

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205266Orig1s000**

**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: 205266  
Application type: 1  
Supporting documents: September 26, 2014  
CDER stamp date: September 26, 2014  
Product: Sonidegib (ODOMZO®)  
Indication: Treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4)  
Applicant: [REDACTED] .  
Novartis Pharmaceuticals Corporation  
Review Division: Division of Hematology Oncology Toxicology  
Reviewer: Alexander H. Putman, Ph.D.  
Supervisor/Team Leader: Whitney S. Helms, Ph.D.  
Division Director: John Leighton, Ph.D.  
Project Manager: Anuja Patel

This is a Pharmacology/Toxicology labeling review for NDA 205266.

Changes were made to nonclinical sections of the sonidegib label based on the most recent practices, to increase clarity, and to be compliant with 21CFR 201.56 and 21 CFR 201.57 on PLLR content and format. Tables below show the “Applicant proposed” language for each section containing nonclinical data and the “Final version” following internal discussions and communications with the Applicant.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### WARNING: EMBRYO-FETAL TOXICITY:

Applicant proposed:	Final version:
(b) (4)	<p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> <li>• ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryotoxic, fetotoxic, and teratogenic in animals. (5.1, 8.1)</li> <li>• Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose. (5.1, 8.3)</li> <li>• Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose. (5.1, 8.3)</li> </ul>

Rationale: Clarifications were based on scientific evidence.

## FULL PRESCRIBING INFORMATION

### Section 5.1 – Embryo-fetal Toxicity:

Applicant proposed:	Final version:
(b) (4)	<p>ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, sonidegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures below the recommended human dose of 200 mg. Advise pregnant women of the potential risk to a fetus [see <i>Use in Specific Populations (8.1)</i>].</p>



(b) (4)

*Females of Reproductive Potential*  
Verify pregnancy status of females of reproductive potential prior to initiating ODOMZO treatment. Advise females to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose [see *Use in Specific Populations (8.3)*].

*Males*  
Advise male patients with female partners to use condoms, even after a vasectomy, during treatment with ODOMZO and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential [see *Use in Specific Populations (8.3)*].

*Blood Donation*  
Advise patients not to donate blood or blood products while taking ODOMZO and for at least 20 months after the last of ODOMZO because their blood or blood products might be given to a female of reproductive potential.

Rationale: For consistency with PLLR. Clarifications were based on scientific evidence. Eight months was chosen for males based on extremely conservative estimates of potential distribution into semen and subsequent maternal exposures because of the significant teratogenic potential of sonedigib, including findings in developmental studies at doses below the limit of detection of the drug..

**Section 8.1 – Pregnancy:**

Applicant proposed:	Final version:
	<p>(b) (4) <i>Risk Summary</i></p> <p>Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman [see <i>Clinical Pharmacology (12.1)</i>]. There are no available data on the use of ODOMZO in pregnant women. In animal reproduction studies, oral administration of</p>

(b) (4)

sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits [see *Data*].

Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

#### *Data*

##### **Animal Data**

Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at  $\geq 5$  mg/kg/day (approximately 0.05 times the recommended human dose based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection.

Rationale: For consistency with PLLR. Language regarding males and females of reproductive potential was moved to Section 8.3 and edited, as described below. Clarifications were based on scientific evidence.

### Section 8.3 – Males and Females of Reproductive Potential:

Applicant proposed:	Final version:
<p>(b) (4)</p>	<p>Based on its mechanism of action and animal data, ODOMZO can cause fetal harm when administered to a pregnant woman [see <i>Use in Specific Populations (8.1)</i>].</p> <p><i>Pregnancy Testing</i> Verify the pregnancy status of females of reproductive potential prior to initiating ODOMZO treatment.</p> <p><i>Contraception</i> <b>Females</b> Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose.</p> <p><b>Males</b> It is not known if sonidegib is present in semen. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose. Advise males not to donate semen during treatment with ODOMZO and for at least 8 months after the last dose.</p>

Rationale: For consistency with PLLR. See rationale for 5.1.

### Section 8.4 – Pediatric Use:

Applicant proposed:	Final version:
<p>(b) (4)</p>	<p>The safety and effectiveness of ODOMZO have not been established in pediatric patients.</p> <p><i>Juvenile Animal Data</i> In a 5-week juvenile rat toxicology study, effects of sonidegib were observed in bone, teeth, reproductive tissues, and nerves at doses <math>\geq 10</math> mg/kg/day (approximately 1.2 times the recommended human dose based on AUC). Bone findings included thinning/closure of bone growth plate, decreased bone length</p>

	and width, and hyperostosis. Findings in teeth included missing or fractured teeth, and atrophy. Reproductive tissue toxicity was evidenced by atrophy of testes, ovaries, and uterus, partial development of the prostate gland and seminal vesicles, and inflammation and aspermia of the epididymis. Nerve degeneration was also noted.
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Rationale: Clarifications were based on scientific evidence

### Section 12.1 – Mechanism of Action:

Applicant proposed: 	Final version: Sonidegib is an inhibitor of the Hedgehog pathway. Sonidegib binds to and inhibits Smoothed, a transmembrane protein involved in Hedgehog signal transduction.
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Rationale: To increase clarity

### Section 13.1 – Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Applicant proposed: 	Final version: Carcinogenicity studies with sonidegib have not been performed.  Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay.  Sonidegib resulted in a lack of fertility when administered to female rats at $\geq 20$ mg/kg/day (approximately 1.3 times the recommended human dose based on body surface area (BSA)). A reduction of the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day (approximately 0.12 times the recommended human dose based on BSA). In addition, in a 6 month repeat-dose toxicology study in rats,
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<p>(b) (4)</p>	<p>effects on female reproductive organs included atrophy of the uterus and ovaries at doses of 10 mg/kg (approximately <math>\geq 2</math> times the exposure in humans at the recommended dose of 200 mg based on AUC). No adverse effects on fertility were noted when male rats were administered sonidegib at doses up to 20 mg/kg/day, the highest dose tested.</p>
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Rationale: Clarifications were based on scientific evidence

**Section 13.2 – Animal Toxicology and/or Pharmacology:**

Applicant proposed:	Final version:
<p>(b) (4)</p>	<p>Body tremors along with significant increases in creatine kinase were observed in rats administered oral sonidegib for 13 weeks or longer at <math>\geq 10</math> mg/kg/day (approximately <math>\geq 2</math> times the recommended human dose based on AUC).</p>

Rationale: Clarifications were based on scientific evidence. (b) (4)

(b) (4)

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/s/  
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ALEXANDER H PUTMAN  
07/21/2015

WHITNEY S HELMS  
07/22/2015

## MEMORANDUM

Odomzo (sonidegib)

**Date:** May 29, 2015

**To:** File for NDA 205266

**From:** John K. Leighton, PhD, DABT

Director, Division of Hematology Oncology Toxicology  
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting and labeling reviews for Odomzo conducted by Dr. Putman, and secondary memorandum and labeling provided by Dr. Helms. I concur with Dr. Helms' conclusion that Odomzo may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/  
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JOHN K LEIGHTON  
05/29/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
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**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of 205266 are owned by Novartis or are data for which Novartis has obtained a written right of reference. Any information or data necessary for approval of 205266 that Novartis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 205266.

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# 1 Executive Summary

## 1.1 Introduction

Sonidegib (ODOMZO®) is an orally administered smoothened (Smo) antagonist, a transmembrane protein that activates the hedgehog signaling transduction pathway. Sonidegib is indicated for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy <sup>(b) (4)</sup>. Based on clinical trials submitted to support the use of ODOMZO in the intended patient population, the recommended dose is 200 mg daily resulting in an average  $C_{max}$  of 1030 ng/mL and an AUC of 22  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .

## 1.2 Brief Discussion of Nonclinical Findings

Nonclinical pharmacology studies conducted *in vitro* and *in vivo* demonstrated that sonidegib is an inhibitor of smoothened (Smo), a transmembrane protein critical for hedgehog signal transduction. In an *in vitro* agonist displacement assay using human Smo, sonidegib showed an  $IC_{50}$  of 11nM. A cell-based reporter gene assay was also used to measure the potency of sonidegib to inhibit Smo-agonist induced hedgehog signaling via the Gli1 transcription factor. Gli1 is one of three transcription factors in the Gli family that mediate hedgehog signaling following activation of Smo. In this assay, sonidegib inhibited Gli-induced transcription following agonist induction with an  $IC_{50}$  of 4nM. Gli activation through hedgehog signaling results in upregulation of *Gli* itself. Thus, to confirm the potency and specificity of sonidegib to inhibit hedgehog signaling, the Applicant measured Gli1 expression levels in human fetal palatal mesenchymal cells stimulated with hedgehog activation proteins and exposed to sonidegib. Sonidegib inhibited Gli1 expression with an  $IC_{50}$  of 12.7 nM. *In vivo*, sonidegib inhibited hedgehog signaling in mouse skin, resulting in hair growth inhibition, an expected pharmacodynamic result of inhibition of hedgehog signaling. Incubation with sonidegib also inhibited basaloid lesion formation resulting from growth in the presence of sonic hedgehog protein and resulted in regression of pre-formed basaloid lesions in an *ex vivo* skin punch from a mouse model of basal cell carcinoma.

Sonidegib was assessed for its off-target activity across a panel of 150 G-protein coupled receptors, transporters, ion channels, nuclear receptors, and enzymes. Sonidegib demonstrated activity at potentially clinically relevant concentrations only for the human melatonin MT1 receptor and rat brain sodium channel type II. In a binding assay using human recombinant melatonin MT1 receptor, sonidegib was identified as a full agonist with an  $EC_{50}$  of 1.75  $\mu\text{M}$ . The Applicant reported that sonidegib showed no effect in an *in vitro* assay of the human Nav1.5 sodium channel.

Safety pharmacology studies with sonidegib consisted of an *in-vitro* evaluation of hERG (human ether-á-go-go-related gene) channel interaction, a combined functional observational battery (FOB) neurological and respiratory assessment in rats, and a cardiovascular safety pharmacology study in dogs. No sonidegib-induced adverse

effects were seen in any of these studies. Sonidegib was a weak hERG blocker with a low potential to induce QT prolongation.

In general, the oral absorption of sonidegib was high in the rat (78%) and moderate in the dog (37.9%). The rate of absorption of sonidegib was moderate to low in animals with the  $T_{max}$  occurring at 4 to 48 hours. Sonidegib was highly bound to plasma proteins in the mouse, rat, dog, and human (97-99%). The tissue distribution of sonidegib was widespread with the highest concentrations observed in the uveal tract, Harderian gland, fat, liver, small intestine, adrenal cortex, and adrenal medulla. Sonidegib crossed the blood:brain barrier.

The metabolism of sonidegib was qualitatively similar but quantitatively different across species. Oxidations and oxidative cleavages (N/O dealkylation) in the morpholine ring appeared to be major metabolic pathways of sonidegib in all species. No unique metabolites were identified in human plasma. The majority of sonidegib was excreted via feces in rats, dogs, and humans.

The toxicity of repeated daily doses of oral sonidegib was assessed by conducting 13- and 26-week toxicity studies in rats and dogs. In both rats and dogs, the major target organs of sonidegib toxicity included the skin, bones, and gastrointestinal tract. Skin toxicity manifested as alopecia with histopathological atrophy of hair follicles in nearly all high-dose animals in both species. Thinning and closure of the growth plate were the primary signs of bone toxicity. In rats, the teeth were also a major target for sonidegib. Teeth abnormalities consisted of missing or broken teeth with histopathological atrophy leading to decreased food consumption and body weight. The adverse effect of sonidegib on teeth was severe enough to warrant the early sacrifice of some animals in the 26-week toxicity study. While the effects on bones and teeth may have little significance for the intended adult patient population, they are of potential relevance for pediatric use of ODOMZO. Gastrointestinal effects were of greater significance in the dogs and consisted of ileum necrosis, and attenuation of the stomach. Additional species specific sonidegib-induced toxicity in rats consisted of lymphoid depletion, generally increased plasma levels of creatine kinase and cholesterol, prostate gland inflammation, and atrophy of the uterus and ovaries. In dogs administration of sonidegib also resulted in adrenal vacuolation, increased cholesterol levels, inconsistent alterations in creatine kinase levels, and decreased uterus weight.

In a 5-week juvenile rat toxicity study, sonidegib-induced toxicity targeted the bone, teeth, reproductive tissues, and nerves. Bone toxicity consisted of thinning/closure of the growth plate, decreased bone length and width, and hyperostosis. Findings in teeth included missing or fractured teeth, and atrophy. Reproductive tissue toxicity was evidenced by atrophy of testes, ovaries, and uterus, partial development of the prostate gland and seminal vesicles, and inflammation and aspermia of the epididymis. Nerve degeneration was also noted.

Musculoskeletal adverse reactions are frequently reported clinically, and rhabdomyolysis has occurred. In animals there were no histopathological signs of muscle degeneration;

however, at high doses there were transient increases in creatine kinase and whole body tremors observed in both species Tremors along with the elevations in creatine kinase are included in Section 13.2 - Animal Toxicology and/or Pharmacology of the ODOMZO® label. This toxicity was consistently seen in rats at doses  $\geq 10$  mg/kg/day (approximately  $\geq 2$  times the recommended human dose based on AUC). Although body tremors were also noted in dogs administered 50 mg/kg/day of sonidegib, this dose exceeded the maximum tolerated dose and resulted in overt toxicity; thus the pharmacological relevance of these tremors is uncertain. The off-target activity of sonidegib on rat sodium brain channel type II provides evidence that body tremors in rats may be unrelated to the muscle issues (including muscle spasms) reported clinically.

Sonidegib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) and was not clastogenic or aneugenic in an in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus test. Carcinogenicity studies were not conducted or required for sonidegib due to its intended use in patients with advanced cancer.

The effect of sonidegib on fertility was evaluated in rats. Sonidegib resulted in a lack of fertility when administered to female rats at  $\geq 20$  mg/kg/day. A reduction in the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day. No adverse effects on reproductive potential were noted in males.

Embryo-fetal toxicity studies with sonidegib were conducted in rabbits. Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at  $\geq 5$  mg/kg/day. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection. A warning for embryofetal risk was recommended for ODOMZO and a black box warning for embryofetal toxicity is included in the label.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

From a Pharmacology/Toxicology perspective, the approval of sonidegib (ODOMZO®) is recommended.

#### **1.3.2 Additional Non-Clinical Recommendations**

Based on the life expectancy of the intended patient population ( $\geq 5$  years after first exposure to sonidegib), the pharmacology/toxicology team recommends two rodent (mouse and rat) carcinogenicity studies as post-marketing requirements.

### 1.3.3 Labeling

The recommendations to the Applicant's proposed labeling were discussed internally and communicated to the Applicant. Information in the non-clinical sections of the label reflects findings of studies reviewed within this document.

## 2 Drug Information

### 2.1 Drug

#### 2.1.1 CAS Registry Number

1218778-77-8

#### 2.1.2 Generic Name

Sonidegib

#### 2.1.3 Code Name

LDE225; NVP-LDE225

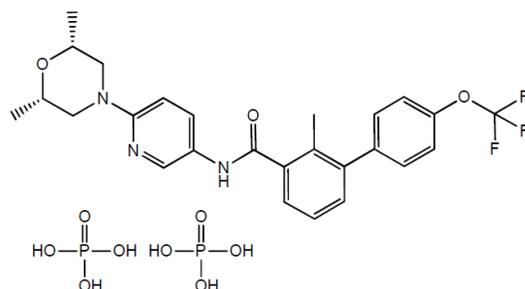
#### 2.1.4 Chemical Name

N-[6-(cis-2,6-Dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)  
[1,1'-biphenyl]-3-carboxamide diphosphate

#### 2.1.5 Molecular Formula/Molecular Weight

$C_{26}H_{26}F_3N_3O_3 \cdot 2H_3PO_4$  / 681.49 g/mol

#### 2.1.6 Structure



#### 2.1.7 Pharmacologic class

Smoothened antagonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 102961

## 2.3 Drug Formulation

Sonidegib (ODOMZO®) is formulated as 200 mg hard gelatin capsules. The capsules are pink, opaque, (b) (4) with black (b) (4) imprint “NVR” on the cap and “SONIDEGIB 200 MG” on the body.

