), 0.25, 0.5, 1, 2 and 4 hours post dose.

The toxicokinetic parameters determined from this study are provided in the following table (copied from the NDA submission).

	Administered Dose (mg/kg/day)		
M+F Parameter	12.5	25	50
Study Day 1			
C_{max} (ng/mL)	395	912	1810
T_{max} (hours)	0.25	0.25	0.25
$AUC_{0\text{-}4\ hr}$ (ng•hr/mL)	202	498	1150
Study Week 26			
C_{max} (ng/mL)	449	643	1300
T_{max} (hours)	0.25	0.25	0.25
$AUC_{0\text{-}4\ hr}$ (ng•hr/mL)	221	465	1090

Abbreviations: Abbreviations: AUC = Area under the plasma concentration curve; C_{max} = Maximal plasma concentration; T_{max} = Time of maximal plasma concentration

There was no gender differences in systemic exposure noted in this study. Therefore, the mean toxicokinetic parameters are provided in this table. There was a dose dependent increase in systemic exposure that was slightly greater than dose proportional noted in this study. No apparent dose accumulation between Day 1 and Week 26 was noted in this study.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 96.4 to 102.8%, which is acceptable.

Study 2

Study title A 104 week dermal oncogenicity study of AN2690 in mice

Study no.:	002-NCL-TX-073-01
Study report location:	SDN 1, electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 27, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, lot # S508S2-06-001, 98.5%
CAC concurrence:	Yes, 10-31-06

Key Study Findings

No treatment related neoplastic findings were noted in this study. A treatment related increased incidence/severity of epidermal hyperplasia, hyperkeratosis and inflammation was noted in treated skin which correlated with treatment related dermal irritation noted at the treatment site.

Adequacy of Carcinogenicity Study

The two year dermal mouse carcinogenicity study appears to be adequate.

Appropriateness of Test Models

Conduct of a dermal mouse carcinogenicity study is appropriate for this drug product to evaluate possible tumors after topical administration which is the clinical route of administration.

Evaluation of Tumor Findings

No treatment related tumors were noted in this study.

Methods

Doses:	0 (vehicle), 5%, 10% and 15% AN2690 solution; 0, 50, 100 and 150 mg/kg/day AN2690
Frequency of dosing:	Once daily
Dose volume:	5 µl/cm^2 through day 14 and 1 µl/g thereafter
Route of administration:	Topical
Formulation/Vehicle:	Propylene glycol/ethanol (20/80, v/v)
Basis of dose selection:	High dose based on maximum feasible dose which was well tolerated in a 13 week dermal mouse toxicity study
Species/Strain:	Mice/CD-1
Number/Sex/Group:	65/sex/group
Age:	6 – 7 weeks; Males: 24.2 – 30.9 grams; Females: 19.7 – 25.5 grams
Animal housing:	Single animal housing
Paradigm for dietary restriction:	N/A
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	TK: 40/sex/group
Deviation from study protocol:	None of significance

Observations and Results

Mortality

Mortality was assessed twice daily. No treatment related effects on mortality were noted in this study. The percent survival at the end of study for vehicle control, low, mid and high groups was 46%, 29%, 43% and 42% for males and 38%, 40%, 45% and 38% for females.

Clinical Signs

Clinical signs were assessed once weekly. No treatment related effects on clinical signs were noted in this study.

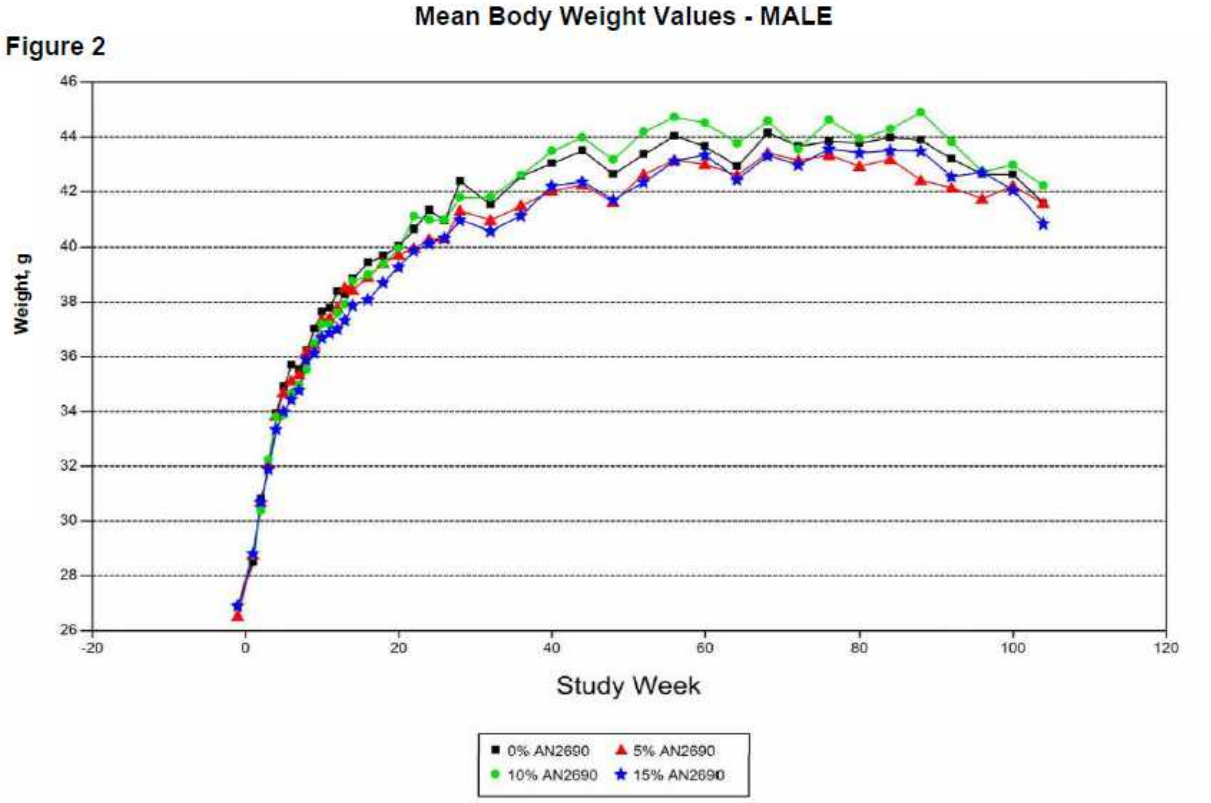
Dermal Irritation

Dermal irritation was assessed once weekly and then monthly thereafter. A slight increase in erythema/eschar findings were noted in high dose animals. These findings ranged from very slight to severe erythema/eschar sporadically throughout the treatment period. A few incidences of a slight increase in edema findings were noted in high dose males.

Body Weights

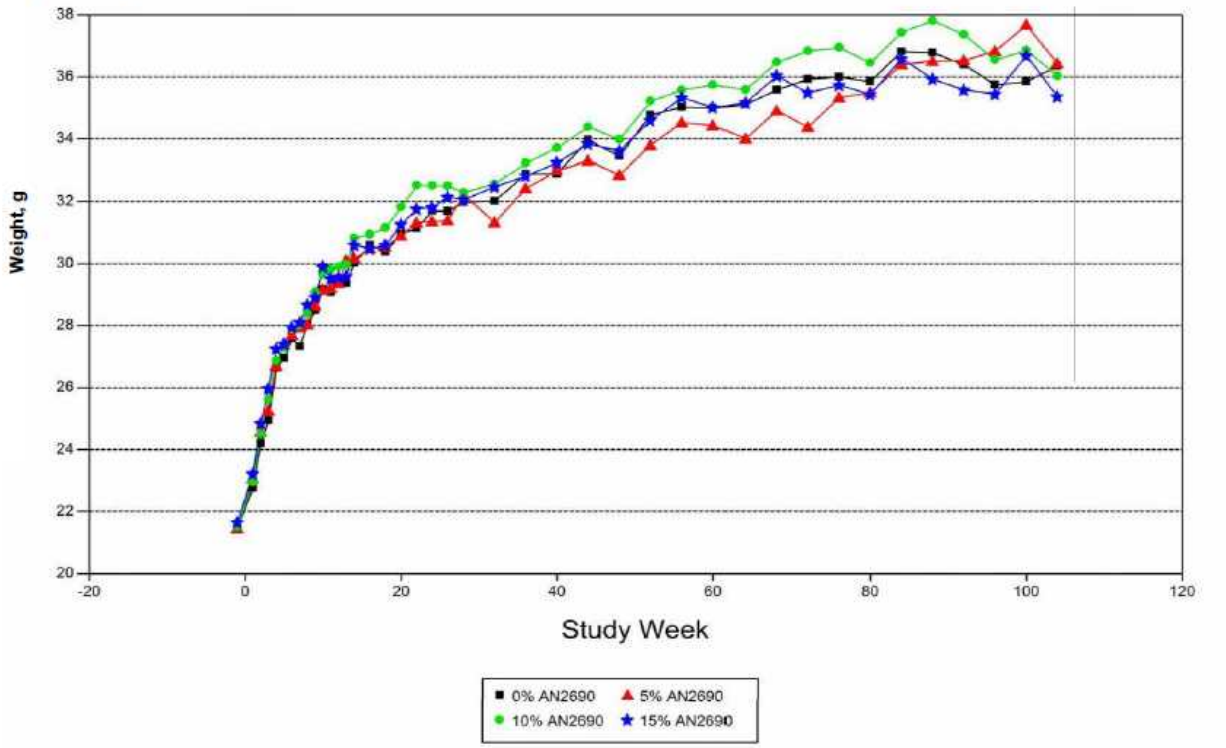
Body weights were assessed weekly for the first 14 weeks, every other week from weeks 16 - 28 and every fourth week from weeks 32 – 104. No treatment related effects on body weight was noted in this study. Male and female body weight curves are provided below (copied from NDA submission).

Figure 2



Mean Body Weight Values - FEMALE

Figure 2A



Feed Consumption

Food consumption was assessed weekly for the first 14 weeks, every other week from weeks 16 - 28 and every fourth week from weeks 32 – 104. No treatment related effects on food consumption was noted in this study.

Ophthalmology

Ophthalmoscopic examinations were conducted prior to necropsy. No treatment related effects on ophthalmologic parameters was noted in this study.

Gross Pathology

A complete gross necropsy with collection of tissues was performed for each animal at the end of treatment. No treatment related effects on macroscopic parameters were noted in this study.

Histopathology

The following tissues were collected for histopathological evaluation: adrenal gland, aorta, bone (femur, sternum), bone marrow (femur, sternum), brain, clitoral gland, coagulating gland, cervix, epididymis, esophagus, eyes, gallbladder, harderian gland, heart, joint (tibiofemoral), intestine (cecum, colon, duodenum, ileum, jejunum, rectum), kidneys, lacrimal gland, larynx, liver, lung, lymph node (mandibular, mesenteric),

mammary gland (females only), nerve (optic, sciatic), ovaries, pancreas, parathyroid gland, Peyers patch, pharynx, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicles, skeletal muscle (biceps femoris), skin (treated, untreated), spinal cord, spleen, stomach (nonglandular and glandular), testes, thymus, thyroid gland, tongue, trachea, ureter, urinary bladder, uterus, vagina, zymbal's gland and gross lesions/masses.
Histopathological evaluation of all collected tissues was performed for all animals in all dose groups in this study.

Peer Review
Yes

Neoplastic

The CDER statistical reviewer, Dr. Steven Thomson, generated the following table in his review that lists the potentially statistically significant results for organ-tumor combinations in mice.

Table 6. Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice

Organ/ Tumor	Overall Results Veh	Low	Med	High	ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Mice								
Systemic								
# Evaluated	65	65	65	65				
Adj. # at Risk	46.7	41.2	46.0	45.9				
HEMANGIOSARCOMA	2	3	7	4	.1546	.3279	.0789	.4450
Adj. # at Risk	46.7	41.7	46.1	45.9				
Hemangioma/Hemangiosacroma	2	4	8	4	.1679	.3279	.0450	.2847
epididymides								
# Evaluated	65	65	65	65				
Adj. # at Risk	46.1	40.9	43.8	44.9				
SARCOMA, HISTIOCYTIC	0	0	0	2	.0636	.2362	.	.
liver								
# Evaluated	65	65	65	65				
Adj. # at Risk	46.7	41.0	46.0	45.9				
HEMANGIOSARCOMA	2	1	7	4	.0935	.3279	.0789	.8517
Adj. # at Risk	46.9	44.7	44.7	44.9				
Hepato.Adenoma/Carcinoma	6	12	10	7	.4606	.4650	.1775	.0769
multicentric neoplasm								
# Evaluated	65	65	65	65				
Adj. # at Risk	46.7	41.2	46.0	45.9				
HEMANGIOSARCOMA	2	3	7	4	.1546	.3279	.0789	.4450
Female Mice								
Systemic								
# Evaluated	65	65	65	65				
Adj. # at Risk	42.7	46.8	45.3	45.4				
GRANULOSA CELL TUMOR	0	0	0	2	.0628	.2646	.	.
brain								
# Evaluated	65	65	65	65				
Adj. # at Risk	42.9	48.9	45.3	47.5				
LYMPHOMA	1	3	0	6	.0649	.0746	1	.3604
large intestine, cecum								
# Evaluated	65	65	65	65				
Adj. # at Risk	42.7	46.8	45.3	46.4				

LYMPHOMA	0	0	0	2	.0650	.2704	.	.
ovaries								
# Evaluated	65	65	65	65				
Adj. # at Risk	42.7	46.8	45.3	45.4				
GRANULOSA CELL TUMOR	0	0	0	2	.0628	.2646	.	.
salivary gland, mandibula								
# Evaluated	65	65	65	65				
Adj. # at Risk	43.7	47.3	47.3	48.2				
LYMPHOMA	2	1	4	6	.0465	.1721	.3819	.8950
skin, subcutis								
# Evaluated	65	65	65	65				
Adj. # at Risk	43.0	48.6	47.1	47.7				
LYMPHOMA	3	3	6	7	.0799	.1965	.2891	.7127
uterus with cervix								
# Evaluated	65	65	65	65				
Adj. # at Risk	42.7	46.8	45.3	45.4				
GRANULOSA CELL TUMOR	0	0	0	2	.0628	.2646	.	.

Reviewer's comment: The incidence of systemic lymphoma in vehicle control, low, mid and high female mice was 9/65, 10/65, 9/65 and 14/65, respectively. The p value for the trend analysis was 0.2035 and the p value for the pairwise comparison of high dose versus vehicle control was 0.2524 per Dr. Thomson's review. No statistical significant difference in the incidence of systemic lymphoma was noted in this study.

The tumors identified by Dr. Thomson in the previous table are considered common tumors. The CDER eCAC criteria for considering a common tumor as treatment related is if both the trend and pairwise comparison for high dose versus vehicle have a p-value less than 0.01. None of the tumors listed in the previous table meet this criteria. Therefore, no treatment related tumors were noted in this study.

Non Neoplastic

A treatment related increased incidence/severity of epidermal hyperplasia, hyperkeratosis and inflammation was noted in treated skin (refer to the table below copied from the NDA submission).

Test Article-Related Effects Died on Study Animals and Terminal Necropsy Male and Female								
Dose level: % AN2690	**0**	**0**	**5**	**5**	**10**	**10**	**15**	**15**
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number Examined	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Skin, treated								
Epidermal hyperplasia	3	12	41	25	49	42	45	47
-minimal	2	9	29	22	27	33	28	27
-mild	1	1	10	3	17	9	10	16
-moderate	0	1	2	0	3	0	5	4
-severe	0	1	0	0	2	0	2	0
Skin, treated								
Hyperkeratosis	0	1	16	1	9	4	8	5
-minimal	0	1	12	1	7	4	8	4
-mild	0	0	4	0	2	0	0	1
Skin, treated								
Inflammation, subacute/chronic	1	3	11	11	16	12	12	18
-minimal	1	1	10	11	12	11	7	16
-mild	0	1	1	0	3	1	1	1
-moderate	0	1	0	0	1	0	4	1

This treatment related finding was not associated with any additional proliferative or neoplastic findings in the skin. This treatment related finding correlated with the dermal irritation noted at the treatment site.

Toxicokinetics

Blood samples for toxicokinetic assessment were collected from 3 animals/sex/group/timepoint on days 1 and 180 at 0 (pre-dose), 0.5, 1, 2, 4 and 6 hours post dose.

The toxicokinetic parameters determined from this study are provided in the following table (copied from the NDA submission).

Summary AN2690 Toxicokinetic Parameters Determined from Mean Plasma AN2690 Concentrations on Day 1 Following Single-Dose Administration and on Day 180 Following Multiple-Dose Administration of 5, 10, and 15% AN2690 Solution Once Daily Topically to the Skin of Male and Female Mice

Group	Gender	Dose (%)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	$t_{1/2}$ (hr)	C_{max}/Dose [(ng/mL) /(%)]	AUC_{0-t}/Dose [(ng*hr/mL) /(%)]	[AUC_{0-t}(Day 180)/ AUC_{0-t}(Day 1)] Ratio
Day 1									
10	Male	5	1920	0.5	1789	1.34	384	358	.
10	Female	5	2040	0.5	2616	1.44	408	523	.
11	Male	10	2490	0.5	4520	1.21	249	452	.
11	Female	10	2590	1	5376	1.27	259	538	.
12	Male	15	2280	0.5	4141	1.99	152	276	.
12	Female	15	2870	1	6877	2.07	191	458	.
Day 180									
6	Male	5	1150	1	2306	0.76	230	461	1.29
6	Female	5	1540	0.5	2988	1.12	308	598	1.14
7	Male	10	2550	0.5	8825	2.23	255	882	1.95
7	Female	10	2780	0.5	6602	1.8	278	660	1.23
8	Male	15	3230	0.5	5714	2.01	215	381	1.38
8	Female	15	3030	1	7765	1.41	202	518	1.13

No measurable amounts of AN2690 were detected in control samples. AN2690 exposure was slightly higher in females compared to males across all dose groups. No significant accumulation of AN2690 was noted in this study. Systemic exposure increased with dose between the low and mid dose groups but appeared to plateau between the mid and high dose groups.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 97.6 to 107.6%, which is acceptable.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Study of fertility and early embryonic development to implantation in rats following oral administration of AN2690

Study no.:	002-NCL TX-068-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8-1-2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# S508S2-06-001, 98.3%

Key Study Findings

One treatment related death was noted in a high dose male. Treatment related effects on clinical signs were noted in high dose animals. A treatment related decrease in body weight gain and corresponding food consumption was noted in high dose males. Treatment related findings of thickening and discoloration of the non-glandular stomach were evident in high dose males. No significant treatment related effects were noted on reproductive organs, fertility or pregnancy indices, and uterine implantation parameters were unaffected by treatment in low, mid and high dose animals. The NOAEL for paternal toxicity is 100 mg/kg/day. The NOAEL for fertility and reproductive performance was 300 mg/kg/day, the highest dose tested in this study.