The detailed composition of 200 mg sonidegib capsules is shown in the following tables.

**Table 1: Composition of Sonidegib 200 mg Capsules**

Ingredient	Amount per capsule	Function	Reference to standards
<b>Capsule fill</b>			
Sonidegib diphosphate (corresponding to Sonidegib)	(b) (4) (200.00)	Active ingredient	Novartis monograph
Crospovidone	(b) (4)		Ph.Eur./ NF
Lactose monohydrate			Ph.Eur./ NF
(b) (4) Poloxamer (b) (4)			Ph.Eur./ NF
(b) (4) Sodium lauryl sulfate			Ph.Eur./ NF
Magnesium stearate <sup>1</sup>			Ph.Eur./ NF
(b) (4) Colloidal silicon dioxide			Ph.Eur./ NF
(b) (4)			Ph.Eur./ USP
<b>Capsule fill weight</b>			
<b>Empty capsule shell, pre-printed</b>			
Capsule shell (theoretical weight) <sup>3</sup>	(b) (4)		Novartis monograph
Printing ink, black <sup>4</sup>			<u>Table 3</u>
<b>Total capsule weight</b>	<b>534.60</b>		
(b) (4)			

<sup>3</sup>The composition of the capsule shell is given in Table 2 below

<sup>4</sup>The composition of the printing ink is shown in Table 3 below

**Table 2: Composition of Capsule Shell**

Capsule shell components	Amount per capsule (mg)	Function	Reference to standards
Gelatin (b) (4)	[REDACTED]	(b) (4)	Ph. Eur./NF
Titanium dioxide (b) (4)			Ph. Eur./USP
Iron oxide, red (b) (4)			EU/231/2012 <sup>2</sup> /NF
Printing ink, black <sup>3</sup>			See Table 1-4

<sup>1</sup> E: Official number used in the European Union for colorants

<sup>2</sup> EU/231/2012: EU regulation for food additives

<sup>3</sup> The qualitative composition of the printing ink is provided in Table 1-4

**Table 3: Qualitative Composition of Black Printing Ink**

Printing ink components	Reference to standards
Shellac	Ph. Eur./NF
Iron oxide, black (b) (4)	EU/231/2012 <sup>2</sup> /21CFR <sup>3</sup>
Propylene glycol	Ph. Eur./USP
Ammonium Hydroxide	Ph. Eur./NF

<sup>1</sup> E: Official number used in the European Union for colorants

<sup>2</sup> EU/231/2012: EU regulation for food additives

<sup>3</sup> CFR: Code of Federal Regulations (USA)

(tables excerpted from Applicant's NDA)

### 2.3.3 Comments on Impurities/Degradants of Concern

All impurities were either qualified in nonclinical studies or within acceptable limits according to ICHQ3A and ICHQ3B.

## 2.6 Proposed Clinical Population and Dosing Regimen

Sonidegib (ODOMZO®) is indicated to treat patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy, (b) (4). The recommended dose and schedule of sonidegib (ODOMZO®) is 200 mg, taken orally once per day.

## 2.7 Regulatory Background

Sonidegib was investigated under IND 102961 for the treatment of basal cell carcinoma (BCC). (b) (4)

### 3 Studies Submitted

#### 3.1 Studies Reviewed

##### Primary Pharmacology:

Study #	Study title
50686	LDE225 in vitro Smo binding
50689	NVP-LDE225 in vitro Smo inhibition
50858	RT-PCR analysis of Gli1 gene regulation by NVP-LDE225-NX-1 in human palatal mesenchymal HepM cells
50628	NVP-LDE225: In vitro safety pharmacology profile
01671	LDE225: Inhibition of hair growth in C57BL/6 mice
51591	Inhibition and regression of basaloid lesions in Ptch <sup>+/-</sup> -LacZ mouse skin punches by smoothed antagonist NVP-LDE225-NX-3

##### Safety Pharmacology:

Study #	Study title
0770728	Oral safety pharmacology study in rats (nervous system and respiratory functions)
0770734	Single-dose oral telemetry study in dogs
0770726	Electrophysiological safety measurements of hERG currents in stably transfected HEK293 cells

##### Repeat-dose Toxicology:

Study #	Study title
0870704	LDE225: A 13-week oral (gavage) toxicity study in the rat with a 8-week recovery
0870705	LDE225: A 13-week oral (gavage) toxicity study in the beagle dog with a 8-week recovery period
1070056	26-week oral gavage toxicity and toxicokinetic study with LDE225 in rats
1070055	26-week oral gavage toxicity and toxicokinetic study with LDE225 in dogs

##### Genetic Toxicology:

Study #	Study title
0770725	Mutagenicity test using salmonella typhimurium
0770727	Induction of chromosome aberrations in cultured human peripheral blood lymphocytes
1070158	Rat bone marrow micronucleus test after oral administration

##### Reproductive and Developmental Toxicology:

Study #	Study title
0970151	An oral (gavage) embryo-fetal development dose range finding

	study in rabbits
0970631	An oral embryo-fetal development study in rabbits
0770903	LDE225: A 5-week oral (gavage) toxicity study in juvenile rats with a 8-week recovery period

### 3.2 Studies Not Reviewed

#### Primary Pharmacology:

Study #	Study title
	(b) (4)
50956	Assessment of cyclin D1 and Gli1 in the mouse hair follicle cycle

#### Safety Pharmacology:

Study #	Study title
0718501	Electrophysiological study of LDE225 in isolated heart
0670734	An oral (capsule) pilot toxicity study in male dogs with non - invasive telemetry
0770514	Oral (gavage) single dose rising-dose study in dogs including non-invasive telemetry
0770120	In vitro 3T3 NRU phototoxicity test

#### Pharmacokinetics:

Study #	Study title
0900883	Absorption, distribution, metabolism, and excretion of [14C]LDE225 in male Göttingen minipigs after single dermal (10 mg/kg) and intravenous (1 mg/kg) administration
1100218	Absorption, metabolism, and excretion in male dogs after single intravenous (1 mg/kg) and oral (10 mg/kg) administration of [14C]LDE225
0500648	Drug-protein adduct formation: in vitro methods and risk assessment
0700977	In vitro metabolism of [14C]LDE225 in mouse, rat, minipig, monkey, dog and human hepatocytes
0700987	In vitro assessment of covalent protein binding potential for LDE225 in rat and human liver microsomes and human hepatocytes
1100465	Stability of CMN964, an acyl glucuronide metabolite of LDE225, in biological matrices

1200697	Correlation of LDE225 metabolites across ADME studies and comparison with reference compounds
50348	LDE225, its metabolites and vismodegib in SHH-stimulated Daoy Gli1 mRNA assay
1100451	Biliary excretion in rats after intravenous (2 mg/kg) administration of [ <sup>14</sup> C]LDE225

**Repeat-dose Toxicology:**

Study #	Study title
0770516	Acute oral (gavage) toxicity study in rats
0970683	Acute oral toxicity study in rats
1270097	5-day oral (gavage) investigative study in male rats to determine reversibility of bone-related effects
0770732	4-week oral (gavage) toxicity study in rats with a 4 week recovery period
0770715	2-week oral (gavage) pilot toxicity study in male rats
0670733	2-week oral (gavage) dose range-finding toxicity study in male rats
0770601	2-week oral dose-range finding study in dogs
0770733	4-week oral (gavage) toxicity study in dogs with a 4 week recovery period
0870112	2-week oral (gavage) daily and Q4D (5 dose) dosing toxicity study in dogs

**Genetic Toxicology:**

Study #	Study title
0614112	Micronucleus test in vitro using TK6 cells

**Reproductive and Developmental Toxicology:**

Study #	Study title
0770836	An oral (gavage) juvenile development dose range-finding study in rats

**Local Tolerance:**

Study #	Study title
0770162	Assessment of contact (photo) allergenic potential with the murine local lymph node assay (LLNA tier I)
(b) (4)	
0970680	Primary skin irritation study in rabbits (4-hour semi-occlusive application)
0970681	Primary eye irritation study in rabbits
0970682	Assessment of contact sensitizing potential with the murine local lymph node assay (LLNA tier I)

**Other Toxicity Studies:**

Study #	Study title
1070375	7-day investigative toxicity study in male rats
1170229	Multiple dose investigative toxicity study in male rats
1170560	A 2-week investigative toxicity study in male rats
1170580	12-day oral (gavage) investigative combination study in female rats
1170644	A 2-week investigative toxicity study in male rats
1100529	Assessment of CK leakage after co-treatment with LDE225 and Simvastatin to skeletal muscle cells in vitro
0700302	Quantitative determination of BFH772 in plasma of rat and minipig by LC-MS/MS
0770454	5-day dermal tolerability study in minipigs
0870361	39-week dermal (topical) toxicity study in minipigs
0970678	Primary skin irritation study in rabbits (4-hour semi-occlusive application)
1070413	6-months dermal toxicity study in minipigs with toxicokinetics
0770795	A 42 day dermal toxicity study in minipigs with a 4 week recovery period

**3.3 Previous Reviews Referenced**

The Pharmacology/Toxicology and other discipline reviews for IND 102961.

**4 Pharmacology****4.1 Primary Pharmacology****Study No. 50686:** LDE225 in vitro Smo binding

This study was conducted to measure the ability of LDE225 to bind the smoothed (Smo) receptor. Binding was assessed by measuring the ability of LDE225 to displace a radiolabeled small molecule Smo agonist, (b) (4), or a fluorescently-labeled small molecule Smo antagonist, BODIPY-cyclopamine. Both assays utilized CHO-K1 cells, stably expressing human or mouse Smo.

In the agonist displacement assay, LDE225 (NVP-LDE225) showed similar activity using human ( $IC_{50} = 11nM$ ) and mouse ( $IC_{50} = 12nM$ ) Smo protein. LDE225 was able to displace the Smo agonist at much lower concentrations than cyclopamine (b) (4) (Table 4). As shown in Table 5, the antagonistic displacement assay yielded similar results.

**Table 4: Smo Binding Assay by Agonist Displacement**

Compound ID	Condition	Agonist Displacement IC <sub>50</sub> (nM)	Standard Error of Mean	Number of Experiments
NVP-LDE225	Human Smo	11	3	5
	Mouse Smo	12	2	5
(b) (4)	Human Smo	280	64	2
	Mouse Smo	1205	735	3

**Table 5: Smo Binding Assay by Antagonistic Displacement**

Compound ID	Condition	Antagonist Displacement IC <sub>50</sub> (nM)	Standard Error of Mean	Number of Experiments
NVP-LDE225	Human Smo	7	3	4
	Mouse Smo	3	1	5
(b) (4)	Human Smo	45	4	2
	Mouse Smo	149	38	2

(tables excerpted from Applicant's NDA)

#### Study No. 50689: NVP-LDE225 in vitro Smo inhibition

Gli1 is one of three transcription factors in the Gli family that mediate hedgehog signaling following activation of the smoothed receptor (Smo). Using a cell-based reporter gene assay, TM3-Gli-Luc, the Applicant measured the potency of LDE225 to inhibit Gli-Luc activity induced by a Smo agonist. In this assay, TM3Hh12 cells (TM3 cells containing Hh-responsive reporter gene construct pTA-8xGli-Luc) were incubated with serial dilutions of LDE225 or the Smo antagonist, cyclopamine (b) (4) for approximately 30 minutes. The Smo agonist (b) (4) (1 or 25 nM) was then added to assay plates and incubated for 48 hours. Bright-Glo (to determine luciferase activity) or MTS reagent (to determine cell viability) were added to the assay plates and IC<sub>50</sub> values were determined by non-linear regression of the Gli-driven luciferase luminescence, or absorbance signal from MTS assay, at a given dose of Smo agonist vs. log<sub>10</sub> (concentration) of test antagonist.

As shown in Table 6, LDE225 antagonized Smo signaling, demonstrated by inhibition of Gli-Luc, with a greater potency than cyclopamine (b) (4). According to the Applicant, cell viability measurements performed using the MTS reagent indicated that LDE225 is not cytotoxic on TM3Hh12 cells at concentrations up to 25 μM (data not shown).

**Table 6: Results of TM3-Gli-Luc Assay**

Compound ID	Condition	TM3 Gli-Luc IC <sub>50</sub> (nM)	Standard Error of Mean	Number of Experiments
LDE225	1 nM Smo agonist	4	4	5
	25 nM Smo agonist	37	14	7
(b) (4)	1 nM Smo agonist	46	17	4
	25 nM Smo agonist	4757	2192	3

(table excerpted from Applicant's NDA)

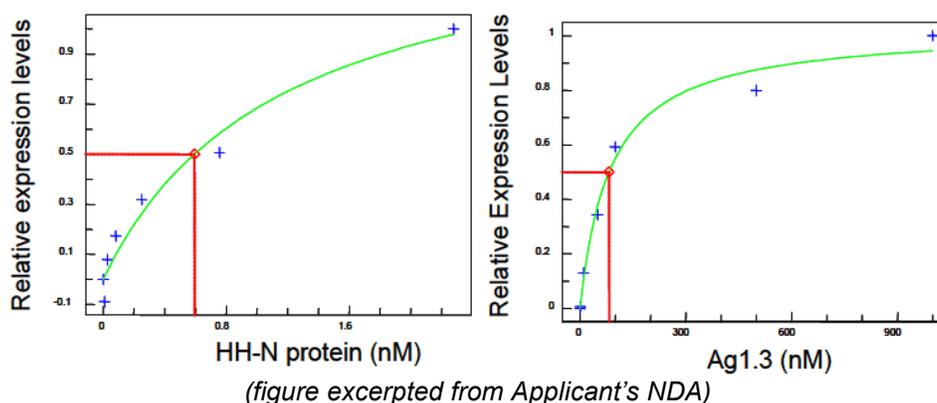
**Study No. 50858:** RT-PCR analysis of Gli1 gene regulation by NVP-LDE225-NX-1 in human palatal mesenchymal HepM cells

The ability of LDE225 to inhibit Gli1 expression induced by hedgehog (HH) proteins (HH-N or Smo agonist HH-Ag 1.3) was measured using real time quantitative polymerase chain reaction (RT-PCR) analysis.

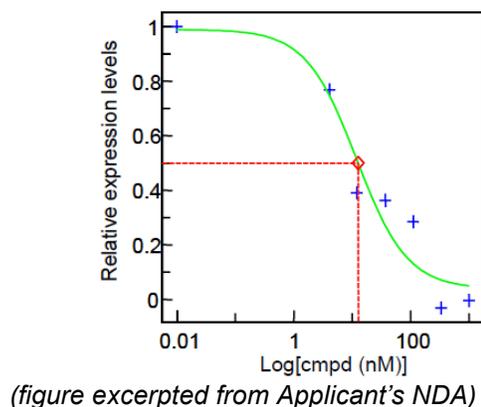
Human fetal palatal mesenchymal HepM cells were stimulated with 17.5  $\mu\text{g}/\text{mL}$  of HH protein and treated with various concentrations of LDE225 (up to 1  $\mu\text{M}$ ). Forty-eight hours later, RNA samples were collected and analyzed using RT-PCR. Gli1 mRNA expression levels were normalized to GAPDH mRNA levels and analyzed using SDS 2.0 software to calculate relative RNA quantities (ng).