Methods

Doses:	0, 30, 100, 300 mg/kg/day*
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	1% carboxymethycellulose (CMC)
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	25/sex/dose
Satellite groups:	N/A
Study design:	Oral (gavage) doses were administered daily starting at 4 weeks prior to mating and during mating for males, and 14 days prior to mating and through gestation day 7 for females. Females were mated on a one to one basis with the correspondingly treated 4 week dosed males. Females showing a sperm positive vaginal smear were separated from the males and remained isolated until sacrifice on gestation day 13. Males were sacrificed after the mating period.
Deviation from study protocol:	None of significance

***** - Doses selected for the rat fertility study were based on results noted in 1 and 3/6 month oral rat toxicity studies. In those studies, AN2690 produced hyperkeratosis and hyperplasia of the non-glandular stomach in rats at 30, 50, 100 and 200 mg/kg/day. However, there were no treatment related mortalities noted in these studies. In the range finding 1 month oral rat toxicity study, doses of 500 and 1000 mg/kg/day produced mortality in 3/5 and 5/5 male rats, respectively. The dose range selected for this study appears reasonable.

Observations and Results

Mortality

Mortality was evaluated daily.

One high dose male was found dead on day 25. Treatment related clinical observations noted prior to death included decreased activity, difficulty breathing, high carriage posture, lacrimation, righting reflex impaired and salivation. At necropsy, this animal was noted with non-glandular stomach tissue raised, thickened and white in appearance and smaller than normal seminal vesicles. This death is treatment related. No other treatment related effects on mortality were noted in this study.

Clinical Signs

Clinical signs were evaluated daily.

Treatment related effects on clinical signs were noted in high dose animals. Treatment related effects included decreased activity, impaired or loss of righting reflex, salivation, low and/or high carriage posture, lacrimation, impaired limb function, red material around the nose and/or mouth, hunched posture, yellow discolored hair around the abdominal and/or anogenital area, skin cold to touch and breathing abnormalities. No treatment related effects on clinical signs were noted in low and mid dose animals.

Body Weight

Male body weight was evaluated twice weekly during the mating period. Female body weight was evaluated twice weekly during the mating period and on gestation days 0, 4, 7, 10 and 13.

Body weight gain was significantly decreased in high dose males (-35.4%) during the premating period (Days 1 – 25) compared to control males. No treatment related effects on body weight were noted in low and mid dose animals and high dose females.

Feed Consumption

Food consumption was evaluated on the same schedule as described for body weights.

Food consumption was decreased in high dose males during the premating period compared to control males. No treatment related effects on food consumption were noted in low and mid dose animals and high dose females.

Toxicokinetics

N/A

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 88.7 to 104.0%, which is acceptable.

Necropsy

A complete necropsy was performed for males after the completion of the mating period and epididymids, prostate, seminal vesicles and testes organ weights were obtained. An analysis (concentration, motility, morphology) of the sperm was performed using the right testis and epididymis. The left testis and epididymis, prostate, and seminal vesicle were preserved for possible histopathological evaluation.

A complete necropsy was performed for females on gestation day 13. Organ weights for uterus and ovaries were obtained for all females. The following parameters were measured during the gross necropsy in females: the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. Ovaries, urterus and vagina were preserved for possible histopathological evaluation.

Treatment related effects on macroscopic parameters in the nonglandular stomach were noted in nine high dose males. These findings consisted of mild to moderate thickening and/or red discoloration. A slight decrease in seminal vesicle weight was noted in high dose males (-11.8%) compared to control males. No treatment related effects on macroscopic parameters or organ weights were noted in low and mid dose animals and high dose females.

Fertility Parameters

The following fertility parameters were evaluated in this study: Copulatory interval, male and female fertility index, male and female mating index, male and female fecundity index and estrous cyclicity (mean cycle time and # cycles/period). Females were evaluated for estrous cyclicity on a daily basis from 14 days prior to mating and until evidence of copulation was noted.

No treatment related effect on estrous cyclicity was noted in this study. No treatment related effects on reproductive indices (mating indices, fertility indices and fecundity indices) were noted in this study. No treatment related effects on copulatory interval was noted in this study.

There were 23, 22, 22 and 19 pregnant females in the control, low, mid and high dose groups, respectively. No treatment related effects on uterine implantation data were noted in this study. The mean number of corpora lutea, uterine implantations, viable embryos, resorptions, pre-implantation loss and post-implantation loss for the low, mid and high dose groups were comparable to the control group.

No treatment related effects on sperm evaluations were noted in this study. Sperm motility, total caudal epididymal sperm concentrations, sperm concentrations per gram tissue and percent abnormal sperm in low, mid and high dose groups were comparable to the control group.

9.2 Embryonic Fetal Development

Study 1

Study title: An oral prenatal developmental toxicity study of AN2690 in rats

Study no.:	002-NCL TX-069-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-26-06
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# 000133-03B-06-03-17, 100%

Key Study Findings

One high dose female died pregnant (not treatment related) and 3 high dose females had all resorbing fetuses. Treatment related effects on clinical signs and a treatment related decrease in body weight gain (-37.6%) and corresponding food consumption over gestation days 6 – 19 was noted in high dose animals compared to control animals. No treatment related effects on clinical signs, body weight/body weight gain or food consumption were noted in low and mid dose groups.

No treatment related effects on the mean numbers of corpora lutea, implantations and mean pre-implantation loss indices were noted in this study. A treatment related increase in the number of resorptions (early + late) was noted in the high dose group compared to controls. No treatment related effects on mean number of resorptions, viable fetuses and post-implantation loss were noted in the low and mid dose groups. A treatment related decrease of 34% in mean gravid uterine weight was noted in the high dose group compared to the control group. No treatment related effect on gravid uterine weights was noted in the low and mid dose groups.

Mean fetal weights were decreased about 38% in the high dose group (males, females and sexes combined) compared to the control group. No treatment related effects on mean fetal weight were noted in the low and mid dose groups. No treatment related effect on fetal sex ratios were noted in this study.

No treatment related effects on fetal external malformations or variations or fetal visceral malformations or variations were noted in this study. Several statistically significant treatment related effects on skeletal malformations and variations suggestive of delayed development were noted in high dose fetuses compared to control fetuses. This delay in ossification may be related to the lower fetal body weights noted in the high dose group. No treatment related effects on fetal skeletal malformations or variations were noted in the low or mid dose groups.

Drug related malformations (with corresponding maternal toxicity) were noted in the high dose group. The NOAEL for drug related malformations was 100 mg/kg/day

AN2690 ($AUC_{0\text{-}4\ hr}$ = 2199 ng·hr/ml on gestation day 19). The NOAEL for maternal and fetal developmental toxicity was also 100 mg/kg/day AN2690.

Methods

Doses:	0, 30, 100 and 300 mg/kg/day AN2690*
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	1% carboxymethylcellulose
Species/Strain:	Rat/Sprague-Dawley (pregnant females)
Number/Sex/Group:	25 females/group
Satellite groups:	TK: 9 females/group
Study design:	Oral (gavage) doses were administered daily from gestation days 6 – 19. All maternal animals were sacrificed on gestation day 20.
Deviation from study protocol:	None of significance

***** - Doses selected for the rat embryofetal study were based on results noted in 1 and 3/6 month oral rat toxicity studies. In those studies, AN2690 produced hyperkeratosis and hyperplasia of the non-glandular stomach in rats at 30, 50, 100 and 200 mg/kg/day. However, there were no treatment related mortalities noted in these studies. In the range finding 1 month oral rat toxicity study, doses of 500 and 1000 mg/kg/day produced mortality in 3/5 and 5/5 male rats, respectively. The dose range selected for this study appears reasonable.

Observations and Results

Mortality

Mortality was evaluated daily.

No treatment related effects on mortality were noted in this study.

Clinical Signs

Clinical signs were evaluated daily.

Treatment related effects on clinical signs were noted in high dose animals. Treatment related effects included decreased activity, impaired or loss of righting reflex, salivation, low and/or high carriage posture, piloerection, hunched posture and skin cold to touch. No treatment related effects on clinical signs were noted in low and mid dose animals.

Body Weight

Maternal body weights were evaluated on gestation days 0, 6, 9, 12, 15, 19 and 20.

Decreased body weight gain was noted in high dose animals (-37.6%) during gestational days 6 – 19 compared to control animals. No treatment related effect on body weight gain was noted in low and mid dose groups.

Feed Consumption

Food consumption was evaluated on gestation days 0, 6, 9, 12, 15, 19 and 20.

A treatment related decrease in food consumption was noted in high dose females during the gestational days 6 – 19 compared to control females.

Toxicokinetics

Blood samples were obtained from TK animals on gestation days 6 and 19 at 0.25, 0.5, 1, 2 and 4 hours post dose.

A summary of the mean pharmacokinetic parameters for AN2690 measured in this study is provided in the following table (copied from the study report).