As shown in Figure 1, HH-N protein (left panel) and Smo agonist HH-Ag 1.3 (right panel) induced Gli1 expression with  $\text{EC}_{50}$ s of 0.59 and 82.4 nM, respectively. LDE225 inhibited Gli1 expression induced by HH-N protein with an  $\text{IC}_{50}$  of 12.7 nM (Figure 2).

**Figure 1: Dose-response Curves of HH-N Protein Treatment (left panel) and Smo Agonist HH-Ag 1.3 (right panel) Inducing Gli1 Expression in HepM cells**



**Figure 2: Dose-response Curve of LDE225 Treatment Inhibiting Gli1 Gene Expression Induced by HH-N Protein in HepM Cells**



**Study No. 50628:** NVP-LDE225: In vitro safety pharmacology profile

LDE225 was assessed for its off-target activity across a panel of 150 G-protein coupled receptors, transporters, ion channels, nuclear receptors, and enzymes. Activities of  $\geq 50\%$  inhibition following incubation with 10  $\mu\text{M}$  of LDE225 were found in 4 assays: human melatonin MT1 receptor ( $\text{IC}_{50} = 1.1 \mu\text{M}$ ;  $\text{K}_i = 0.55 \mu\text{M}$ ), human cannabinoid CB2 receptor ( $\text{IC}_{50} = 9.7 \mu\text{M}$ ;  $\text{K}_i = 6.5 \mu\text{M}$ ), rat brain sodium channel type II ( $\text{IC}_{50} = 0.82 \mu\text{M}$ ;  $\text{K}_i = 0.75 \mu\text{M}$ ), and rabbit vesicular monoamine transporter VMAT2 ( $\text{IC}_{50} = 10 \mu\text{M}$ ;  $\text{K}_i =$  not available). Human acetylcholinesterase enzyme showed 49% inhibition following 10  $\mu\text{M}$  of LDE225. In a GTP $\gamma$ S binding assay using human recombinant MT1 receptor, LDE225 was identified as a full agonist with an  $\text{EC}_{50}$  of 1.75  $\mu\text{M}$ .

**Study No. 01671:** LDE225: Inhibition of hair growth in C57BL/6 mice

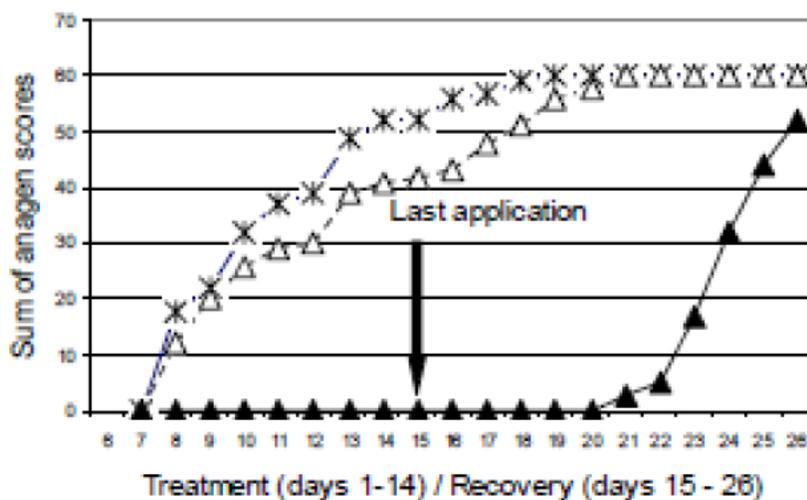
Since hair follicles have active hedgehog signaling and inhibition of the smoothed (Smo) receptor has been shown to interfere with the generation of hair follicles in vitro (Oro and Higgins, 2003; Nanba D, et. al., 2003), the Applicant examined the ability of LDE225 to inhibit hair growth on C57BL/6 mice.

All mature melanocytes in truncal skin of C57BL/6 mice are confined to the hair follicles and melanogenesis is strictly coupled to the growth phase of the hair cycle. Thus, the change in back skin color is a reliable marker for the differentiation between skin in the resting phase of the hair cycle (telogen) and during hair growth (anagen) (Slominski and Paus, 1997). Skin color will change from pink (telogen) to gray (early anagen) to black (late anagen).

Fifteen mice per treatment group were depilated on the dorsal truck to induce anagen. One to 2 days later, the depilated area was exposed daily to 150  $\mu\text{l}$  of 0.1% LDE225, 1.0% LDE225, or vehicle, for 14 days. As soon as a change from telogen to anagen was observed in a single mouse, all animals were examined for changes which were scored from 0 to 4 (0: total test area telogen, 1: 1/10 of test area anagen, 2: 1/3 of test area anagen, 3: 2/3 of test area anagen, 4: total test area anagen).

As shown in Figure 3, while all vehicle-treated animals showed anagen induction by Day 10, all animals treated with 1.0% LDE225 remained in telogen until day 20 (the 5th day after the last application of LDE225).

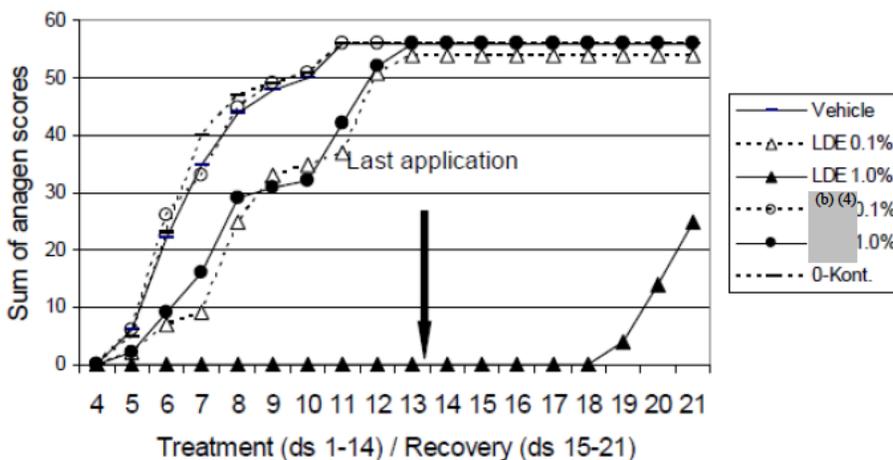
**Figure 3: Anagen Development in C57BL7/6 Mice following Topical LDE225**



---x--- vehicle; ---Δ--- 0.1% LDE225; ---▲--- 1% LDE225  
 (figure excerpted from Applicant's NDA)

To confirm these results, a similar study was completed with the addition of comparing the activity of LDE225 with the Smo antagonist, cyclopamine. In contrast to 1% LDE225, 1% cyclopamine <sup>(b) (4)</sup> only weakly inhibited anagen (approximately 2 days), with results similar to 0.1% LDE225 (Figure 4).

**Figure 4: Anagen Development in C57BL7/6 Mice following Topical LDE225 or Cyclopamine**



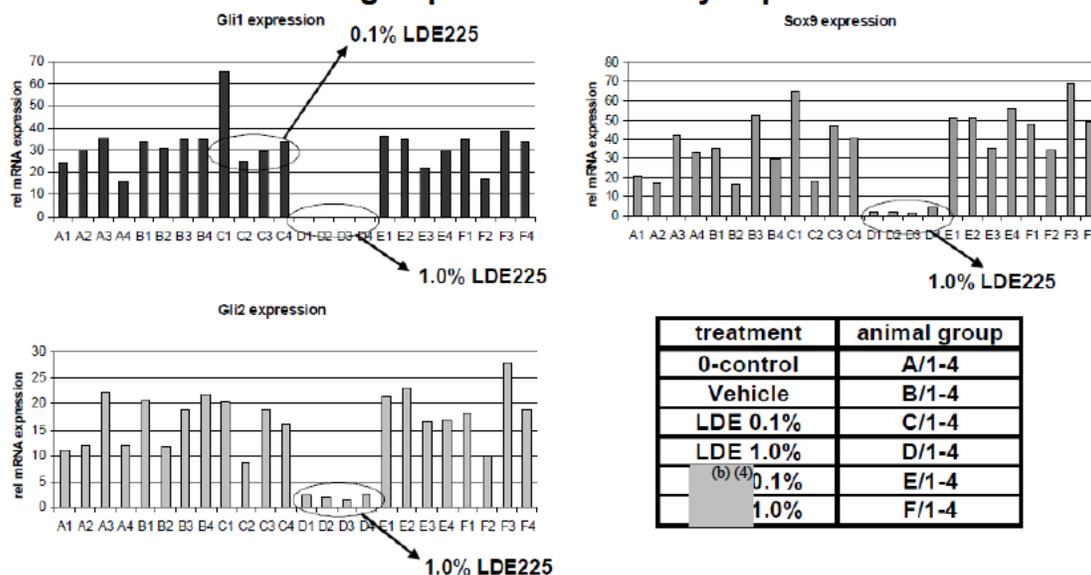
0-Kont. denotes no treatment

(figure excerpted from Applicant's NDA)

On Day 14, skin samples were taken from 4 animals from each treatment group to measure the gene expression of the hedgehog signaling genes, Gli1, Gli2, and Sox9 using quantitative reverse transcription polymerase reaction (RT-PCR) analysis. As shown in Figure 5, consistent with anagen inhibition in mice, 1% LDE225 inhibited the expression of Gli1, Gli2, and Sox9. No significant inhibition of Gli1/2 or Sox-9 was

detected in control animals or mice treated with 0.1% LDE225 or cyclopamine (BFQ). Similar gene expression results were also noted in a separate study in which mice were depilated and treated daily with topical 1% LDE225 for only 7 days (data not shown).

**Figure 5: Quantitative PCR Analysis of Gli1, Gli2 and Sox-9 Expression in Skin following Topical LDE225 or Cyclopamine**

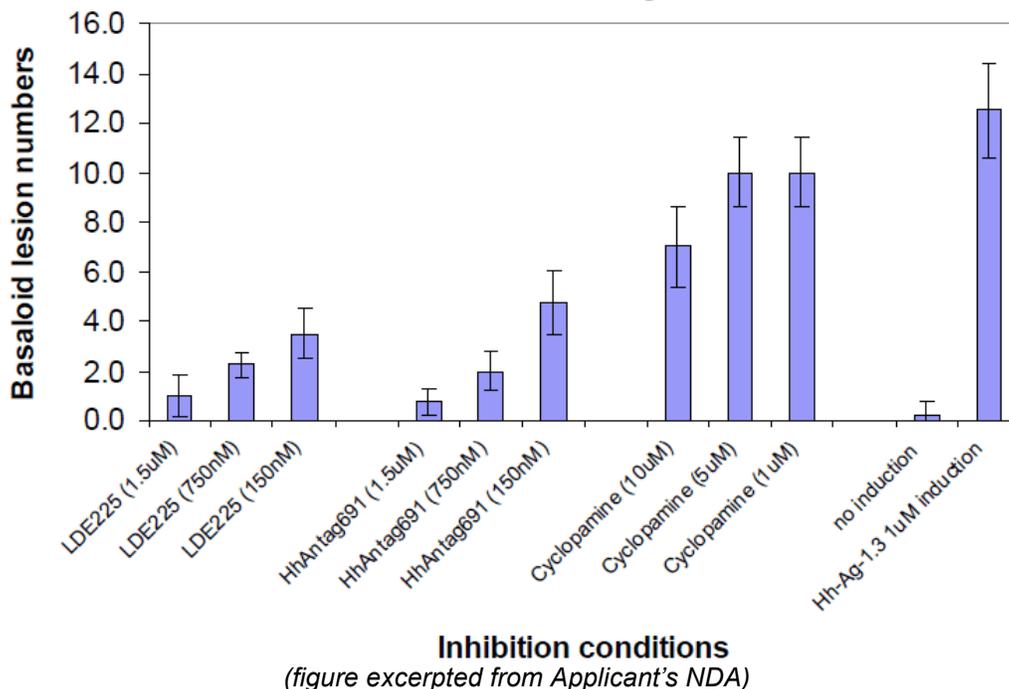


(figure excerpted from Applicant's NDA)

**Study No. 51591: Inhibition and regression of basaloid lesions in Ptch<sup>+/-</sup>-LacZ mouse skin punches by smoothed antagonist NVP-LDE225-NX-3**

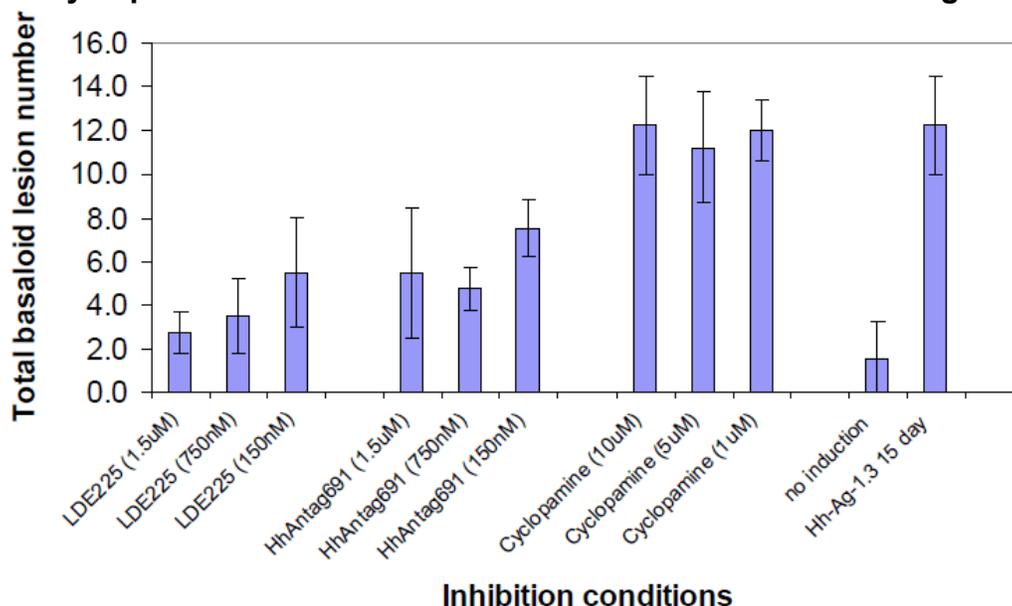
Mouse embryonic skin punches derived from Ptch<sup>+/-</sup>-LacZ heterozygous mice form basaloid nest lesions when cultured and stimulated with recombinant Shh protein or small molecule Smo agonists ex-vivo (Williams et. al., 2003). Thus, these skin punches may be utilized as a mouse model of basal cell carcinoma to evaluate the activity of Smo antagonists. The activity of LDE225, Hh-Antag691, and cyclopamine on mouse skin punches was evaluated by inhibition of basaloid lesion formation on embryonic day 17.5 and postnatal day 1 skin punches from the Ptch<sup>+/-</sup>-LacZ heterozygous mice, and regression of pre-formed basaloid lesions. As shown in Figure 6, LDE225 and Hh-Antag691 dose-dependently blocked basaloid lesion formation in embryonic day 17.5 mouse skin punches induced using 1µM of the Smo agonist, Hh-Ag-1.3. According to the Applicant, cyclopamine was not effective in blocking Hh signaling due to poor solubility and possibly poor permeability into the skin punches. Similar results were seen in postnatal day 1 mouse skin punches (data not shown).

**Figure 6: Inhibition of Basaloid Lesion Formation by LDE225, Hh-Antag691, and Cyclopamine in Embryonic Day 17.5 Mouse Skin Punches Stimulated with Hh-Ag-1.3**



Pre-treatment of mouse embryonic skin punches with Hh-Ag-1.3 for 7 days induced significant basaloid lesion formation. As shown in Figure 7, an additional 8 days of treatment with LDE225 or Hh-Antag691 resulted in regression of the pre-formed basaloid lesions. Similar to previous results, cyclopamine showed no effect.