Table 1. Summary AN2690 Toxicokinetic Parameters Determined from Mean Plasma AN2690 Concentrations on Gestation Day 6 Following Single-Dose Administration and on Gestation Day 19 Following Multiple-Dose Administration of 30, 100, and 300 mg/kg/day AN2690 Once Daily by Oral Gavage to Female Rats

Group Number	Gestation Day	Dose (mg/kg/day)	t_{MAX} (hr)	C_{MAX} (ng/mL)	AUC_T (ng*hr/mL)	AUC[a] (ng*hr/mL)	$t_{1/2,Z}$ (hr)	Rac	C_{MAX}/Dose [(ng/mL) /(mg/kg)]	AUC[a]/Dose [(ng*hr/mL) /(mg/kg)]
6	6	30	0.25	946	409	435	0.534	.	31.5	14.5
7	6	100	0.244	6080	4299	4337	0.638	.	60.8	43.4
8	6	300	0.517	17700	20958	25121	1.68	.	59	83.7
6	19	30	0.239	729	439	450	0.281	.	24.3	15
7	19	100	0.494	2230	2199	2298	0.986	0.53	22.3	23
8	19	300	1.01	32500	43223	47452	1.07	1.89	108	158

[a] AUC = AUC_∞ for Gestation Day 6 and AUC = AUC_τ for Gestation Day 19.
. Not determined.

A greater than dose proportional increase in systemic exposure was noted in pregnant females on gestation days 6 and 19. Dose accumulation was not apparent in low and mid dose groups but was apparent in the high dose group.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 88.0 to 103.0%, which is acceptable.

Necropsy

The maternal gross necropsy performed after sacrifice on gestational day 20 consisted of examination of the thoracic and abdominal cavities.

No treatment related effects on maternal macroscopic parameters were noted in this study.

Cesarean Section Data

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination.

The pregnancy index was 100%, 100%, 96% and 96% providing 25, 25, 24 and 20 litters in control, low, mid and high dose groups, respectively, for evaluation on gestation day 20. One mid dose and one high dose female did not get pregnant. One high dose female died pregnant (not treatment related) and 3 high dose females had all resorbing fetuses. No treatment related effects on the mean numbers of corpora lutea, implantations and mean pre-implantation loss indices were noted in this study. A treatment related increase in the number of resoptions (early + late) was noted in the high dose group compared to controls. No treatment related effects on mean number of resorptions, viable fetuses and post-implantation loss were noted in the low and mid dose groups. A treatment related decrease of 34% in mean gravid uterine weight was noted in the high dose group compared to the control group. No treatment related effect on gravid uterine weights was noted in the low and mid dose groups.

Mean fetal weights were decreased about 38% in the high dose group (males, females and sexes combined) compared to the control group. No treatment related effects on mean fetal weight were noted in the low and mid dose groups. No treatment related effect on fetal sex ratios were noted in this study.

Offspring

Half of the fetuses were examined for soft tissue abnormalities and half of the fetuses were examined for skeletal abnormalities.

No treatment related effects on fetal external malformations or variations or fetal visceral malformations or variations were noted in this study. Several statistically significant treatment related effects on skeletal malformations and variations suggestive of delayed development were noted in high dose fetuses compared to control fetuses. Skeletal malformations in the high dose group consisted of absent, fused, or misshapen neural arches, absent or fused ribs, and larger than normal cranial frontanelle. In addition, skeletal variations noted in high dose fetuses included rib variations (smaller than normal ribs and 13^{th} rib missing), incomplete or unossified structures of cervical and sacral vertebrae, bones of the fore- and hind limbs, pelvic girdle, skull and sternum. The study report indicates that this delay in ossification was consistent with the lower fetal body weights noted in the high dose group. No treatment related effects on fetal skeletal malformations or variations were noted in the low or mid dose groups.

Study 2

Study title: A dermal prenatal developmental toxicity study of AN2690 in New Zealand White rabbits

Study no.:	002-NCL TX-067-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-24-06
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# 000133-03B-06-03-17, 100%

Key Study Findings

No treatment related effects on maternal mortality, clinical observations, body weight/body weight gain, food consumption or uterine implantation data were noted in this study. A dose dependent increase in dermal irritation was noted in mid and high dose groups with the dermal irritation noted in the mid dose group being sporadic and the dermal irritation achieving severe erythema in high dose animals near the end of the dosing period. No treatment related effects on fetal evaluations (external, visceral, and skeletal) were noted in this study. However, a decrease in fetal body weight (decrease of 7 – 10%) was noted in the high dose group compared to the control group.

No drug related malformations were noted in this study. The NOAEL for drug related malformations was 10% AN2690 solution ($AUC_{0\text{-}4\ hr}$ = 2766 ng·hr/ml on gestation day 28). The NOAEL for maternal and fetal developmental toxicity was 5% AN2690 solution ($AUC_{0\text{-}4\ hr}$ = 1977 ng·hr/ml on gestation day 28).

Methods

Doses:	0, 1%, 5% and 10% AN2690 solution* (0.33, 1.65 and 3.3 mg/kg/day assuming 100% systemic absorption)**
Frequency of dosing:	Once daily
Dose volume:	5 µl/cm^2 to 10% BSA (~115 µl)
Route of administration:	Topical
Formulation/Vehicle:	Propylene glycol/ethanol (20/80, v/v)
Species/Strain:	Rabbit/New Zealand White (pregnant females)
Number/Sex/Group:	25 females/group
Satellite groups:	N/A
Study design:	Test article was administered topically once daily from gestation days 6 to 28. Elizabethan collars were applied for a 2 hour duration post dose. Test article was removed from the treatment site prior to administration of the next dose. All maternal animals were sacrificed on

gestation day 29.
Deviation from study protocol: None of significance

***** - Doses selected for the dermal rabbit embryofetal study were based on results noted in a dermal rabbit range-finding prenatal development study and 28 day, 90 day and 180 day dermal minipig toxicity studies which indicated that 5% and 10% AN2690 solution were locally irritating to the application sites of the test species.

** - Approximate mg/kg/day doses were calculated based on an average 3.5 kg rabbit and using the formulation $A = 10 \times W^{2/3}$ were A is body surface area in cm^2 and W is body weight in gms. The total body surface area (BSA) of a 3.5 kg rabbit is 230 cm^2 ($A = 10 \times 3500^{2/3}$; $A = 230\ cm^2$). The mg/kg/day dose for the 1% AN2690 dose applied to 10% of BSA is 0.33 mg/kg/day (5 µl/cm^2 x 23 cm^2 x 10 mg/ml x 1 ml/1000 µl ÷ 3.5 kg = 0.33 mg/kg).

Observations and Results

Mortality

Mortality was evaluated daily.

No treatment related effects on mortality were noted in this study.

Clinical Signs

Clinical signs were evaluated daily.

Treatment related effects on clinical signs were noted in high dose animals. Treatment related effects included decreased activity, impaired or loss of righting reflex, salivation, low and/or high carriage posture, piloerection, hunched posture and skin cold to touch. No treatment related effects on clinical signs were noted in low and mid dose animals.

Dermal Irritation

Dermal irritation was evaluated daily.

Very slight to severe erythema was noted at the dosing site in high dose animals. Slight erythema was first noted in high dose animals as early as gestation day 9 and the incidence and severity increased as the dosing period progressed. By gestation day 24 over half (56%) of the high dose animals exhibited severe erythema at the dosing site. Sporadic findings of very slight to well defined erythema were also noted in mid dose animals. These findings were noted in mid dose animals from gestation day 16 through gestation day 29.

Body Weight

Maternal body weights were evaluated on gestation days 0, 7, 10, 13, 16, 18, 21, 25 and 29.

No treatment related effects on maternal body weight were noted in this study.

Feed Consumption

Food consumption was evaluated daily.

No treatment related effects on food consumption were noted in this study.

Toxicokinetics

Blood samples were obtained from TK animals on gestation days 6 and 28 at 0.25, 0.5, 1, 2 and 4 hours post dose.

A summary of the mean pharmacokinetic parameters for AN2690 measured in this study is provided in the following table (copied from study report).

Table 1. Summary AN2690 Toxicokinetic Parameters on Gestation Day 6 Following Single-Dose Administration and on Gestation Day 28 Following Multiple-Dose Administration of 1, 5, and 10% AN2690 Once Daily Dermally to Female Rabbits

	Group (n)	AN2690 Dose (%)	t_{MAX} (hr)	C_{MAX} (ng/mL)	AUC_T (ng*hr/mL)	AUC[a] (ng*hr/mL)	$t_{1/2,Z}$ (hr)	Rac	C_{MAX}/Dose [(ng/mL) /(mg/kg)]	AUC[a]/Dose [(ng*hr/mL) /(mg/kg)]
Gestation Day 6										
Mean	6 (n=4)	1	1.18	456	566	628	.	.	456	628
SD			0.631	321	409	370	.	.	321	370
Mean	7 (n=4)	5	1.17	527	957	970	0.722	.	105	194
SD			0.623	180	364	383	.	.	36	76.6
Mean	8 (n=4)	10	1.67	806	1499	1928	1.59	.	80.6	193
SD			1.6	494	879	1213	0.275	.	49.4	121
Gestation Day 28										
Mean	6 (n=4)	1	1.7	89.9	171	222	.	.	89.9	222
SD			0.478	15.2	35.9	27.2	.	.	15.2	27.2
Mean	7 (n=4)	5	0.875	1043	1977	2041	0.744	2.32	209	408
SD			0.25	246	569	563	0.1	0.758	49.3	113
Mean	8 (n=4)	10	0.383	1855	2766	3128	1.1	3.94	186	313
SD			0.173	447	704	663	0.213	4.29	44.7	66.3

[a] AUC = AUC_∞ (or AUC_{ALL}) for Gestation Day 6 and AUC = AUC_τ (or AUC_{ALL}) for Gestation Day 28.
. Not determined.

A less than dose proportional increase in systemic exposure was noted in pregnant females on gestation days 6 and 28. Dose accumulation was not apparent in low dose animals but was apparent in mid and high dose animals.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 94.3 to 109.0%, which is acceptable.