**Figure 7: Basaloid Lesion Regression by LDE225, Hh-Antag691, or Cyclopamine in Mouse Skin Punches Pre-treated with Hh-Ag-1.3**



(figure excerpted from Applicant's NDA)

### 4.3 Safety Pharmacology

**Study title:** Oral safety pharmacology study in rats (nervous system and respiratory functions)

Study no: 0770728  
Study report location: 4.2.1.3  
Conducting laboratory and location: Preclinical Safety  
Novartis Pharma AG  
Basel, Switzerland  
Date of study initiation: February 25, 2008  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

A single oral dose of 600 mg/kg of LDE225 did not result in any toxicologically significant adverse effects on neurobehavioral or respiratory parameters.

**Methods:**

Dose: 0 or 600 mg/kg  
Frequency of dosing: Single dose  
Route of administration: Oral gavage  
Dose volume: 10 mL/kg  
Formulation/Vehicle: 0.5% (w/v) methylcellulose aqueous solution (MC) using Nanopure water containing 1% (v/v) Tween 80  
Species/Strain: Rat / HanRcc: Wist (SPF)  
Number/Sex/Group: 10 males  
Age: 10 weeks  
Weight: 268 to 302 grams  
Satellite groups: None  
Dose justification: Based on results from a 4-week oral gavage toxicity study in rats in which a single dose of 600 mg/kg was well tolerated.

**Observations and Results:**

**Mortality:** none

**Clinical signs:** unremarkable

**Body weights:** unremarkable

**Functional observational battery [observed at 4 ( $C_{max}$ ) and 24 hours post-dose]:**  
unremarkable

**Plethysmography [recorded at 0, 4, 7, and 24 hours post-dose]:**  
Results on tidal volume, respiratory rate, and minute volume were unremarkable.

**Study title:** Single-dose oral telemetry study in dogs

Study no: 0770734  
Study report location: 4.2.1.3  
Conducting laboratory and location: Preclinical Safety  
Novartis Pharma AG  
Basel, Switzerland  
Date of study initiation: May 5, 2008  
GLP compliance: Yes; however, automated analysis  
software used for ECG analysis was not  
fully validated  
QA statement: Yes  
Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

A single oral dose of up to 1000 mg/kg of LDE225 in dogs did not result in any toxicologically significant adverse effects on arterial pressure, body temperature, heart rate, or electrocardiographic intervals.

**Methods:**

Doses: 0, 100, 300, or 1000 mg/kg/day  
Frequency of dosing: Single dose with monitoring up to 21 hours post-dose  
Route of administration: Oral suspension  
Dose volume: 10 mL/kg  
Formulation/Vehicle: 0.5 % (w/v) methylcellulose/1 % (v/v) Tween 80  
and 6 N NaOH  
Species/Strain: Dog / Beagle  
Number/Sex/Group: 4 males  
Age: 16-47 months  
Weight: 9.7 to 13.5 kg  
Satellite groups: None  
Dose justification: Based on results from a 2-week oral dose-range  
finding study in dogs, in which up to 1000  
mg/kg/day of LDE225 was well tolerated.

**Observations and Results:**

**Mortality:** none

**Clinical signs:** unremarkable

**Core body temperature:** unremarkable

**Heart rate:** unremarkable

**Mean systolic arterial pressure:** unremarkable

**Mean diastolic arterial pressure:** unremarkable

**Electrocardiograph:** unremarkable

**QT/QTc intervals:** unremarkable

**Study title:** Electrophysiological safety measurements of hERG currents in stably transfected HEK293 cells

Study no:	0770726
Study report location:	4.2.1.3
Conducting laboratory and location:	Preclinical Safety Operations Novartis Pharma AG Basel, Switzerland
Date of study initiation:	May 21, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LDE225, 0751003, 100%

**Key study findings:**

Under the conditions tested, LDE225 may be a weak hERG blocker, with a low potential to induce QT prolongation.

**Methods:**

Strains/species/cell line:	Human Embryonic Kidney Cells
Controls:	0.1 % DMSO in extracellular solution
Concentrations:	Up to 0.5 $\mu$ M
Test system:	Standard hERG assay

**Results:**

At the highest concentration tested (0.5  $\mu$ M), LDE225 decreased hERG channel activity by 20.7%; however, the concentration originally prepared was 7.8  $\mu$ M, indicating a 93% decrease in test-article concentration between preparation and the end of patch clamp measurements. In consideration of this test-article stability issue, the validity of these results is unknown.

## 5 Pharmacokinetics/ADME

### 5.1 PK/ADME

The absorption, distribution, metabolism, and excretion (ADME) program for LDE225 was comprised of single dose studies in animals using radiolabelled LDE225. A human ADME study was also conducted with radiolabelled LDE225, administered as a single, 800 mg, oral dose to healthy male adult volunteers.

In general, the oral absorption of LDE225 was high in the rat (78%) and moderate in the dog (37.9%). The rate of absorption of LDE225 was moderate to low in animals with the  $T_{max}$  occurring at 4 to 48 hours following a single oral dose in the rat and dog ADME studies. In contrast, oral absorption of LDE225 was estimated to be low (~6-7%) in humans while the rate of absorption appeared to be moderate to high, with a median  $T_{max}$  at 2 hours. The oral bioavailability of LDE225 in the dog was comparable to absorption, demonstrating a minimal first-pass metabolic effect. In humans, a strong positive food effect on the bioavailability of LDE225 was identified. Specifically, the  $AUC_{inf}$  and  $C_{max}$  of LDE225 were approximately 7 times higher when administered after a high-fat meal compared to fasting subjects.

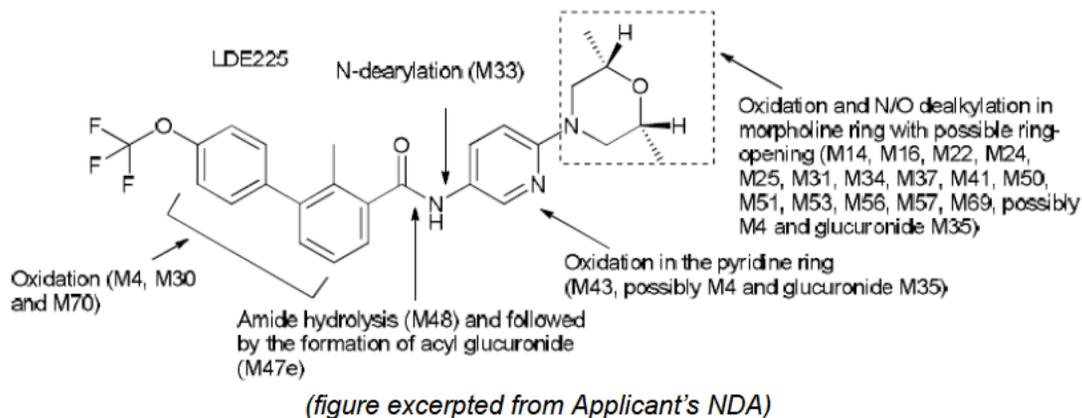
LDE225 showed little or no affinity for blood cells in all species tested. LDE225 was highly bound to plasma proteins in the mouse, rat, dog, and human (97-99%). The binding was independent of concentration in all five species. LDE225 was very strongly bound to isolated human plasma proteins: serum albumin (HSA) and  $\alpha$ 1-acid glycoprotein (AGP).

Following administration of a single oral dose of LDE225 to rats, the tissue distribution of LDE225 was widespread, with the highest concentrations observed 4 hours post-dose for most tissues. The highest tissue distribution was observed in the uveal tract, followed by the hardierian gland, fat, liver, small intestine, adrenal cortex, and adrenal medulla. The elimination of LDE225 was slow in rat tissues with measurable radioactivity observed in most tissues up to 168 hours post-dose. The radioactivity in blood consisted mainly of the carboxylic acid metabolite LGE899. The highest  $AUC_{last}$  tissue to blood ratios were observed in the eye choroid (2.49), ciliary body of the eye (1.52), hardierian gland (1.05), lung (0.763), tooth pulp (0.636), and liver (0.603). Long half-lives of radioactivity in the range of 77-257 hours were observed for most tissues. Even longer half-lives were found in the adrenal cortex (309 hours), vitreous body of the eye (310 hours), brain (316 hours), bone mineral (368 hours), choroid plexus (441 hours), eye choroid (504 hours), and white fat (562 hours). Measurable radioactivity concentrations in brain and spinal cord were observed for 7 days post-dose with an approximate tissue to blood AUC value of 0.2. The radioactivity was also detected in the testis through 168 hours post-dose with a tissue/blood AUC value of 0.34.

The metabolism of LDE225 was qualitatively similar but quantitatively different across species. Oxidations and oxidative cleavages (N/O dealkylation) in the morpholine ring appeared to be major metabolic pathways of LDE225 in all species. Among these oxidative metabolites, the most abundant metabolite was M31 in rat and M37 in dog.

Amide hydrolysis was another minor pathway in rat and dog, which led to the M48 (LGE899) metabolite. This metabolite had a long half-life in all species studied (~86 hours in dog; ~451 hours in human). Oxidations in the pyridine ring and in the biphenyl moiety, N-dearylation at the amide nitrogen, glutathione conjugation at the pyridine ring with follow-up reactions, and other biotransformations appeared to be additional minor pathways. Glucuronidation after oxidation or amide hydrolysis (formation of the isomeric acyl glucuronides M47a-f) was also observed. No unique metabolites were identified in human plasma. A summary of LDE225 metabolism is displayed in the following figure.

**Figure 8: Summary of LDE225 Metabolism**



In regard to LDE225 excretion, the majority of radioactivity was excreted via feces across all species tested. Specifically, following a single dose of radiolabelled LDE225, the recovery of radioactivity in the feces was approximately 90%, 80%, and 93% in the rat, dog, and human, respectively.

## 6 General Toxicology

### 6.2 Repeat-Dose Toxicity

**Study title:** LDE225: A 13-week oral (gavage) toxicity study in the rat with a 8-week recovery

Study no.: 0870704

Study report location: 4.2.3.2

Conducting laboratory and location:

(b) (4)

Date of study initiation: January 13, 2009

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

- LDE225 was tolerated at all doses tested, up to 20 mg/kg/day.
- LDE225-induced toxicity was primarily seen following 20 mg/kg/day of LDE225 and targeted the teeth, skin, and bone.
- Teeth abnormalities consisted of missing or broken teeth with histopathological atrophy leading to decreased food consumption and body weight.
- Nearly all 20 mg/kg/day animals had alopecia with histopathological atrophy of hair follicles.
- Additional LDE225-induced toxicity consisted of thinning/closure of the growth plate in various bones, increases in cholesterol levels, generally increased creatinine kinase levels, and a dose-responsive decrease in uterus weight.

**Methods:**

Doses: 0, 0.2, 2, or 20 mg/kg/day  
Frequency of dosing: Daily for 13-weeks with a 8-week recovery period  
Route of administration: Oral gavage  
Dose volume: 5 mL/kg  
Formulation/Vehicle: 0.5% (w/v) methylcellulose, Type 400cPs (MC) aqueous solution containing 0.5% (v/v) Tween 80 NF (0.5% MC with Tween)  
Species/Strain: Rat / CrI:WI(Han)  
Number/Sex/Group: 10 - main group  
6 - recovery group for control and high-dose  
Age: 8 weeks  
Weight: 153-256 g  
Dose justification: The dose levels were selected by the Applicant based on results from a 4-week toxicity study of LDE225 in rats.

**Observations and Results:****Mortality [observations made twice daily]**

None

**Clinical Signs [daily]**

20 mg/kg/day of LDE225 was associated with broken teeth, loss of teeth, malocclusion, loss of whiskers (females only), swollen muzzle and/or lower jaw, salivation, thin fur (alopecia) on the lower jaw, tremors, dry skin, and dehydration. Except for swollen muzzle and/or lower jaw, dry skin, and dehydration, all findings were irreversible by the end of the recovery period.

**Body Weights [daily]**

At the end of the treatment period, 25% and 15% decreases in body weight were noted in males and females, respectively, at the 20 mg/kg/day dose level. This effect was irreversible by the end of the recovery period.

**Food Consumption [weekly]**

At the end of the treatment period, 8% and 25% decreases in food consumption were noted in males and females, respectively, following 20 mg/kg/day of LDE225. This effect was partially reversible by the end of the recovery period.

**Ophthalmoscopy [pre-dose; week 13]**

Unremarkable

**Hematology [pre-dose; week 5 and 13]**

At the end of the treatment period, neutrophil counts were increased by approximately 97% following administration of 20 mg/kg/day of LDE225. This effect was reversible by the end of the recovery period.

**Bone Marrow [pre-dose; week 5 and 13]**

Unremarkable

**Clinical Chemistry [pre-dose; week 5 and 13]****Week 5 - % change in clinical chemistry vs. control**

	Males			Females		
	0.2 mg/kg	2 mg/kg	20 mg/kg	0.2 mg/kg	2 mg/kg	20 mg/kg
Cholesterol	+2	-8	+11	+4	+4	+27
Creatine kinase	+159	-12	-15	+88	+48	+22
Aspartate aminotransferase	+27	-6	+32	+17	+3	+30

At the end of the treatment period (week 13), creatine kinase levels were normalized, while elevations in cholesterol and aspartate aminotransferase were still noted. A reversible decrease (up to 12%) in albumin was noted following 20 mg/kg/day of LDE225. By the end of the recovery period, all changes were reversible or on a trend of reversibility.

**Urinalysis [pre-dose; week 5 and 13]**

Unremarkable

**Gross Pathology [at sacrifice]**

Except tooth-related findings, the following treatment-related macroscopic changes were reversible or on a trend of reversibility by the end of the recovery period.

**Treatment-related Macroscopic Findings: Terminal Necropsy**

Tissue/Finding	Sex	Male				Female			
Dose levels in base (mg/kg/day)		0	0.2	2.0	20.0	0	0.2	2.0	20.0
Number of animals examined		10	10	10	10	10	10	10	10
<b>Tooth</b>									
Not found/present (one or more)		-	-	-	7	-	-	-	7
	Loose	-	-	-	8	-	-	-	5
	Protrusion	-	-	-	7	-	-	-	5
	Small	-	-	-	2	-	-	-	2
	Fracture	-	-	-	-	-	-	-	1
<b>Skin</b>									
	Alopecia	-	-	-	7	-	1	-	9
	Thickening	-	-	-	8	-	-	-	10
<b>Mandibular lymph node</b>									
	Enlargement	-	1	-	4	-	-	-	2
<b>Uterus</b>									
	Small					-	-	-	2

(table excerpted from Applicant's NDA)

**Organ Weights [at sacrifice]**

Except for increased testis weight, the following weight changes were reversible or on a trend of reversibility by the end of the recovery period.

**% change in organ weights (relative to body weight) vs. control**

	Males			Females		
	0.2 mg/kg	2 mg/kg	20 mg/kg	0.2 mg/kg	2 mg/kg	20 mg/kg
Brain	x	x	+29	x	x	+18
Heart	x	x	+14	x	x	+17
Kidney	x	x	+29	x	x	+21
Testis	x	x	+31	-	-	-
Ovary	-	-	-	x	x	+63
Uterus	-	-	-	x	-26	-47

x denotes no change

**Histopathology [at sacrifice]**

A partially reversible increase in plasmacytosis and/or lymphoid hyperplasia was reported in the mandibular lymph nodes of 5/10 males and 5/10 females following 20

mg/kg/day of LDE225. All other treatment-related histopathological findings are noted in the following table. Atrophy of hair follicles and periodontal inflammation were reversible or on a trend of reversibility by the end of the recovery period. All other histopathological findings were irreversible by the end of the recovery period.

### Treatment-related Microscopic Findings: Terminal Necropsy

Tissue/Finding	Sex	Males				Females			
Dose levels in base (mg/kg/day)	0	0.2	2.0	20.0	0	0.2	2.0	20.0	
Number examined	10	10	10	10	10	10	10	10	
<b>Bone-rib</b>									
Closure: growth plate									
Total number affected	-	-	-	10	-	-	-	10	
Moderate	-	-	-	10	-	-	-	8	
Marked	-	-	-	-	-	-	-	2	
<b>Bone-sternum</b>									
Closure: growth plate									
Total number affected	-	-	-	10	-	-	-	10	
Moderate	-	-	-	10	-	-	-	7	
Marked	-	-	-	-	-	-	-	3	
<b>Bone-femorotibial joint</b>									
Closure: growth plate									
Total number affected	-	-	-	10	-	-	-	10	
Marked	-	-	-	10	-	-	-	10	
Thinning: trabeculae									
Total number affected	-	-	-	6	-	-	-	9	
Minimal	-	-	-	-	-	-	-	1	
Slight	-	-	-	4	-	-	-	6	
Moderate	-	-	-	2	-	-	-	2	
<b>Skin (routine sample)</b>									
Atrophy: hair follicle									
Total number affected	-	-	-	4	-	-	-	7	
Minimal	-	-	-	2	-	-	-	4	
Slight	-	-	-	2	-	-	-	3	
<b>Skin (miscellaneous)</b>									
Atrophy: hair follicle									
Total number affected	-	-	-	10	-	-	-	10	
Slight	-	-	-	7	-	-	-	4	
Moderate	-	-	-	3	-	-	-	6	
<b>Tooth</b>									
Atrophy: tooth roots									
Total number affected	-	-	-	6	-	-	-	6	
Moderate	-	-	-	2	-	-	-	-	
Marked	-	-	-	4	-	-	-	6	
Degeneration: ameloblast									
Total number affected	-	-	-	6	-	-	-	6	
Moderate	-	-	-	1	-	-	-	-	
Marked	-	-	-	5	-	-	-	6	
Inflammation: periodontal									
Total number affected	-	-	-	2	-	-	-	2	
Minimal	-	-	-	2	-	-	-	1	
Moderate	-	-	-	-	-	-	-	1	

(table excerpted from Applicant's NDA and slightly amended)

**Toxicokinetics [pre-dose, and 0.5, 1, 3, 7, and 24 hrs post-dose on day 1 and week 11]**

- LDE225 exposure (AUC) was greater than dose-proportional from 0.2 to 2 mg/kg/day and approximately dose-proportional from 2 to 20 mg/kg/day.
- On Day 74, exposure levels were greater in females than males at the high dose level.
- Drug accumulation was apparent.
- Details are shown in Table 7.

**Table 7: Summary of Toxicokinetic Parameters from 13-week Toxicity Study in Rats**

Parameters	Day	Group 2		Group 3		Group 4	
		Males	Females	Males	Females	Males	Females
T <sub>max</sub> (h)	1	1.00	1.00	3.00	1.00	3.00	3.00
	74	1.00	0.500	1.00	3.00	0.500	3.00
C <sub>max</sub> (ng/mL)	1	10.4	889	346	447	3080	3060
	74	25.4	31.4	629	600	6000	8090
AUC <sub>(0-24h)</sub> (ng·h/mL)	1	20.0	33.3*	3950	3800	37700	27700
	74	65.1	66.3	8090	6720	75800	156000

\*: the calculated AUC<sub>(0-24h)</sub> and AUC/dose without the outlier value

Group 2, 3, and 4 denotes 0.2, 2, and 20 mg/kg/day of LDE225  
(table excerpted from Applicant's NDA)

**Study title:** 26-week oral gavage toxicity and toxicokinetic study with LDE225 in rats

Study no.: 1070056  
 Study report location: 4.2.3.2  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: February 16, 2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

- LDE225-induced toxicity was primarily seen following 10 mg/kg/day of LDE225 and targeted the teeth, skin, bone, gastrointestinal tract, lymphoid tissues, prostate, and uterus/ovaries.
- Teeth abnormalities consisted of loose, missing, or broken teeth with histopathological atrophy leading to decreased food consumption and body weight. This was severe enough to warrant the early sacrifice in 3/40 animals.
- Nearly all 10 mg/kg/day animals had alopecia with histopathological atrophy of hair follicles.
- Atrophy was also noted in the teeth, uterus, and ovaries.
- Inflammation was seen in the gastrointestinal tract and prostate gland.

- Additional LDE225-induced toxicity consisted of thinning/closure of the growth plate in various bones, lymphoid depletion, and non-dose responsive increases in creatine kinase.

**Methods:**

Doses: 0, 0.5, 3, or 10 mg/kg/day  
Frequency of dosing: Daily for 26-weeks  
Route of administration: Oral gavage  
Dose volume: 5 mL/kg  
Formulation/Vehicle: 0.5% (w/v) methylcellulose, Type 400cPs (MC) aqueous solution containing 0.5% (v/v) Tween 80 NF (0.5% MC with Tween)  
Species/Strain: Rat / CrI:WI(Han)  
Number/Sex/Group: 20  
Age: 7-8 weeks  
Weight: 144-249 g  
Dose justification: The dose levels were selected by the Applicant based on results from a 13-week toxicity study of LDE225 in rats (Study 0870704).

**Observations and Results:****Mortality [observations made twice daily]**

On Day 141, two 10 mg/kg/day males and one 10 mg/kg/day female were sacrificed in moribund condition due to teeth abnormalities (loose, missing, and broken teeth), low food consumption, and reduced body weight.

**Clinical Signs [daily]**

10 mg/kg/day of LDE225 was associated with broken teeth, loss of teeth, malocclusion, clear and red eye discharge, alopecia, thin appearance, and tremors. Reversibility was not assessed.

**Body Weights [daily]**

At the end of the treatment period, 19% and 16% decreases in body weight were noted in males and females, respectively, administered 10 mg/kg/day of LDE225. Reversibility was not assessed.

**Food Consumption [weekly]**

At the end of the treatment period, an approximate 15% decrease in food consumption was noted following 10 mg/kg/day of LDE225. Reversibility was not assessed.

**Ophthalmoscopy [pre-dose; week 13 and 26]**

Unremarkable

**Hematology [pre-dose; week 13 and 26]**

Unremarkable

**Bone Marrow [pre-dose; week 13 and 26]**

Unremarkable

**Clinical Chemistry [pre-dose; week 13 and 26]**

Reversibility was not assessed.

**Week 26 - % change in clinical chemistry vs. control**

	Males			Females		
	0.5 mg/kg	3 mg/kg	10 mg/kg	0.5 mg/kg	3 mg/kg	10 mg/kg
Cholesterol	x	x	x	x	x	+40
Creatine kinase	+35	+28	+35	-17	+19	+22
Aspartate aminotransferase	x	x	+31	x	x	+18

*x denotes no change***Urinalysis [pre-dose; week 13 and 26]**

Unremarkable

**Gross Pathology [at sacrifice]**

Following 10 mg/kg/day of LDE225, fractured incisor teeth were noted in 13/20 males and 14/20 females, and alopecia was noted in 12/20 males and 19/20 females. Reversibility was not assessed.

**Organ Weights [at sacrifice]**

Reversibility was not assessed.

**Change in organ weights (relative to body weight) vs. control**

Sex	Mean values (grams)								
	Dose group	0	0.5	3.0	10.0	0	0.5	3.0	10.0
Terminal body weight (g)	447	431	439	361*	249	249	249	210*	
Percent difference from control	-	↓ 3.6	↓ 1.8	↓ 19	-	0	0	↓ 16	
<b>Uterus</b>									
Adjusted (to body) weights	-	-	-	-	0.7408	0.7601	0.7759	0.5270*	
Percent difference from control	-	-	-	-	-	↑ 2.6	↑ 4.7	↓ 29	
<b>Liver</b>									
Adjusted (to body) weights	12.2389	12.3138	12.6517	13.1769*	8.0812	8.1478	7.9196	7.8809	
Percent difference from control	-	↑ 0.6	↑ 3.4	↑ 7.7	-	↑ 0.8	↓ 2.0	↓ 2.5	
<b>Kidney</b>									
Adjusted (to body) weights	2.3618	2.3848	2.3465	2.5136	1.5368	1.5136	1.5550	1.6822*	
Percent difference from control	-	↑ 1.0	↓ 0.6	↑ 6.4	-	↓ 1.5	↑ 1.2	↑ 9.5	

- = No difference noted; ↓ = Decrease; ↑ = Increase.

\* = Statistically significant.

(table excerpted from Applicant's submission)

**Histopathology [at sacrifice]**

At the 10 mg/kg/day dose level of LDE225, minimal to marked atrophy of hair follicles was seen in nearly all animals. Minimal to slight inflammation of the prostate was noted in 9/20 males at the dose level. Slight to moderate atrophy was noted in the uterus (13/20) and ovary (5/20) of 10 mg/kg/day females. Additional LDE225-induced microscopic observations occurred in bone, gastrointestinal tract, lymphoid tissues, and teeth, and are detailed in the following tables. Reversibility was not assessed.

**Bone: Treatment-related Microscopic Findings**

	Sex	Males				Females			
		Dose level	0	0.5	3.0	10.0	0	0.5	3.0
<b>Bone, femur</b>									
	No. examined	20	20	20	20	20	20	20	20
Thinning/closure, growth plate									
	Minimal	0	0	0	6	0	0	0	0
	Slight	0	0	0	8	0	0	0	0
	Moderate	0	0	0	4	0	0	0	4
	Marked	0	0	0	1	0	0	0	4
	Severe	0	0	0	0	0	0	0	11
Decreased, trabeculae/primary spongiosa									
	Minimal	0	0	0	2	0	0	0	0
	Slight	0	0	0	3	0	0	0	1
	Moderate	0	0	0	3	0	0	0	0
	Marked	0	0	0	1	0	0	0	0
<b>Bone, sternum</b>									
	No. examined	20	20	20	20	19	19	19	20
Thinning/closure, growth plate									
	Minimal	0	0	0	8	0	0	0	0
	Slight	0	0	0	8	0	0	0	2
	Moderate	0	0	0	3	0	0	0	8
	Marked	0	0	0	0	0	0	0	7
<b>Joint, stifle</b>									
	No. examined	20	20	20	20	20	20	20	20
Thinning/closure, growth plate									
	Minimal	0	0	0	7	0	0	0	0
	Slight	0	0	0	6	0	0	0	0
	Moderate	0	0	0	5	0	0	0	0
	Marked	0	0	0	2	0	0	0	4
	Severe	0	0	0	0	0	0	0	15
Decreased, trabeculae/primary spongiosa, proximal tibia									
	Slight	0	0	0	2	0	0	0	0
	Moderate	0	0	0	2	0	0	0	0
<b>Bone, rib</b>									
	No. examined	20	20	19	19	18	20	20	19
Thinning/closure, growth plate									
	Minimal	0	0	0	2	0	0	0	1
	Slight	0	0	0	17	0	0	0	7
	Moderate	0	0	0	0	0	0	0	9

(table excerpted from Applicant's NDA)

**Gastrointestinal Tract: Treatment-related Microscopic Findings**

	Sex	Males				Females			
		Dose level	0	0.5	3.0	10.0	0	0.5	3.0
Stomach, glandular									
	No. examined	20	20	20	20	20	20	20	20
Inflammation, gland									
	Minimal	0	0	0	0	0	0	0	12
	Slight	0	0	0	0	0	0	0	1
Duodenum									
	No. examined	20	20	20	20	20	20	20	20
Inflammation, crypt									
	Minimal	0	0	0	9	0	0	0	10
	Slight	0	0	0	3	0	0	0	8
	Moderate	0	0	0	0	0	0	0	1
Rectum									
	No. examined	20	20	20	20	20	20	20	19
Inflammation, crypt									
	Minimal	0	0	0	4	0	0	0	5
	Slight	0	0	0	0	0	0	0	8
	Moderate	0	0	0	1	0	0	0	4

(table excerpted from Applicant's NDA)

**Lymphoid Tissues: Treatment-related Microscopic Findings**

	Sex	Males				Females			
		Dose level	0	0.5	3.0	10.0	0	0.5	3.0
Spleen									
	No. examined	20	20	20	20	20	20	20	20
Depletion, lymphocytes									
	Minimal	0	0	0	0	0	0	0	2
	Slight	0	0	0	2	0	0	0	0
Lymph node, mandibular									
	No. examined	20	19	20	19	20	20	20	20
Depletion, lymphocytes									
	Minimal	0	0	0	6	0	0	0	1
	Slight	0	0	0	2	0	0	0	3
	Moderate	0	0	0	0	0	0	0	1
Infiltrate, macrophages									
	Minimal	0	1	1	8	1	0	2	2
	Slight	0	0	0	1	2	3	1	3
Erythrocytes, sinus									
	Minimal	6	4	4	8	3	2	2	1
	Slight	0	1	1	3	3	1	2	0
	Moderate	0	0	0	0	0	2	0	1
Lymph node, mesenteric									
	No. examined	20	20	20	20	20	20	20	20
Depletion, lymphocytes									
	Minimal	0	0	0	5	0	0	0	5
	Slight	1	0	0	2	0	0	2	2
Erythrocytes, sinus									
	Minimal	2	1	2	8	0	0	0	3
	Slight	0	0	0	1	0	0	0	1
Infiltrate, macrophages									
	Minimal	0	1	0	5	2	4	1	12
	Slight	0	0	0	11	1	0	6	2
	Moderate	0	0	0	1	0	0	0	0
	Marked	0	0	0	1	0	0	0	0

(table excerpted from Applicant's NDA)

**Teeth: Treatment-related Microscopic Findings**

	Sex	Males				Females			
		Dose level	0	0.5	3.0	10.0	0	0.5	3.0
Tooth, left lower incisor									
	No. examined	20	20	20	20	20	20	20	20
Atrophy, roots									
	Slight	0	0	0	1	0	0	0	0
	Moderate	0	0	0	4	0	0	0	0
	Marked	0	0	0	11	0	0	0	13
	Severe	0	0	0	4	0	0	0	7
Tooth, right lower incisor									
	No. examined	20	20	20	20	20	20	20	20
Atrophy, roots									
	Slight	0	0	0	1	0	0	0	0
	Moderate	0	0	0	5	0	0	0	1
	Marked	0	0	0	10	0	0	0	14
	Severe	0	0	0	4	0	0	0	5

(table excerpted from Applicant's NDA)

**Toxicokinetics [0.5, 1, 3, 7, and 24 hours post-dose on day 1, 24, and 149]**

- On Day 1, LDE225 exposure (AUC) was greater than dose proportional from 0.5 to 3 mg/kg/day.
- On Day 24, LDE225 exposure (AUC) was greater than dose proportional.
- On Day 149, LDE225 exposure (AUC) was greater than dose proportional in females and approximately dose proportional from 3 to 10 mg/kg/day in males.
- Drug accumulation was apparent and greatest in 10 mg/kg/day females on Day 149.
- Details are shown in Table 9.