Necropsy

The maternal gross necropsy performed after sacrifice on gestational day 29 consisted of examination of the thoracic and abdominal cavities.

No treatment related effects on maternal macroscopic parameters were noted in this study.

Cesarean Section Data

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination.

No treatment related effects on maternal macroscopic parameters were noted in this study. The pregnancy index was 92%, 100%, 92% and 100% providing 23, 25, 23 and 25 litters in control, low, mid and high dose groups, respectively, for evaluation on gestation day 29. No treatment related effects on the mean numbers of corpora lutea, implantations, fetuses and resorptions and mean pre- and post-implantation loss indices were noted in this study. No treatment related effect on gravid uterine weights was noted in this study.

Mean fetal weights were decreased 7 – 10% in the high dose group (males, females and sexes combined) compared to the control group. No treatment related effects on mean fetal weight were noted in the low and mid dose groups. No treatment related effect on fetal sex ratios were noted in this study.

Offspring

All fetuses were examined for soft tissue abnormalities and skeletal abnormalities.

No treatment related effects on fetal external malformations or variations, fetal visceral malformations or variations or fetal skeletal malformations or variations were noted in this study.

Study 3

Study title: Embryo-fetal developmental toxicity and toxicokinetic study of SCH 900340 administered orally by gavage in rabbits

Study no.:	002-NCL TX-080-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10-14-08
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 900340, Lot # 08PAHT101, 100%

Key Study Findings

An increase in mortality and significant body weight loss was noted in high dose animals. There was a significant increase in post implantation loss (81.1% in high dose group compared to 3.1% in the control group on gestation day 29), which was mainly due to an increased incidence in early resorptions. Only four high dose dams delivered

viable fetuses with two high dose dams delivering only a single fetus. This resulted in a total of only 19 live fetuses in the high dose group.

No treatment related effects on fetal external malformations or variations, fetal visceral malformations or variations or fetal skeletal malformations or variations were noted in this study. The NOAEL for drug related malformations was 150 mg/kg/day ($AUC_{0\text{-}4\ hr}$ = 11800 ng·hr/ml). The NOAEL for maternal toxicity and embryofetal toxicity was 50 mg/kg/day ($AUC_{0\text{-}4\ hr}$ = 1220 ng·hr/ml).

Methods

Doses:	0, 15, 50, and 150 mg/kg/day SCH 900340*
Frequency of dosing:	Once daily
Dose volume:	5 ml/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% aqueous methylcellulose
Species/Strain:	Rabbit/New Zealand White (pregnant females)
Number/Sex/Group:	20 females/group
Satellite groups:	N/A
Study design:	Oral (gavage) doses were administered once daily from gestation day 7 – 19. All maternal animals were sacrificed on gestation day 29.
Deviation from study protocol:	None of significance

***** - Doses selected for the oral rabbit embryofetal development study were based on results noted in an oral rabbit range finding embryofetal development study. Oral (gavage) doses of 0 (vehicle: 0.4% methylcellulose), 75, 250 and 450 mg/kg/day SCH 900340 were administered to pregnant rabbits (gestational days 7 – 19) in the rabbit range finding embryofetal development study. One high dose doe was found dead on gestation day 9. On gestation day 12, two high dose does exhibited poor food consumption, hypoactivity, soft and/or scant feces. All remaining high dose does were sacrificed on gestation day 12. At necropsy, the high dose does that were sacrificed had discolored and/or pitted stomach linings. Mid dose does exhibited body weight loss during the dosing period and red material in the cage pan. All fetuses were found to be resorbed in the mid dose group. In the low dose group, there were no treatment related maternal or reproductive findings, but there was a slight decrease in mean fetal body weight. The NOAEL for maternal toxicity was 75 mg/kg/day. No NOAEL for embryofetal toxicity was identified in this study.

Observations and Results

Mortality

Mortality was evaluated daily.

Two high dose does were found dead on gestation days 12 or 17. Both of these rabbits exhibited poor food consumption and scant stools for a few days prior to death. The rabbit found dead on gestation day 17 exhibited discoloration of the stomach lining.

Two other does in the high dose group were sacrificed on gestation day 12 or 14 due to declining condition. The rabbit that was sacrificed on gestation day 12 exhibited poor food consumption and scant stools on gestation days 9 and 12. In addition, on gestation day 12, this rabbit was prostrate, hypoactive, moribund and exhibited a loss of righting reflex. At necropsy, watery feces were found in the large intestine of this rabbit. The rabbit that was sacrificed on gestation day 14 exhibited poor food consumption and scant stools on gestation days 10 through 14 along with a decrease in body weight gain.

Four additional does in the high dose group were sacrificed due to evidence of abortion between gestation days 19 and 22.

One doe in the mid-dose group exhibited evidence of abortion on gestation day 29.

Clinical Signs

Clinical signs were evaluated daily.

Nine does in the high dose group exhibited scant or loose stool finding for two or more days between gestation days 8 and 22. Ten high dose does exhibited red material in the cage pan for one to 10 days between gestation days 14 and 26. These rabbits had no viable fetuses upon Cesarean section.

Six does in the mid-dose group exhibited scant stools during the dosing period. The stools from three of these rabbits were associated with a decrease in food consumption. An additional seven does in the mid-dose group exhibited fecal stained fur, alopecia or an unkempt appearance.

Body Weight

Maternal body weights were evaluated on gestation days 0, 7, 10, 13, 16, 18, 21, 25 and 29.

During the dosing period from gestation days 7 to 19, pregnant rabbits in the high dose group exhibited a significant body weight loss or decreased body weight gain (mean of 210 gram loss versus mean of 120 gram gain in the control group). Post-implantation loss may have contributed to these changes in body weight.

Feed Consumption

Food consumption was evaluated daily.

Decreased food consumption was noted in high and mid dose animals. No treatment related effects on food consumption was noted in the low dose animals in this study.

Toxicokinetics

Blood samples were obtained from TK animals on gestation day 19 at 0.25, 0.5, 0.75, 1, 2 and 4 hours post dose.

A summary of the pharmacokinetic parameters for SCH 900340 measured in this study on gestation day 19 is provided in the following table (copied from the study report).

Sex	Gestation Day	SCH 900340 Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	tf (hr)[a]	AUC(tf) (ng·hr/mL)	AUC(0-4 hr) (ng·hr/mL)
Female	19	15	217 (31)	0.25	(0.25 - 0.75)	NR[b]	NR
		50	1550 (13)	0.25	(1 - 2)	1050 (18)	1220 (16)
		150	9120 (25)	0.25	4	11800 (39)	11800 (39)

a: Minimum – Maximum
b: NR = Not reported. AUC not reported when less than 4 consecutive quantifiable time points.

A greater than dose proportional increase in systemic exposure was noted in pregnant females on gestation day 19.

Dosing Solution Analysis

The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 85.7 to 101%, which is acceptable.

Necropsy

The maternal gross necropsy performed after sacrifice on gestational day 29 consisted of examination of the thoracic and abdominal cavities.

No treatment related effects on maternal macroscopic parameters were noted in this study.

Cesarean Section Data

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination.

A summary of the cesarean section data from this study is provided in the following table (copied from the study report).

EMBRYO-FETAL DEVELOPMENTAL TOXICITY AND TOXICOKINETIC STUDY
OF SCH 900340 ADMINISTERED ORALLY BY GAVAGE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 900340 15 MG/KG	GROUP 3 SCH 900340 50 MG/KG	GROUP 4 SCH 900340 150 MG/KG
Pregnant	N	20	19	17	10
Dams with Viable Fetuses	N	20	19	17	4
Corpora Lutea	TOTAL	218	194	185	107
No. per animal	MEAN	10.9	10.2	10.9	10.7
	S.D.	1.71	1.55	1.76	2.87
Implantation Sites	TOTAL	202	178	158	89
No. per animal	MEAN	10.1	9.4	9.3	8.9
	S.D.	1.77	1.54	2.39	1.66
Preimplantation Loss	TOTAL	16	16	27	18
No. per animal	MEAN	0.8	0.8	1.6	1.8
	S.D.	0.89	1.01	1.58	3.05
% per animal	MEAN%	7.2	8.0	14.9	13.2
	S.D.	8.09	9.15	15.57	18.56
Live Fetuses	TOTAL	195	172	155	19
left horn		88	95	77	10
right horn		107	77	78	9
No. per animal	MEAN	9.8	9.1	9.1	1.9
	S.D.	1.65	1.51	2.15	3.51
Males	TOTAL	106	93	74	14
	MEAN%	54.7	52.6	49.6	41.0
	S.D.	15.50	18.43	19.52	47.65
Females	TOTAL	89	79	81	5
	MEAN%	45.3	47.4	50.4	59.0
	S.D.	15.50	18.43	19.52	47.65

EMBRYO-FETAL DEVELOPMENTAL TOXICITY AND TOXICOKINETIC STUDY
OF SCH 900340 ADMINISTERED ORALLY BY GAVAGE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 900340 15 MG/KG	GROUP 3 SCH 900340 50 MG/KG	GROUP 4 SCH 900340 150 MG/KG
Postimplantation Loss	TOTAL	7	6	3	70
No. per animal	MEAN	0.3	0.3	0.2	7.0
	S.D.	0.67	0.95	0.53	3.06
% implants per animal	MEAN%	3.1 k	3.0	1.4	81.1*
	S.D.	5.92	8.30	4.07	35.15
Dead Fetuses	TOTAL	0	0	0	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
% of implants per animal	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
Resorptions: early+late	TOTAL	7	6	3	70
No. per animal	MEAN	0.3	0.3	0.2	7.0
	S.D.	0.67	0.95	0.53	3.06
% of implants per animal	MEAN%	3.1	3.0	1.4	81.1
	S.D.	5.92	8.30	4.07	35.15
Resorptions: Early	TOTAL	4	1	1	67
No. per animal	MEAN	0.2	0.1	0.1	6.7
	S.D.	0.52	0.23	0.24	3.23
% of implants per animal	MEAN%	1.8	0.8	0.5	77.8
	S.D.	4.51	3.28	1.87	36.79
Resorptions: Late	TOTAL	3	5	2	3
No. per animal	MEAN	0.2	0.3	0.1	0.3
	S.D.	0.49	0.93	0.33	0.67
% of implants per animal	MEAN%	1.4	2.3	0.9	3.3
	S.D.	4.45	7.86	2.55	8.05

Statistics performed: k=Kruskal Wallis +/- Dunn * = p<0.05

There was a significant increase in post implantation loss (81.1% in high dose group compared to 3.1% in the control group on gestation day 29), which was mainly due to an increased incidence in early resorptions. Only four high dose dams delivered viable fetuses with two high dose dams delivering only a single fetus. This resulted in a total of only 19 live fetuses in the high dose group.