**Table 8: Summary of Toxicokinetic Parameters from 26-week Toxicity Study in Rats**

Sex	Dose (mg/kg/day)	Study day	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>(0-24h)</sub> (ng*Hours/mL)	AUC <sub>(0-24h)</sub> /dose (ng*Hours/mL/mg/kg/day)
Males	0.5	1	1.00	36.5	93.3	187
			3.0	401	3220	1070
			10	747	12400	1240
	0.5	24	0.500	94.1	213	426
			3.0	555	4490	1500
			10	1600	25400	2540
	0.5	149	1.00	172	437	873
			3.0	705	6470	2160
			10	1300	19800	1980
Females	0.5	1	0.500	35.7	102	204
			3.0	278	2730	910
			10	727	10900	1090
	0.5	24	1.00	75.9	272	544
			3.0	610	4460	1490
			10	1530	28600	2860
	0.5	149	0.500	129	429	858
			3.0	1420	7140	2380
			10	3540	61500	6150

(table excerpted from Applicant's NDA)

**Study title:** LDE225: A 13-week oral (gavage) toxicity study in the beagle dog with a 8-week recovery period

Study no.: 0870705  
Study report location: 4.2.3.2  
Conducting laboratory and location:  (b) (4)  
Date of study initiation: January 14, 2009  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

- LDE225 was tolerated at all doses tested, up to 10 mg/kg/day.
- LDE225-induced toxicity primarily targeted skin and bone.
- At doses  $\geq 1$  mg/kg/day, nearly all animals had alopecia but only 10 mg/kg/day animals showed histopathological atrophy of hair follicles.
- Additional LDE225-induced toxicity consisted of thinning/closure of the growth plate in various bones, increases in cholesterol levels, inconsistent alterations in creatine kinase, necrosis in the ileum, and a decrease in uterus weight.

**Methods:**

Doses: 0, 0.1, 1, or 10 mg/kg/day  
Frequency of dosing: Daily for 13-weeks with a 8-week recovery period  
Route of administration: Oral  
Formulation/Vehicle: 0.5% (w/v) methylcellulose, Type 400cPs (MC) aqueous solution containing 0.5% (v/v) Tween 80 NF (0.5% MC with Tween)  
Species/Strain: Dog / Beagle  
Number/Sex/Group: 3 - main group  
2 - recovery group for control and high-dose  
Age: 9 months  
Weight: 5.7-11.6 kg  
Dose justification: The dose levels were selected by the Applicant based on results from a 4-week toxicity study of LDE225 in dogs.

**Observations and Results:**

**Mortality [observations made twice daily]**

None

**Clinical Signs [weekly]**

10.0 mg/kg/day of LDE225 was associated with alopecia on various areas of the body, including loss of eyelashes and whiskers.

**Body Weights [weekly]**

Unremarkable

**Food Consumption [weekly]**

Unremarkable

**Ophthalmoscopy [pre-dose; week 13]**

Unremarkable

**Electrocardiography [pre-dose; week 13]**

Unremarkable

**Hematology [pre-dose; week 5 and 13]**

Unremarkable

**Coagulation [pre-dose; week 5 and 13]**

Unremarkable

**Bone Marrow [pre-dose; week 5 and 13]**

Unremarkable

**Clinical Chemistry [pre-dose; week 5 and 13]**

The following changes were reversible or on a trend of reversibility by the end of the recovery period.

**Week 13 - % change in clinical chemistry vs. control**

	Males			Females		
	0.1 mg/kg	1 mg/kg	10 mg/kg	0.1 mg/kg	1 mg/kg	10 mg/kg
Cholesterol	+17	+3	+83	-1	+5	+63
Creatine kinase	+28	-7	+39	-18	-52	-51

**Bone-specific alkaline phosphatase assay [pre-dose; week 5 and 13]**

The following changes were reversible or on a trend of reversibility by the end of the recovery period.

**Week 13 - % change in bone-specific alkaline phosphatase vs. control**

	Males			Females		
	0.1 mg/kg	1 mg/kg	10 mg/kg	0.1 mg/kg	1 mg/kg	10 mg/kg
Bone-specific phosphatase	-1	-31	-61	-38	-40	-58

**Urinalysis [pre-dose; week 5 and 13]**

Unremarkable

**Gross Pathology [at sacrifice]**

At the end of the treatment period, alopecia with or without thickening of the skin was reported in nearly all dogs that received  $\geq 1$  mg/kg/day of LDE225 (2/3 males and 2/3 females at 1 mg/kg/day and 3/3 males and 3/3 females following 10 mg/kg/day of LDE225). The alopecia was confined to the muzzle, interdigital skin of the forepaws, and occasionally the periorbital skin. Enlargement of joints in the forepaws was also noted in 2/3 males and 1/3 females following 10 mg/kg/day of LDE225. These findings were reversible or on a trend of reversibility by the end of the recovery period.

**Organ Weights [at sacrifice]**

At the end of the treatment period, a 51% decrease in uterus weight was noted following 10 mg/kg/day of LDE225. This finding was reversible by the end of the recovery period.

**Histopathology [at sacrifice]**

Treatment-related histopathological findings are noted in the following table. Skin and ileum findings were reversible or on a trend of reversibility by the end of the recovery period. All other bone-related histopathological findings were irreversible by the end of the recovery period.

**Treatment-related Microscopic Findings: Terminal Necropsy**

Tissue/Finding	Sex	Males				Females			
		0	0.1	1	10	0	0.1	1	10
Dose (mg/kg/day)									
Number of animals examined		3	3	3	3	3	3	3	3
<b>Bone - rib</b>									
Closure: growth plate									
Total number affected		-	-	-	3	-	-	-	3
Marked		-	-	-	3	-	-	-	3
Thinning: trabeculae									
Total number affected		-	-	-	3	-	-	-	3
Slight		-	-	-	2	-	-	-	3
Moderate		-	-	-	1	-	-	-	-
<b>Bone - sternum</b>									
Closure: growth plate									
Total number affected		-	-	3	3	-	-	3	3
Minimal		-	-	1	-	-	-	1	-
Slight		-	-	2	-	-	-	2	-
Marked		-	-	-	3	-	-	-	3
Thinning: trabeculae									
Total number affected		-	-	1	3	-	-	-	3
Minimal		-	-	1	-	-	-	-	-
Slight		-	-	-	2	-	-	-	3
Moderate		-	-	-	1	-	-	-	-
<b>Skin</b>									
Atrophy: hair follicle									
Total number affected		-	-	-	3	-	-	-	2
Minimal		-	-	-	1	-	-	-	1
Slight		-	-	-	-	-	-	-	1
Moderate		-	-	-	2	-	-	-	-
<b>Ileum</b>									
Necrosis: cryptal									
Total number affected		-	-	-	2	-	-	-	2
Minimal		-	-	-	1	-	-	-	2
Slight		-	-	-	1	-	-	-	-

(table excerpted from Applicant's NDA and slightly amended)

**Toxicokinetics [pre-dose, and 1, 3, 7, and 24 hrs post-dose on day 1 and week 11]**

- On Day 1, LDE225 exposure (AUC) was approximately dose proportional.
- On Day 74, LDE225 exposure (AUC) was approximately dose proportional from 0.1 to 1 mg/kg/day and greater than dose proportional from 1 to 10 mg/kg/day.
- Drug accumulation was apparent.
- No significant sex differences were noted.
- Details are shown in Table 8.

**Table 9: Summary of Toxicokinetic Parameters from  
13-week Toxicity Study in Dogs**

Parameters	Day	Group 2		Group 3		Group 4	
		Males	Females	Males	Females	Males	Females
T <sub>max</sub> (h)	1	0.5	0.667	1.00	1.67	1.00	2.33
	77	0.833	0.5	1.00	1.00	0.833	1.00
C <sub>max</sub> (ng/mL)	1	13.0	10.7	87.8	65.4	614	668
	77	12.4	15.4	126	167	4140	5160
AUC <sub>(0-24h)</sub> (ng·h/mL)	1	54.0	64.9	471	518	4750	6980
	77	125	153	1600	1610	82500	95700

Group 2, 3, and 4 denotes 0.1, 1, and 10 mg/kg/day of LDE225  
(table excerpted from Applicant's NDA)

**Study title:** 26-week oral gavage toxicity and toxicokinetic study with LDE225 in dogs

Study no.: 1070055  
 Study report location: 4.2.3.2  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: February 9, 2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

- 50 mg/kg/day of LDE225 was not tolerated.
- LDE225-induced toxicity was primarily seen following 10 mg/kg/day of LDE225 and targeted the skin, bone, and gastrointestinal tract.
- All 10 mg/kg/day animals had alopecia with histopathological atrophy of hair follicles.
- Cholesterol levels were increased by approximately 68% following 10 mg/kg/day of LDE225.
- Additional histopathological findings consisted of closure of the rib growth plate, attenuation of the stomach, and adrenal vacuolation.

**Methods:**

Doses: 0, 0.1, 0.5, 10, or 50/30\* mg/kg/day  
 Frequency of dosing: Daily for 26-weeks  
 Route of administration: Oral gavage  
 Dose volume: 5 mL/kg  
 Formulation/Vehicle: 0.5% (w/v) methylcellulose 400 cps and 0.5% (v/v) Tween 80 NF  
 Species/Strain: Dog / Beagle  
 Number/Sex/Group: 4  
 Age: 10-11 months  
 Weight: 6.9-11.3 kg

Dose justification: The dose levels were selected by the Applicant based on results from a 13-week toxicity study of LDE225 in dogs.

\*dose was lowered from 50 to 30 mg/kg/day on Day 95 and 100. Dosing was suspended on Days 96 and 97, and terminated on Day 101. Since 50/30 mg/kg/day dosing only lasted 14-weeks, this dose group was excluded from a detailed analysis; however, a summary of adverse findings in these animals is noted below.

**LDE225-induced toxicity in 50/30 mg/kg/day animals:**

According to the Applicant, two males and two females were sacrificed in moribund condition between Days 63 and 101 following 50/30 mg/kg/day of LDE225. Clinical observations included few to no feces, vomiting, tremors, ataxia, excessive salivation, severe body weight loss, and reduced to no food consumption. Dosing with 50/30 mg/kg/day of LDE225 was associated with a 13% increase in QRS duration and a 6% increase in corrected QT interval in males, versus control. The only notable clinical pathology findings consistent across all four animals were increased cholesterol levels (up to 232%). Histopathological findings included the absence of rib growth plates, gastrointestinal degeneration/necrosis, lymphoid depletion, and adrenal vacuolation.

**Observations and Results:**

**Mortality [observations made twice daily]**

None

**Clinical Signs [daily]**

10 mg/kg/day of LDE225 was associated with alopecia.

**Body Weights [weekly]**

At the end of the treatment period, body weight gain was decreased by 10% and 13% following 10 mg/kg/day of LDE225 in males and females, respectively. Reversibility was not assessed.

**Food Consumption [weekly]**

At the end of the treatment period, weekly food consumption was reduced by 9, 11, and 21% in females following 0.1, 0.5, and 10 mg/kg/day of LDE225. Food consumption in males was unremarkable. Reversibility was not assessed.

**Ophthalmoscopy [pre-dose; week 13 and 26]**

Unremarkable

**Electrocardiography [pre-dose; week 13 and 26]**

Unremarkable

**Hematology [pre-dose; week 13 and 26]**

Unremarkable

**Coagulation [pre-dose; week 13 and 26]**

Unremarkable

**Clinical Chemistry [pre-dose; week 13 and 26]**

Cholesterol levels were increased by 75% and 61% following 10 mg/kg/day of LDE225 in males and females, respectively. Reversibility was not assessed.

**Urinalysis [pre-dose; week 13 and 26]**

Unremarkable

**Gross Pathology [at sacrifice]**

Alopecia was noted in all animals following 10 mg/kg/day of LDE225. Reversibility was not assessed.

**Organ Weights [at sacrifice]**

Unremarkable

**Histopathology [at sacrifice]**

The following histopathological findings were noted in all animals at the 10 mg/kg/day dose level of LDE225; closed growth plate in the ribs, marked atrophy of hair follicles, and attenuation of the stomach. Attenuation of the stomach was also noted in 2/4 males and 1/4 females following 0.5 mg/kg/day of LDE225. The only other adverse finding was minimal adrenal cortex vacuolation, which was noted in 1/4 females following 10 mg/kg/day of LDE225. Reversibility was not assessed.

**Toxicokinetics [0.5, 1, 3, 7, and 24 hours post-dose on day 1, 23, and 149]**

- On Day 1, LDE225 exposure (AUC) was less than dose proportional from 0.5 to 10 mg/kg/day.
- On Day 23 and 149, LDE225 exposure (AUC) was greater than dose proportional from 0.5 to 10 mg/kg/day.
- Drug accumulation was apparent.
- No significant differences were noted between sexes.
- Details are shown in Table 10.

**Table 10: Summary of Toxicokinetic Parameters from 26-week Toxicity Study in Dogs**

Study Day	Dose (mg/kg/day)	T <sub>max</sub> Mean	C <sub>max</sub> Mean	C <sub>max</sub> /Dose Mean	AUC <sub>(0-24h)</sub> Mean	AUC <sub>(0-24h)</sub> /Dose Mean
<b>Male</b>						
1	0.1	0.500	24.0	240	56.7	567
	0.5	0.625	68.1	136	159	319
	10	0.875	224	22.4	1890	189
	50	3.38	544	10.9	7570	152
23	0.1	0.500	19.4	194	81.4	814
	0.5	0.500	75.7	151	274	548
	10.0	*0.5-24	1220	122	19600	1960
	50	*0.5-24	18300	366	350000	7000
149	0.1	0.500	18.8	188	97.9	979
	0.5	0.625	59.6	119	349	698
	10.0	*0.5-24	2990	299	56900	5690
<b>Female</b>						
1	0.1	0.500	15.7	157	36.6	366
	0.5	0.750	49.1	98.5	151	302
	10.0	0.750	321	32.1	2670	267
	50	3.50	1270	25.4	17100	343
23	0.1	0.625	12.9	129	49.1	491
	0.5	*0.5-24	132	263	1070	2140
	10.0	1.25	1290	129	17700	1770
	50	*0.5-24	18900	378	399000	7980
149	0.1	0.625	16.1	161	68.3	683
	0.5	0.625	68.1	136	397	792
	10.0	*0.5-24	1900	190	34700	3470

Units: Dose (mg/kg/day); T<sub>max</sub> (h); C<sub>max</sub> (ng/mL); C<sub>max</sub>/Dose (ng/mL)/(mg/kg/day); AUC (ng\*Hours/mL); AUC/Dose (ng\*Hours/mL)/(mg/kg/day); AUC Interval (0-24h); C<sub>0</sub> (ng/mL).

\* = The individual T<sub>max</sub> in the LIMS cannot be selected when the T<sub>max</sub> is 24h, therefore the t<sub>max</sub> mean has been documented with the lower and higher values

(table excerpted from Applicant's submission)

## 7 Genetic Toxicology

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

**Study title:** Mutagenicity test using salmonella typhimurium. Reviewed by Robenna Aziz, Ph.D. and slightly modified for this NDA review.

Study no.: 0770725  
 Study report location: 4.2.3.3  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: March 6, 2008

GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: LDE225, 0751003, 100%

### Key study findings:

- LDE225 was not mutagenic in the presence or absence of microsomal enzymes under the conditions tested.

### Methods:

Strains: *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA102 and TA1535

Concentrations used in definitive study:

First experiment (plate incorporation) test with and without S-9 activation:	8, 40, 200, 1000, and 5000 µg/plate
Second experiment (plate incorporation) test with and without S-9 activation:	0.32, 1.6, 8, 40, 200 µg/plate
Third experiment (pre-incubation):	6.25, 12.5, 25, 50, 100, 200 µg/plate

Negative control:

DMSO

Positive controls:

Strain	At 0.5 ug/plate	At 2 ug/plate	At 3 ug/plate	At 10 ug/plate	At 100 ug/plate
TA97a	-	-	-	2-Aminoanthracene	9-Aminoacridine
TA98	-	2-Nitrofluorene	2-Aminoanthracene Benzo(a)pyrene	-	-
TA100	-	-	2-Aminoanthracene Sodium azide	-	-
TA102	Mitomycin C	-	-	2-Aminoanthracene	-
TA1535	-	-	2-Aminoanthracene Sodium azide	-	-

### Results:

Study validity:

- Three replicate plates were used in the confirmatory study.
- Assay validation criteria:
  - The results of a test are valid if the negative control data lie within the range of the historical control data and the positive controls induce a positive effect as defined by the criteria below.
  - A test item or positive control is considered mutagenic if it produces, in at least one concentration and one strain, a response equal to twice (or more) the negative control incidence. The only exception is strain TA102, which has a relatively high spontaneous revertant number, where an increase by a factor of 1.5 above the negative control level is taken as an indication of a mutagenic effect. If a clear decision is not possible after

two experiments, further tests are performed using only the critical strains and test items concentrations close to the critical range previously identified.