Mean male fetal weights were decreased 13.8% in the high dose group compared to the control group. However, the mean male fetal weight was calculated from a total of only 14 male fetuses in the high dose group. No treatment related effects on mean fetal weight were noted in the low and mid dose groups. No apparent treatment related effect on fetal sex ratios were noted in this study.

Offspring

All fetuses were examined for soft tissue abnormalities and skeletal abnormalities.

No treatment related effects on fetal external malformations or variations, fetal visceral malformations or variations or fetal skeletal malformations or variations were noted in this study.

9.3 Prenatal and Postnatal Development

Study title: Prenatal and postnatal developmental toxicity and maternal function study of SCH 900340 (AN2690) administered orally by gavage in rats

Study no.:	002-NCL TX-074-01
Study report location:	Electronic, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9-7-07
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AN2690, Lot# S508S2-06-001, 98.5%

Key Study Findings

Treatment related effects on clinical signs, which included decreased motor activity and excess salivation (slight to moderate), were noted in high dose F_0 dams. No other treatment related effects were noted in F_0 dams.

No treatment related effects on the evaluated physical and behavioral development parameters were noted in F_1 animals. No treatment related effects on viability, body weight, clinical signs or macroscopic parameters were noted in F_2 pups.

The NOAEL for F_0 maternal toxicity is 60 mg/kg/day and for F_1 and F_2 offspring is 100 mg/kg/day AN2690, the highest dose evaluated in this study.

Methods

Doses:	0, 15, 60, 100 mg/kg/day*
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	1% carboxymethylcellulose
Species/Strain:	Rat/Sprague-Dawley (pregnant females)
Number/Sex/Group:	25 females/group
Satellite groups:	N/A
Study design:	Oral doses were administered daily from gestation day 6 – lactation day 20
Deviation from study protocol:	None of significance

* - Doses selected for the oral rat pre- and post-natal development study were based on results noted in the oral rat embryofetal development study conducted with 30, 100 and 300 mg/kg/day AN2690. Treatment related effects on clinical signs and a treatment related decrease in body weight gain (-37.6%) and corresponding food consumption over gestation days 6 – 19 was noted in high dose animals compared to control animals. No treatment related effects on clinical signs, body weight/body weight gain or food consumption were noted in low and mid dose groups.

Observations and Results

F_0 Dams

Survival:	Evaluated daily. No treatment related effects on mortality were noted in F_0 dams.
Clinical signs:	Evaluated daily. Treatment related effects on clinical signs noted in high dose F_0 dams included decreased motor activity and excess salivation (slight to moderate).
Body weight:	Evaluated on gestation days 0, 6, 9, 12, 15, 17 and 21 and lactation days 1, 4, 7, 10 and 14. No treatment related effects on body weights were noted in F_0 dams.
Feed consumption:	Evaluated on gestation days 0, 6, 12, 17 and 20 and lactation days 1, 4, 7, 10 and 14. No treatment related effects on food consumption were noted in F_0 dams.
Uterine content:	N/A
Necropsy observation:	F_0 dams were sacrificed for necropsy evaluation on lactation day 21. No treatment related effects on macroscopic parameters were noted in F_0 dams.
Toxicokinetics:	N/A
Dosing Solution Analysis:	The dosing solution analysis demonstrated that the concentration of the dose groups ranged from 94.2 to 109.3%, which is acceptable.
Other:	F_1 pups were examined after birth for sex, litter size, number of stillborn and liveborn pups, number of males and females, individual body weights and gross abnormalities. F_1 pups were culled to a litter size of 4 males and 4 females, where possible, on lactation day 4. No treatment related effects on abortion or premature or abnormal delivery were noted in F_0 dams. The pregnancy rate was 96%, 100%, 84% and 92% in control, low, mid and high dose groups, respectively. There were 24, 25, 21 and 23 litters with live pups for evaluation in the control, low, mid and high dose groups, respectively. No treatment related difference in mean gestation length was noted in this study. No treatment related effect on F_1 pup survival or sex ratio were noted in this study.

F_1 Generation

Survival:	Evaluated daily. No treatment related effects on mortality were noted in F_1 animals.
Clinical signs:	Evaluated daily. No treatment related effects on clinical signs were noted in F_1 animals.
Body weight:	Evaluated on lactation days 1, 4, 7, 14 and 21. No treatment related effects on body weights were noted in F_1 animals.
Feed consumption:	N/A
Physical development:	The following parameters were evaluated in one male and one female F_1 pup: motor activity (postnatal days 22 and 61), vaginal opening (daily in female pus from postnatal day 28), and preputial separation (daily in male pups from postnatal day 39). No treatment related effects on sexual maturation as measured by the average day of vaginal patency or day of preputial separation were noted in F_1 animals.
Neurological assessment:	The following parameters were evaluated in one male and one female F_1 pup: acoustic startle habituation (postnatal days 23 and 62) and passive avoidance testing (postnatal day 24). No treatment related effects on motor activity, acoustic startle habituation (a measure of learning), memory or learning (as measured by passive avoidance testing) were noted in F_1 animals.
Reproduction:	The reproductive potential was evaluated at 94 - 97 days of age in one male and one female from each litter which were not used in the behavior test. Males and females from the same dose group were mated on a 1:1 basis for 2 weeks. F_1 females estrous cycle was evaluated daily beginning 14 days prior to mating, during the mating period and until a copulatory plug was detected. F1 female and F1 male body weights were determined weekly during the cohabitation period and for F1 females on gestational days 0, 6, 9, 12, 17, 21 and on lactation days 1, 4 and 7. No treatment related effects on mating and fertility or estrous cycles were noted in F_1 animals. No treatment related effects on parturition (duration of gestation) were noted in F_1 animals.
Other:	N/A

F_2 Generation

Survival:	Evaluated daily. No treatment related effects on mortality was noted in F_2 pups.
Body weight:	Evaluated on postnatal days 1, 4 and 7. No treatment related effects on body weight was noted in F_2 pups.
External evaluation:	N/A
Male/Female ratio:	Sex determination was made on postnatal day 7. No treatment related effects on F_2 pup male/female ratio was noted in this study.
Other:	Gross necropsy was performed on postnatal day 7. No treatment related effects on macroscopic parameters was noted in F_2 pups.

10 Special Toxicology Studies

Tavaborole solution, 10% and vehicle (propylene glycol/ethanol, 20/80, v/v) are slightly irritating to intact rabbit skin after a 24 hour topical application under occlusion. Tavaborole solution, 10% and vehicle (propylene glycol/ethanol, 20/80, v/v) are ocular irritants in rabbits, with the 10% tavaborole solution showing a more severe response. The 10% tavaborole solution and vehicle (propylene glycol/ethanol, 20/80, v/v) were classified as non-sensitizers in a guinea pig maximization test. The need for a nonclinical photoirritation study was waived for the tavaborole solution, 7.5% since no absorption was noted from 225 nm – 700 nm.

The sponsor submitted an initial Pediatric Study Plan (PSP) in the original NDA submission. In the initial PSP, the sponsor requested a waiver for pediatric subjects age (b) (4) years old and a deferral for pediatric subjects age (b) (4) years. (b) (4)

(b) (4)

Typically, the Division has requested conduct of pediatric clinical studies in subjects 12 years and older as a post-market requirement to support use of drug products being developed for the treatment of onychomycosis. The sponsor's proposal to evaluate subjects age (b) (4) older is unusual. (b) (4)

Reviewer's comment: The clinical review team informed the sponsor during the Mid Cycle Communication teleconference conducted on January 21, 2014 that clinical studies in the pediatric population age (b) (4) years are not needed for the onychomycosis indication. The sponsor agreed with this recommendation. The sponsor submitted a revised PSP on January 21, 2014. In the revised PSP, the sponsor proposed to extrapolate the efficacy and safety data from the adult population to the adolescent population (ages 12 to 17) because the clinical presentation in adolescents is similar to the adult disease. Therefore, the sponsor has requested a waiver for conduct of clinical studies in pediatric subjects age 0 – (b) (4) years. In the revised PSP, the sponsor does not plan to conduct any nonclinical juvenile animal toxicity studies for tavaborole solution. The sponsor's proposal is acceptable from a Pharmacology/Toxicology perspective.

The Clinical review team has requested that the sponsor conduct a clinical safety/PK study in subjects 12 – 17 years old and recommends a waiver for under 12 years old. Refer to the Clinical review for more detailed information, if needed.

11 Integrated Summary and Safety Evaluation

Tavaborole is an oxaborole antifungal agent and represents a new molecular entity. Tavaborole is being developed for the topical treatment of onychomycosis. Comprehensive nonclinical studies have been conducted with tavaborole and/or tavaborole solution to support the safety of tavaborole solution.

Repeat dose oral toxicity studies up to 6 months in rats have been conducted with tavaborole and repeat dose dermal toxicity studies up to 9 months in minipigs have been conducted with tavaborole solution. In the 6 month oral toxicity study in rats, oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 30, 50, 100 and 200 mg/kg/day tavaborole were administered once daily. A treatment related decrease in body weight was noted in high dose animals compared to vehicle control animals. Treatment related microscopic findings (epithelial hyperplasia and hyperkeratosis) were noted in the nonglandular stomach in mid-low, mid-high and high dose groups. A dose dependent increase in severity and incidence was noted for the epithelial hyperplasia and hyperkertaosis findings in the nonglandular stomach. The treatment related findings in the nonglandular stomach were not noted in recovery animals. Very minimal treatment related histopathological effects were noted in the nonglandular stomach in low dose animals. The NOAEL was identified as 30 mg/kg/day tavaborole ($AUC_{0\text{-}3\ hr}$ =

0.21 and 0.24 µg·hr/ml in males and females, respectively) in rats after administration for 6 months, under the conditions of this study.

In the 9 month dermal toxicity study in minipigs, dermal doses of 0 (untreated control), 0 (vehicle control: propylene glycol/ethanol, 20/80, v/v), 0.3%, 1%, 3% and 3% (+ degradants) tavaborole solution were administered once daily. The degradants were (b) (4) The only treatment related toxicity that was noted in this study was a dose dependent increase in the incidence and severity of dermal effects at the treatment sight. There were no differences in the dermal findings between the 3% tavaborole group with and without degradants. The systemic NOAEL for tavaborole solution was 3% tavaborole solution ($AUC_{0\text{-}8\ hr}$ = 753 ng·hr/ml). A dermal NOAEL for the tavaborole solution was not established in this study. Limited systemic exposure was noted after dermal administration of tavaborole solution to minipigs. Systemic exposure was only noted in the high dose group, 3% tavaborole solution, in this study.

The multiples of human exposure for the systemic NOAELs identified in the 6 month oral toxicity study in rats and the 9 month dermal toxicity study in minipigs are provided in the following table.

Duration of toxicity study	Species	Route	NOAEL	AUC (ng·hr/ml)	Multiples of human exposure*
6 months	Rat	Oral	30 mg/kg/day	225	3
9 months	Minipig	Dermal	3%	753	10

* - mean human AUC_{tau} under maximal use conditions = 75.8 ng·hr/ml per the clinical pharmacology reviewer, Dr. An-Chi Lu.

The target organ of toxicity identified in oral rat toxicity studies was the nonglandular stomach which exhibited as epithelial hyperplasia and hyperkeratosis. The nonglandular stomach is absent in humans. Therefore, the clinical significance of this finding is unclear. The target organ of toxicity identified in the dermal minipig toxicity studies was the skin at the site of application which exhibited a dose dependent increase in the incidence and severity of dermal irritation. Both the treatment related effects on the nonglandular stomach in rats and at the treatment site in minipigs were reversible after stopping treatment. The clinical concentration of tavaborole solution is 5% which is greater than the highest concentration of tavaborole solution of 3% used in the 9 month dermal toxicity study in minipigs. The high dose used in the 9 month dermal toxicity study in minipigs was acceptable because a higher concentration would not have been tolerated for 9 months of daily topical application to the skin. Since reversible dermal irritation was the only treatment related effect noted in the 9 month dermal toxicity study in minipigs, it is anticipated that dermal irritation can be noted easily after clinical use of this topical drug product and will resolve after stopping treatment.

An ICH battery of genotoxicity studies were conducted with tavaborole. Tavaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

An oral carcinogenicity study in rats was conducted with tavaborole and a dermal carcinogenicity study in mice was conducted with tavaborole solution. In the oral carcinogenicity study in rats, oral (gavage) doses of 0 (vehicle), 12.5, 25 and 50 mg/kg/day tavaborole were administered to Sprague-Dawley rats (65/sex/dose) once daily for 104 weeks. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

No drug related neoplastic findings were noted at oral doses up to 50 mg/kg/day tavaborole ($AUC_{0\text{-}3\ hr}$ = 1090 ng·hr/ml). A treatment related increased incidence of hyperplasia of the non-glandular stomach was noted at 50 mg/kg/day tavaborole. However, the clinical significance of this finding is unclear since the nonglandular stomach is absent in humans.

In the dermal carcinogenicity study in mice, topical doses of 0 (vehicle), 5, 10 and 15% tavaborole solution were administered to CD-1 mice (65/sex/dose) once daily for 104 weeks. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v). The dose volume was 5 µl/cm^2 through day 14 and 1 µl/g thereafter.

A treatment related increased incidence/severity of epidermal hyperplasia, hyperkeratosis and inflammation was noted in treated skin which correlated with treatment related dermal irritation noted at the treatment site. No drug related neoplastic findings were noted at daily topical doses up to 15% tavaborole solution ($AUC_{0\text{-}4\ hr}$ = 6740 ng·hr/ml).

The multiples of human exposure for the systemic NOAELs identified in the oral carcinogenicity study in rats and the dermal carcinogenicity study in mice are provided in the following table.

Duration of carcinogenicity study	Species	Route	NOAEL	AUC (ng·hr/ml)	Multiples of human exposure*
104 weeks	Rat	Oral	50 mg/kg/day	1090	14
104 weeks	Mouse	Dermal	15%	6740	89

* - mean human AUC_{tau} under maximal use conditions = 75.8 ng·hr/ml per the clinical pharmacology reviewer, Dr. An-Chi Lu.

The potential reproductive toxicity of tavaborole was evaluated in an oral fertility study in rats, oral embryofetal development studies in rats and rabbits, a dermal embryofetal development study in rabbits and an oral pre- and post-natal development study in rats.

In the oral fertility study in rats, oral (gavage) doses of 0 (vehicle), 30, 100 and 300 mg/kg/day tavaborole were administered to Sprague-Dawley rats (25/sex/dose) once daily starting at 4 weeks prior to mating and during mating for males, and 14 days prior to mating and through gestation day 7 for females. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

Treatment related effects noted at 300 mg/kg/day included one male death, decrease in body weight gain and thickening and discoloration of the nonglandular stomach in males. No treatment related effects on fertility were noted in rats at oral doses up to 300 mg/kg/day tavaborole. The NOAEL for paternal toxicity is 100 mg/kg/day tavaborole. The NOAEL for fertility and reproductive performance was 300 mg/kg/day tavaborole, the highest dose tested in this study. The $AUC_{0\text{-}4\ hr}$ value for the 300 mg/kg/day dose in the oral rat fertility study is 8077 ng·hr/ml. This AUC value is based on a linear extrapolation of the 200 mg/kg/day AUC value for male and female rats combined after 3 months of treatment in the 6 month oral rat toxicity study.

In the oral embryofetal development study in rats, oral (gavage) doses of 0 (vehicle), 30, 100 and 300 mg/kg/day tavaborole were administered to pregnant female Sprague-Dawley rats (25 females/dose) once daily from gestation days 6 – 19. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

A treatment related increase in embryofetal resorption and/or embryofetal death was noted at an oral dose of 300 mg/kg/day tavaborole in rats which correlated with maternal toxicity (significant body weight decrease). Drug related skeletal malformations and variations suggestive of delayed development were noted in fetuses at the 300 mg/kg/day tavaborole dose in rats. This delay in ossification may be related to the lower fetal body weights noted at the 300 mg/kg/day tavaborole dose. The AUC at the 300 mg/kg/day tavaborole dose was 43,223 ng·hr/ml on gestation day 19. The multiple of human exposure at this dose is 570 (43,223 ng·hr/ml ÷ 75.8 ng·hr/ml = 570). The NOAEL for drug related malformations was 100 mg/kg/day tavaborole ($AUC_{0\text{-}4\ hr}$ = 2199 ng·hr/ml on gestation day 19). The NOAEL for maternal and fetal developmental toxicity was also 100 mg/kg/day tavaborole.

In the dermal embryofetal development study in rabbits, topical doses of 0 (vehicle), 1, 5, and 10% tavaborole solution were administered to pregnant female New Zealand White rabbits (25/sex/dose) once daily from gestation days 6 to 28. Elizabethan collars were applied for a 2 hour duration post dose. Test article was removed from the treatment site prior to administration of the next dose. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v). The dose volume was 5 µl/cm^2 administered to 10% BSA.

A dose dependent increase in dermal irritation was noted in the 5% and 10% tavaborole solution dose groups in the dermal embryofetal development study in rabbits. No treatment related effects on fetal evaluations (external, visceral, and skeletal) were noted in this study. However, a decrease in fetal body weight (decrease of 7 – 10%) was noted in the high dose compared to the control group. No drug related malformations was noted in this study. The NOAEL for drug related malformations was 10% tavaborole solution ($AUC_{0\text{-}4\ hr}$ = 2766 ng·hr/ml on gestation day 28). The NOAEL for maternal and fetal developmental toxicity was 5% tavaborole solution ($AUC_{0\text{-}4\ hr}$ = 1977 ng·hr/ml on gestation day 28).