- The results have greater significance if a concentration-related increase in the number of revertant colonies is observed. When conclusions have to be drawn from borderline effects, the variations between individual plates are also taken into consideration.
- The negative and positive control values were within the historical control data ranges.
- Study design is valid.

#### Study outcome:

- In the plate incorporation test (experiments 1 and 2) precipitation of the test item was seen at  $\geq 200$   $\mu\text{g}/\text{plate}$ . Under pre-incubation conditions (experiment 3) precipitation of LDE225 was observed at  $\geq 50$   $\mu\text{g}/\text{plate}$  in all strains +/- S9.
- Values  $\leq 60\%$  are normally taken as an indication of bacteriotoxicity; however, since the reduction of colony numbers was smaller at higher concentrations, the findings were not considered to indicate bacteriotoxicity.
- Bacteriotoxicity was observed in strain TA102, in the absence of S9, under pre-incubation conductions in the third experiment, at a concentration  $\geq 100$   $\mu\text{g}/\text{plate}$ .
- In experiment 2, in the absence of S9, strain TA98 showed a 60% decrease in the number of colonies at a concentration of 40  $\mu\text{g}/\text{plate}$ .
- In experiment 3, in the absence of S9, strain TA1535 showed a 55% decrease in the number of colonies at 50  $\mu\text{g}/\text{plate}$ .
- As shown in the following tables, no positive increases in the mean number of revertants were noted in any of the bacterial strains tested, in the presence or absence of S9.

**Table 11: Ames Assay - Experiment 1 - Plate Incorporation**

Strain:		TA1535		TA97a		TA98		TA100		TA102	
S9:		-	+	-	+	-	+	-	+	-	+
Concentration ( $\mu\text{g}/\text{plate}$ ):	0	21	16	206	238	25	36	138	168	395	433
	8	20	20	241	220	22	38	127	148	402	448
	40	28	21	212	238	20	37	149	143	363	422
	200	22p	23p	213p	244p	21p	40p	138p	140p	331p	440p
	1000	22p	23p	220p	239p	33p	53p	145p	186p	372p	403p
	5000	p*	p*	p*	p*	p*	p*	165p**	p*	p*	p*

p: precipitation, p\*:precipitation preventing colony counting, p\*\*: precipitation making evaluation of background growth impossible

**Table 12: Ames Assay - Experiment 2 - Plate Incorporation**

Strain:		TA1535		TA97a		TA98		TA100		TA102	
S9:		-	+	-	+	-	+	-	+	-	+
Concentration (µg/ plate):	0	20	14	173	179	35	33	130	112	364	444
	0.32	19	14	178	173	31	38	129	111	371	472
	1.6	21	17	173	174	37	37	99	118	333	450
	8	22	14	163	199	26	33	104	116	317	460
	40	22	11	178	166	21	36	109	113	276	431
	200	20p	15p	198p	192p	28p	42p	89p	123p	280p	478p

p: precipitation

**Table 13: Ames Assay - Experiment 3 - Pre-incubation**

Strain:		TA1535		TA97a		TA98		TA100		TA102	
S9:		-	+	-	+	-	+	-	+	-	+
Concentration (µg/ plate):	0	20	14	193	164	25	45	129	116	367	431
	6.25	17	17	204	162	29	40	127	123	359	486
	12.5	17	14	226	171	26	37	126	122	347	459
	25	16	12	211	175	29	41	126	129	375	465
	50	11p	15p	206p	190p	25p	33p	124p	135p	323p	461p
	100	16p	15p	219p	183p	27p	33p	114p	157p	363pt	531p
	200	16p	12p	228p	194p	27p	36p	134p	148p	291pt	478p

p: precipitation, t: toxicity

(tables excerpted from Applicant's NDA)

## 7.2 In Vitro Assays in Mammalian Cells

**Study title:** Induction of chromosome aberrations in cultured human peripheral blood lymphocytes

Study no.: 0770727

Study report location: 4.2.3.3

Conducting laboratory and location:

(b) (4)

Date of study initiation: May 19, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: LDE225, 0751003, 100%

### Key study findings:

- The test article did not induce chromosome aberrations in cultured human peripheral blood lymphocytes with or without metabolic activation under the conditions tested.

**Methods:**

Cell line: Human peripheral blood lymphocytes, pooled from three healthy female volunteers

Concentrations used in definitive study:

<b>Experiment 1:</b>	
3 hours treatment with 17 hour recovery without S9 activation	1,000, 2,000, 4,000, 64,000 µg/mL
3 hours treatment with 17 hour recovery with S9 activation	2,000, 4,000, 8,000, 32,000 µg/mL
<b>Experiment 2:</b>	
20 hours treatment with 0 hour recovery without S9 activation	4,000, 6,000, 8,000, 64,000 µg/mL
3 hours treatment with 17 hour recovery with S9 activation	4,000, 6,000, 8,000, 64,000 µg/mL

Negative control:  
DMSO

Positive controls:

Without S-9	4- Nitroquinoline 1-oxide (NQO)
With S-9	cyclophosphamide (CPA)

Incubation and sampling times:

3 hour exposure with a 17 hour recovery period (3+17), or 20 hours after treatment with no recovery period (20+0)

**Results:**

Study validity:

- Two replicate plates were used in the confirmatory study.
- Assay validation criteria:
  - The test item was considered positive for chromosomal aberrations if; 1) a proportion of cells with structural aberrations at one or more concentrations exceeded the normal range observed in both replicate cultures; 2) a statistically significant increase in the proportion of cells with structural aberrations (excluding gaps) was observed ( $p \leq 0.05$ ); and 3) a concentration-related trend in the proportion of cells with structural aberrations (excluding gaps).
  - Results which only partially satisfy the above criteria were dealt with on a case-by-case basis. Evidence of a concentration-related effect is considered useful but not essential in the evaluation of a positive result.

- The negative and positive control values were within the historical control data ranges.
- Study design is valid.

Study outcome:

- As shown in the following tables, exposure to LDE225, in the presence or absence of S9, did not result in an increased frequency of cells with structural or numerical chromosomal aberrations.

**Table 14: Chromosome Aberration Assay - Experiment 1 (3+17 without S9) - Cells with Structural Aberrations**

Treatment (µg/mL)	Replicate	Cells Scored	Cells with Aberrations		MIH (%)
			Including Gaps	Excluding Gaps	
Vehicle	A	100	2	2	
	B	100	2	1	
	Totals	200	4	3	-
1.000	A	100	1	1	
	B	100	0	0	
	Totals	200	1	1	0
2.000	A	100	1	1	
	B	100	2	1	
	Totals	200	3	2	0
4.000	A	100	<b>5#</b>	3	
	B	100	1	1	
	Totals	200	6	4	0
64.00	A	100	1	0	
	B	100	1	0	
	Totals	200	2	0	9
NQO, 5.00	A	100	<b>21#</b>	<b>19#</b>	
	B	86	<b>16#</b>	<b>16#</b>	
	Totals	186	37	35 <sup>a</sup>	

Binomial Dispersion Test  $\chi^2 = 2.36$ , not significant

<sup>a</sup> Statistical significance  $p \leq 0.001$

# Numbers highlighted exceed historical negative control range ([Appendix 2: Historical control data](#))

# Bolded numbers exceeded historical negative control range  
(table excerpted from Applicant's NDA)

**Table 15: Chromosome Aberration Assay - Experiment 1 (3+17 with S9) - Cells with Structural Aberrations**

Treatment ( $\mu\text{g/mL}$ )	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	MIH (%)
Vehicle	A	100	0	0	
	B	100	2	2	
	Totals	200	2	2	-
2.000	A	91	1	0	
	B	100	0	0	
	Totals	191	1	0	13
4.000	A	100	1	0	
	B	100	4	3	
	Totals	200	5	3	5
8.000	A	100	0	0	
	B	100	1	1	
	Totals	200	1	1	27
32.00	A	100	3	1	
	B	100	1	1	
	Totals	200	4	2	32
CPA, 6.25	A	23	<b>10#</b>	<b>10#</b>	
	B	72	<b>34#</b>	<b>30#</b>	
	Totals	95	44	40 <sup>a</sup>	

Binomial Dispersion Test  $\chi^2 = 6.07$ , not significant

<sup>a</sup>Statistical significance  $p \leq 0.001$

# Numbers highlighted exceed historical negative control range ([Appendix 2: Historical control data](#))

# Bolded numbers exceeded historical negative control range  
(table excerpted from Applicant's NDA)

**Table 16: Chromosome Aberration Assay - Experiment 2 (20+0; without S9) - Cells with Structural Aberrations**

Treatment ( $\mu\text{g/mL}$ )	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	MIH (%)
Vehicle	A	100	1	1	
	B	100	0	0	
	Totals	200	1	1	-
4.000	A	100	0	0	
	B	100	1	1	
	Totals	200	1	1	5
6.000	A	100	1	1	
	B	100	1	0	
	Totals	200	2	1	5
8.000	A	100	0	0	
	B	100	3	1	
	Totals	200	3	1	4
64.00	A	100	1	0	
	B	100	1	0	
	Totals	200	2	0	44
NQO, 5.00	A	53	<b>22#</b>	<b>20#</b>	
	B	47	<b>21#</b>	<b>20#</b>	
	Totals	100	43	40 <sup>a</sup>	

Binomial Dispersion Test  $\chi^2 = 4.02$ , not significant

<sup>a</sup> Statistical significance  $p \leq 0.001$

# Numbers highlighted exceed historical negative control range ([Appendix 2: Historical control data](#))

# Bolded numbers exceeded historical negative control range  
(table excerpted from Applicant's NDA)

**Table 17: Chromosome Aberration Assay - Experiment 2 (20+0; with S9) - Cells with Structural Aberrations**

Treatment ( $\mu\text{g/mL}$ )	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	MIH (%)
Vehicle	A	100	0	0	
	B	100	1	1	
	Totals	200	1	1	-
4.000	A	100	1	1	
	B	100	0	0	
	Totals	200	1	1	0
6.000	A	100	0	0	
	B	100	1	1	
	Totals	200	1	1	0
8.000	A	100	0	0	
	B	100	1	1	
	Totals	200	1	1	0
64.00	A	100	2	2	
	B	100	1	1	
	Totals	200	3	3	0
CPA, 12.50	A	30	<b>21#</b>	<b>20#</b>	
	B	50	<b>21#</b>	<b>20#</b>	
	Totals	80	42	40 <sup>a</sup>	

Binomial Dispersion Test  $\chi^2 = 4.36$ , not significant

<sup>a</sup> Statistical significance  $p \leq 0.001$

# Numbers highlighted exceed historical negative control range ([Appendix 2: Historical control data](#))

# Bolded numbers exceeded historical negative control range  
(table excerpted from Applicant's NDA)

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

**Study title:** Rat bone marrow micronucleus test after oral administration

Study no: 1070158  
Study report location: 4.2.3.3  
Conducting laboratory and location: Novartis Pharma AG  
Basel, Switzerland  
Date of study initiation: April 7, 2010  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: LDE225, 0751001, 100%

#### **Key Study Findings:**

- LDE225 did not induce micronuclei in bone marrow cells of rats under the conditions tested.

#### **Methods:**

Doses in definitive study: 0, 200, 632, or 2000 mg/kg/day  
Frequency of dosing: Daily for 2 days  
Route of administration: Oral gavage  
Dose volume: 10 mL/kg  
Formulation/Vehicle: 0.5 (w/v) hydroxypropyl methylcellulose with 0.1% Tween 80  
Species/Strain: Rat / HanRcc: Wist (SPF)  
Age/Weight: 8 weeks old / 217-259 g  
Number/Sex/Group: 7 males/group  
Satellite groups: 3 males and females per group in dose (as part of range finding study at 2000 mg/kg)  
Basis of dose selection: Based on results from range finding study  
Negative control: 0.5% methylcellulose with 0.5% Tween 80  
Positive control: Cyclophosphamide (10 mg/kg/day)

#### **Analysis:**

- All rats were sacrificed 24 hours after receiving their final dose and femoral bone marrow smears were prepared. Smears were stained and analyzed automatically using the ROBIAAS 3 image analyzer "Robias MNT in vivo V3.0".
- In general, 2000 polychromatic erythrocytes per animal were analyzed for the presence of micronuclei.

#### **Criteria for positive results:**

A test item was classified as mutagenic in the rat micronucleus test if it induced a micronucleus frequency that was statistically significantly above the control level.

**Study Validity:**

Dosing appeared to be adequate based upon dose ranging study results (piloerection, reduced activity, and increased startle response), the positive controls exhibited a clear unequivocal positive response, and the vehicle control data for this study were within laboratory historical data ranges.

**Results:**

As shown in the following table, no bone marrow toxicity was noted since all treatment and control groups showed similar percentages of polychromatic erythrocytes (PCE). No statistically significant differences between the mean micronucleus frequencies in the treatment groups and the negative control group were noted. Thus, LDE225 did not induce micronuclei in bone marrow cells of rats, under the conditions tested.

**Table 18: Results of Bone Marrow Micronucleus Assay in Rats**

Group	Dose (mg/kg/ day)	Sex	No. of animals	Frequency (%)*	
				MPE	PCE
Vehicle	0	Male	7	0.11 +/- 0.07	38.7 +/- 4.0
CP	10	Male	3	2.56 +/- 0.19	32.1 +/- 8.5
LDE225	200	Male	7	0.11 +/- 0.03	45.3 +/- 10.3
LDE225	632	Male	7	0.11 +/- 0.05	47.3 +/- 10.9
LDE225	2000	Male	7	0.12 +/- 0.06	43.4 +/- 4.1

4000 cells/animal were analyzed.

Note: Each value represents mean  $\pm$  SD (standard deviation) of a treatment group.

\*Frequencies were calculated as follows:

Frequency MPE: number of MPE x 100 / number of PCE

Frequency PCE: number of PE x 100 / number of (PCE+NCE)

(table excerpted from Applicant's NDA)

## 9 Reproductive and Developmental Toxicology

### 9.1 Fertility and Early Embryonic Development

**Study title:** An oral (gavage) fertility and early embryonic development study in rats

Study no.: 0970632  
 Study report location: 4.2.3.5  
 Conducting laboratory and location: Novartis Pharmaceuticals Corporation  
 East Hanover, New Jersey 07936  
 Date of study initiation: April 6, 2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key Study Findings:**

- LDE225 was tolerated in rats at all doses tested.
- No adverse effects on reproductive potential were noted in males.
- LDE225 had no effect on precoital interval, estrous cycling, and the mating index in females.
- 2 mg/kg/day of LDE225 resulted in a 16% reduction in the number of pregnant females, a statistically significant increase (429%) in the number of early resorptions, and a significant decrease (61%) in the number of live fetuses per litter.
- 20 mg/kg/day of LDE225 resulted in a lack of fertility.

**Methods:**

Doses: 0, 0.2, 2, or 20 mg/kg/day  
Frequency of dosing: Daily  
Dose volume: 5 mL/kg  
Route of administration: Oral gavage  
Formulation/Vehicle: 0.5% (w/v) Methyl cellulose (MC), Type 400 cPs, aqueous solution containing 0.5% (v/v) Tween 80, NF (0.5% MC with Tween)  
Species/Strain: Rat / CrI:WI(Han)  
Number/Sex/Group: 25  
Satellite groups: None  
Study design: Males were dosed daily for at least 50 days prior to mating, during the 2-week mating period with untreated females, and until terminal necropsy. Females were dosed daily for the five week pre-mating period, during mating with untreated males, and through gestation day 6.