In the oral embryofetal development study in rabbits, oral (gavage) doses of 0 (vehicle), 15, 50 and 150 mg/kg/day tavaborole were administered to pregnant female New Zealand White rabbits (20/sex/dose) once daily from gestation days 7 to 19. The vehicle used in this study was 0.4% aqueous methylcellulose and the dose volume was 5 ml/kg/day.

An increase in mortality and significant body weight loss was noted at 150 mg/kg/day tavaborole in the oral embryofetal development study in rabbits. There was a treatment related increase in post implantation loss at 150 mg/kg/day tavaborole which was mainly due to an increased incidence in early resorptions. A significant decrease in live fetuses was noted at 150 mg/kg/day tavaborole. No treatment related effects on fetal external malformations or variations, fetal visceral malformations or variations or fetal skeletal malformations or variations were noted in this study. The NOAEL for drug related malformations was 150 mg/kg/day ($AUC_{0\text{-}4\ hr}$ = 11800 ng·hr/ml). The NOAEL for maternal toxicity and embryofetal toxicity was 50 mg/kg/day ($AUC_{0\text{-}4\ hr}$ = 1220 ng·hr/ml).

In the oral pre- and post-natal development study in rats, oral (gavage) doses of 0 (vehicle), 15, 60 and 100 mg/kg/day tavaborole were administered to pregnant female Sprague-Dawley rats (25 females/dose) once daily from gestation days 6 to lactation day 20. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

No treatment related effects on pre- and post-natal development were noted in rats at doses up to 100 mg/kg/day tavaborole. The $AUC_{0\text{-}4\ hr}$ value used for the 100 mg/kg/day dose in the oral rat pre- and post-natal development study is 2199 ng·hr/ml, which is the same as the AUC value obtained from the oral rat embryofetal development study on gestation day 19.

The multiples of human exposure for the systemic NOAELs identified in reproductive toxicity studies conducted in rats and rabbits are provided in the following table.

Type of study	Species	Route	NOAEL	AUC (ng·hr/ml)	Multiples of human exposure*
Fertility	Rat	Oral	300 mg/kg/day	8077	107
Embryofetal development	Rat	Oral	100 mg/kg/day	2199	29
Embryofetal development	Rabbit	Dermal	10% 5%	2766 1977	36 26
Embryofetal development	Rabbit	Oral	100 mg/kg/day 50 mg/kg/day	11800 1220	155 16
Pre- and Post-natal development	Rat	Oral	100	2199	29

* - mean human AUC_{tau} under maximal use conditions = 75.8 ng·hr/ml per the clinical pharmacology reviewer, Dr. An-Chi Lu.

Tavaborole solution was slightly irritating to intact rabbit skin after a single 24 hour topical application under occlusion and was an ocular irritant in rabbits. Tavaborole solution was classified as a non-sensitizer in guinea pigs. The need for a nonclinical photoirritation study was waived for tavaborole solution since no absorption was noted from 225 nm – 700 nm.

The toxicity profile of tavaborole solution has been well characterized by the nonclinical studies conducted by the sponsor. There is no significant safety concern for tavaborole solution at the proposed clinical dose. This NDA is approvable from a pharmacology/toxicology perspective. No nonclinical postmarketing requirement is recommended for this NDA.

12 Appendix/Attachments

Appendix 1: Clean copy of recommended wording for Nonclinical sections of the label

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
Tavaborole is an oxaborole antifungal indicated for the topical treatment of onychomycosis.

8.1 Pregnancy
Teratogenic effects: Pregnancy Category C.

There are no adequate and well-controlled studies with KERYDIN Topical Solution in pregnant women. KERYDIN 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 and a dermal embryofetal development study was conducted in rabbits. In an oral embryofetal development study in rats, oral doses of 30, 100 and 300 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and drug related skeletal malformations and variations suggestive of delayed development (i.e., a delay in ossification) were noted in fetuses at 300 mg/kg/day tavaborole [570 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No developmental toxicity was noted in rats at 100 mg/kg/day tavaborole (26 times the MRHD based on AUC comparisons).

In an oral embryofetal development study in rabbits, oral doses of 15, 50 and 150 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 7-19) to pregnant female rabbits. In the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 150 mg/kg/day tavaborole. No drug related malformations were noted in rabbits at 150 mg/kg/day tavaborole (155 times the MRHD based on AUC comparisons). No embryofetal mortality was noted in rabbits at 50 mg/kg/day tavaborole (16 times the MRHD based on AUC comparisons].

In a dermal embryofetal development study in rabbits, topical doses of 1, 5 and 10% tavaborole solution were administered during the period of organogenesis (gestational days 6-28) to pregnant female rabbits. A dose dependent increase in dermal irritation at the treatment site was noted at 5 and 10% tavaborole solution. A decrease in fetal bodyweight was noted at 10% tavaborole solution. No drug related malformations were noted in rabbits at 10% tavaborole solution (36 times the MRHD based on AUC comparisons). No embryofetal toxicity was noted in rabbits at 5% tavaborole solution (26 times the MRHD based on AUC comparisons).

Nonteratogenic effects:

In an oral pre- and post-natal development study in rats, oral doses of 15, 60 and 100 mg/kg/day tavaborole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development were noted at 100 mg/kg/day (29 times the MRHD based on AUC comparisons).

12.1 Mechanism of Action

KERYDIN Topical Solution is an oxaborole antifungal agent [*see Clinical Pharmacology (12.4)*].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 12.5, 25 and 50 mg/kg/day tavaborole were administered to rats once daily for 104 weeks. No drug

related neoplastic findings were noted at oral doses up to 50 mg/kg/day tavaborole (14 times the MRHD based on AUC comparisons).

In a dermal carcinogenicity study in CD-1 mice, topical doses of 5, 10 and 15% tavaborole solution were administered to mice once daily for 104 weeks. No drug related neoplastic findings were noted at topical doses up to 15% tavaborole solution (89 times the MRHD based on AUC comparisons).

Tavaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility were observed in male and female rats that were administered oral doses up to 300 mg/kg/day tavaborole (107 times the MRHD based on AUC comparisons) prior to and during early pregnancy.

Appendix 2: Executive CAC meeting minutes

Executive CAC
Date of Meeting: December 10, 2014

Committee: David Jacobson Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
David Joseph, Ph.D., DGIEP, Alternate Member
Barbara Hill, Ph.D., DDDP, Presenting Reviewer /Supervisor

Author of Minutes: Barbara Hill, Ph.D.

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

NDA #: 204427
Drug Name: Tavaborole solution, 5%
Sponsor: Anacor Pharmaceuticals Inc.

Background:

Tavaborole is a (b) (4) borinic acid complex that exhibits anti-fungal activity. Tavaborole solution is being developed for the topical treatment of onychomycosis. An oral rat carcinogenicity study report and a dermal mouse carcinogenicity study report were submitted to the original NDA to support approval.

Oral Rat Carcinogenicity Study:

Oral (gavage) doses of 0 (vehicle), 12.5, 25 and 50 mg/kg/day tavaborole were administered to Sprague-Dawley rats (65/sex/dose) once daily for 104 weeks. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

A treatment related increased incidence of hyperplasia of the non-glandular stomach was noted in high dose animals. However, the clinical significance of this finding is unclear since the nonglandular stomach is absent in humans. No statistically significant differences in tumor incidence were observed in rats of either gender according to the statistical criteria used by the Executive CAC.

Dermal Mouse Carcinogenicity Study:

Topical doses of 0 (vehicle), 5, 10 and 15% tavaborole solution were administered to CD-1 mice (65/sex/dose) once daily for 104 weeks. The vehicle used in this study was propylene glycol/ethanol (20/80, v/v). The dose volume was 5 µl/cm^2 through day 14 and 1 µl/g thereafter.

A treatment related increased incidence/severity of epidermal hyperplasia, hyperkeratosis and inflammation was noted in treated skin which correlated with treatment related dermal irritation noted at the treatment site. No statistically significant differences in tumor incidence were observed in mice of either gender according to the statistical criteria used by the Executive CAC.

Executive CAC Recommendations and Conclusions:

Oral Rat Carcinogenicity Study

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that the study was negative for drug related neoplasms.

Dermal Mouse Carcinogenicity Study

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that the study was negative for drug related neoplasms.

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

cc:\

/Division File, DDDP
/BHill/Reviewer/Supervisor, DDDP
/CAttinello/PM, DDDP
/ASeifried, OND IO

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/s/

BARBARA A HILL
02/06/2014

Comments on NDA 204427 tavaborole solution

From: A. Jacobs, AD

Date 1/27/14

1. I concur that there are no pharm-tox approvable issues with this NDA, and that the division's proposed pregnancy category C and labeling wording for pharm-tox sections are appropriate.

2. I have conveyed a few very minor suggestions to the supervisor and they will be addressed as appropriate.

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/s/

ABIGAIL C JACOBS
01/27/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204427 **Applicant:** Anacor Pharmaceuticals, Inc., Palo Alto, CA **Stamp Date:** 07/29/2013

Drug Name: (tavaborole) Topical Solution, 5% **NDA Type:** Original-New Molecular Entity

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 stability characteristics. Such minor changes are not considered significant regarding the toxicity profile and 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 submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	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
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 Nos. (b) (4) Four letters authorizing the Agency to refer to these DMFs were provided in this NDA submission.
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.

NA.

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

None.

Linda Pellicore, Ph.D. — See the sign-off date

Reviewing Pharmacologist — Date

Barbara Hill, Ph.D. — See the 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
09/04/2013

BARBARA A HILL
09/05/2013