**Observations and Results:****Mortality [observations made daily]**

None

**Clinical Signs [twice daily]**

Males – Following 20 mg/kg/day of LDE225, adverse clinical signs consisted of tremors, split teeth, long upper incisors, salivation, swollen mucocutaneous junction, hair loss, piloerection, and pale appearance.

Females – Unremarkable

**Body Weight [twice weekly]**

Males – Following 20 mg/kg/day of LDE225, body weights were reduced up to 23%, compared to control animals, beginning on Day 39 and continuing until termination. Terminal body weight was reduced approximately 20%, compared to control animals.

Females – No adverse effect on body weight was noted during the pre-mating period. During the gestation period (Days 9-13), 2 mg/kg/day of LDE225 reduced mean body weight gains by 27%, compared to control animals. Gestation body weights were not assessed in females dosed with 20 mg/kg/day of LDE225 due to lack of pregnancy.

**Food Consumption [weekly]**

Males – Following 20 mg/kg/day of LDE225, food consumption was reduced by 11-16%, compared to control animals, beginning on Day 29 and continuing until the end of the treatment period.

Females – Following 20 mg/kg/day of LDE225, food consumption was reduced by 8%, compared to control animals, on Days 22-29 of the pre-mating period. No adverse effect on body weight was noted during the gestation period. Food consumption during the gestation period was not assessed in females dosed with 20 mg/kg/day of LDE225 due to lack of pregnancy.

**Toxicokinetics**

Not conducted

**Necropsy**

Unremarkable

**Fertility Parameters**

Males – Unremarkable

Females – There were no treatment-related effects on pre-coital interval, estrous cycling, and the mating index. Following 2 mg/kg/day of LDE225, there was a 16% reduction in the number of females that were pregnant, a statistically significant increase (429%) in the number of early resorptions, and a significant decrease (61%) in the number of live fetuses per litter. Following 20 mg/kg/day of LDE225, there were no pregnant females.

## 9.2 Embryonic Fetal Development

**Study title:** An oral (gavage) embryo-fetal development dose range finding study in rabbits

Study no.: 0970151  
Study report location: 4.2.3.5  
Conducting laboratory and location: Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936  
Date of study initiation: Not available  
GLP compliance: No  
QA statement: No  
Drug, lot #, and % purity: LDE225, 0751003, 100%

### Key Study Findings:

- Doses of LDE225  $\geq$  10 mg/kg/day were not tolerated by pregnant rabbits as evidenced by spontaneous abortions, resorption of fetuses, and/or moribundity.
- Live fetuses were only noted in 5 mg/kg/day pregnant animals and had severe external and skeletal malformations and variations.

### Methods:

Doses: 0, 5, 10, 20, 25, 50, 100, or 200 mg/kg/day  
Frequency of dosing: Daily  
Dose volume: 5 mL/kg  
Route of administration: Oral gavage  
Formulation/Vehicle: 0.5% (w/v) Methyl cellulose (MC), Type 400 cPs, aqueous solution containing 0.5% (v/v) Tween 80, NF  
Species/Strain: Rabbit / Hra:(NZW)SPF  
Number/Sex/Group: 6 for control  
3 for treatment groups  $\leq$  25 mg/kg/day  
4 for treatment groups  $\geq$  50 mg/kg/day  
Satellite groups: None  
Study design: Daily dosing on gestation Day 7-20. Terminal caesarean section was conducted on Day 29 (Day 21 for TK animals).  
Study deviations: 5, 10, and 20 mg/kg/day dose groups erroneously received 17.8, 35.65, and 71.5 mg/kg/day of LDE225 on the 1<sup>st</sup> day of dosing due to a concentration error. This error was corrected for all additional dose administrations.

**Observations and Results:****Mortality [observations made daily]**

The following animals were sacrificed.

<b>LDE225 dose group</b>	<b># of females sacrificed</b>	<b>Gestation day</b>	<b>Reason</b>
5 mg/kg/day	0	-	-
10 mg/kg/day	2 (67%)	19-20	Spontaneous abortion
20 mg/kg/day	0	-	-
25 mg/kg/day	3 (100%)	20-23	Spontaneous abortion
50 mg/kg/day	2 (50%)	18-20	Spontaneous abortion
100 mg/kg/day	4 (100%)	15	Moribund condition
200 mg/kg/day	4 (100%)	15	Moribund condition

**Clinical Signs [twice daily]**

Red stains in cage pan were noted in LDE225 dose groups prior to spontaneous abortions. 100 and 200 mg/kg/day animals showed soft/decreased/no stool and red stains in cage pan as early as gestation day 8.

**Body Weight [twice weekly]**

All LDE225 dose groups  $\geq$  10 mg/kg/day showed minimal to no body weight gain vs a 18% increase in body weight gain in control animals by the end of the treatment period.

**Food Consumption [daily]**

Following 100 and 200 mg/kg/day of LDE225, food consumption was markedly reduced after the first dose. Food consumption was minimal to zero 2-3 days prior to moribund sacrifice on gestation day 15.

**Toxicokinetics**

Not conducted

**Maternal necropsy**

Unremarkable

### Reproductive parameters and fetal weight

Following 5 mg/kg/day of LDE225, each of the four females had a litter with 2 live fetuses (total of 8 fetuses) and 3-7 early resorptions. The live fetuses had body weights that were reduced by approximately 35%, compared to controls. All animals in LDE225 dose groups between 10 and 50 mg/kg/day had a litter of animals that were all either aborted or early resorptions. Since all 100 and 200 mg/kg/day animals were sacrificed in moribund condition on gestation day 15, reproductive parameters were not assessed in these animals.

### Offspring necropsy

- External Malformations: Of the 8 live fetuses from the 5 mg/kg/day maternal exposure group, external malformations consisted of severe cranial malformations (n=6), cranial protrusions (n=5), hyperflexed paws (n=7), malpositioned hindlimbs, gastroschisis (n=4), micrognathia (n=2), acaudate (n=2), absent eye bulge (n=1), and/or ectrodactyly (n=1).
- External Variations: Short tail was noted in one fetus from the 5 mg/kg/day maternal exposure group.
- Skeletal Malformations: Of the 8 live fetuses from the 5 mg/kg/day maternal exposure group, skeletal malformations consisted of misshapen maxilla, premaxilla, squamosal, supraoccipital and zygomatic; branched or fused ribs; fused, absent, or misaligned cervical centrum; fused, absent, malpositioned, misshapen or hemicervical vertebra; fused or misaligned thoracic centrum; malpositioned, fused or hemi thoracic vertebra; misaligned, misshapen or fused lumbar centrum; malpositioned or fused lumbar vertebra; absent, misaligned or fused sacral centrum and malpositioned, fused, hemi or absent sacral vertebra.
- Skeletal Variations: Of the 8 live fetuses from the 5 mg/kg/day maternal exposure group, skeletal variations were observed that included incomplete ossification of the frontal, hyoid, interparietal, maxilla, nasal, parietal, premaxilla, squamosal, supraoccipital, zygomatic, metacarpal, forepaw phalanx and sternebra; unossified metacarpal, forepaw phalanx, sternebra and cervical centrum; bipartite ossification of the cervical centrum, thoracic centrum, thoracic vertebra, lumbar centrum and sacral centrum; dumbbell ossification of the cervical or thoracic centrum; bent hyoid; misshapen or fused sternebra; supernumerary (short or full), detached or thickened ribs and absent lumbar or sacral vertebra (including centrum).

**Study title:** An oral embryo-fetal development study in rabbits

Study no.: 0970631

Study report location: 4.2.3.5

Conducting laboratory and location: Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

Date of study initiation: June 21, 2010  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key Study Findings:**

- Maternal exposures (AUC) achieved in this study were approximately 20-fold lower than those observed clinically at steady-state (22348 ng\*h/mL) with the 200 mg recommended dose of LDE225.
- Although fetal exposure to LDE225 was only demonstrated consistently following 5 mg/kg/day, the dose-dependent incidence of fetal skeletal variations confirmed drug exposure at all doses.
- Malformations: One fetus in the 0.01 mg/kg/day dose group had ectrodactyly.
- Variations: Following 5 mg/kg/day of LDE225, a small gallbladder was noted in 40% of fetuses, compared to 11% in control animals. Statistically significant increases in skeletal variations were generally dose-responsive and consisted of incomplete ossification of the frontals, metacarpals, cervical centrum, hyoid, and interparietals, and unossified metacarpals. Dumbbell ossification of the thoracic centrum also occurred following 5 mg/kg/day of LDE225.

**Methods:**

Doses: 0, 0.01, 0.1, or 5 mg/kg/day  
Frequency of dosing: Daily  
Dose volume: 5 mL/kg  
Route of administration: Oral Gavage  
Formulation/Vehicle: 0.5% (w/v) Methyl cellulose (MC), Type 400 cPs, aqueous solution containing 0.5% (v/v) Tween 80, NF  
Species/Strain: Rabbit / Hra:(NZW)SPF  
Number/Sex/Group: 20  
Satellite groups: 3 for control  
5 for treatment groups  
Study design: Daily dosing on gestation Day 7-20. Terminal caesarean section was conducted on Day 29 (Day 21 for TK animals).

**Observations and Results:****Mortality [observations made daily]**

None

**Clinical Signs [twice daily]**

Unremarkable

**Body Weight [twice weekly]**

Unremarkable

**Food Consumption [daily]**

Unremarkable

**Toxicokinetics [0.5, 1, 3, 7 and 24 hours post-dose on gestation day 20]**

- Following 0.01 mg/kg/day, maternal exposure to LDE225 was below the lower limit of quantification (LLOQ; 0.05 ng/mL).
- Maternal peak and overall ( $C_{max}$  and  $AUC_{0-24}$ , respectively) exposures were greater than dose-proportional from 0.1 to 5 mg/kg/day.
- Fetal exposure (mean = 27.2 ng/g) to LDE225 was only demonstrated consistently following 5 mg/kg/day.
- Maternal exposures (AUC) achieved at the high dose level in this study were approximately 20-fold lower than those observed clinically at steady-state (22348 ng\*h/mL) with the 200 mg recommended dose of LDE225.
- Details are shown in Table 19.

**Table 19: Toxicokinetic Parameters in Female Rabbit Plasma on Gestation Day 20**

Dose	T <sub>max</sub>		C <sub>max</sub>		AUC(0-24h)		AUC(0-24h)/Dose		C <sub>0</sub>		n
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
0.1	0.625	0.250	0.368	0.108	2.28	0.587	22.8	5.87	0.00	0.00	4
5.0	0.600	0.224	149	51.4	1080	237	215	47.3	14.2	6.18	5

Dose (mg/kg/day), T<sub>max</sub> (Hours), C<sub>max</sub> and C<sub>0</sub> (ng/mL), C<sub>max</sub>/Dose ((ng/mL)/(mg/kg/day)), AUC (ng\*Hours/mL), AUC/Dose ((ng\*Hours/mL)/(mg/kg/day)), AUC Interval (Hours),

For the 0.01 mg/kg/day dose, no toxicokinetic parameters were calculated due to sample values below the LLOQ (0.05 ng/mL).

(table excerpted from Applicant's NDA)

**Maternal necropsy**

Unremarkable

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

Unremarkable

**Offspring necropsy**

- External Malformations: One fetus from the 0.01 mg/kg/day maternal exposure group had ectrodactyly.
- External Variations: Unremarkable

- Visceral Malformations: Unremarkable
- Visceral Variations: Following 5 mg/kg/day to females, a small gallbladder was noted in 40% of fetuses, compared to 11% in control animals.
- Skeletal Malformations: Unremarkable
- Skeletal Variations: Statistically significant increases in the incidence of skeletal variations are detailed in Table 20.

**Table 20: LDE225-induced Skeletal Observations and Historical Ranges**

<b>Skeletal Variation</b>	<b>Concurrent Control</b>	<b>0.01 (mg/kg/day)</b>	<b>0.1 (mg/kg/day)</b>	<b>5 (mg/kg/day)</b>	<b>Historical Control Range</b>
<b>Frontal – incomplete ossification</b>					
Fetal incidence (%)	0	1(0.6)	8(4.8)**	12(6.4)**	0-4(0-2.5)
Litter incidence (%)	0	1 (5.0)	4(20.0)	5(25.0)*	0-3 (0-15.8)
<b>Hyoid – incomplete ossification</b>					
Fetal incidence (%)	56(35.9)	50 (28.4)	63 (38.2)	110(55.8)**	10-41(5.9-25.5)
Litter incidence (%)	14 (77.8)	16 (80.0)	17 (85.0)	19(95.0)	5-15(26.3-75.0)
<b>Interparietal – incomplete ossification</b>					
Fetal incidence (%)	6(3.8)	6(3.4)	8(4.8)	20(10.7)*	1-2(0.3-1.2)
Litter incidence (%)	3(16.7)	3(15.0)	3(15.0)	7(35.0)	0-1(0-5.6)
<b>Metacarpals</b>					
<b>Incompletely ossified</b>					
Fetal incidence (%)	29(18.6)	52(29.5)*	38(23.0)	80(42.8)**	9-51(5.6-33.1)
Litter incidence (%)	12(66.7)	17(85.0)	14 (70.0)	15(75.0)	3-15(16.7-83.3)
<b>Unossified</b>					
Fetal incidence (%)	2(1.3)	12(6.8)*	13(7.9)**	28(15.0)**	0-22(0-14.0)
Litter incidence (%)	2(11.1)	6(30.0)	4(20.0)	13(65.0)**	0-6(0-31.6)
<b>Cervical centrum – incompletely ossified</b>					
Fetal incidence (%)	2(1.3)	1(0.6)	5(3.0)	30(16.0)**	0-2(0-1.3)
Litter incidence (%)	1(5.6)	1(5.0)	1(5.0)	8(40.0)*	0-1(0-5.3)
<b>Thoracic centrum – dumbbell ossification</b>					
Fetal incidence (%)	0	0	0	9(4.8)**	0-3(0-1.7)
Litter incidence (%)	0	0	0	3(15.0)	0-3(0-15.8)

\* Statistically significant at P<0.05; \*\* Statistically significant at P<0.01.

(table excerpted from Applicant's NDA)

**Study title:** LDE225: A 5-week oral (gavage) toxicity study in juvenile rats with a 8-week recovery period

Study no.: 0770903

Study report location: 4.2.3.5

Conducting laboratory and location:

(b) (4)

Date of study initiation: March 18, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: LDE225, 0751003, 100%

**Key study findings:**

- Mortality occurred at 30 mg/kg/day of LDE225.
- LDE225-induced toxicity was primarily seen following 10 mg/kg/day of LDE225 and targeted the teeth, skin, and bone, gastrointestinal tract, and reproductive organs.
- Adverse clinical signs included tremors, ataxia, and abdominal distention.
- Nearly all animals treated at 10 and 30 mg/kg/day had missing, fractured, thin, or soft teeth with histopathological atrophy leading to decreased food consumption and body weight.
- Hair follicle atrophy was noted in nearly all 10 and 30 mg/kg/day animals.
- Bone toxicity consisted of decreased length and width, thinning/closure of the growth plate, and hyperostosis.
- Physical sexual development (vaginal opening and preputial separation) was delayed up to 6 days following  $\geq 10$  mg/kg/day of LDE225. These differences may be related to overall delayed growth.
- Additional LDE225-induced toxicity consisted of lymphoid depletion and degeneration of the thoracic spinal cord and sciatic nerve.



**Body Weights [weekly]**

At the end of the treatment period, 39% and 45% decreases in body weight were noted in animals treated with 10 and 30 mg/kg/day of LDE225, respectively. This effect was irreversible by the end of the recovery period.

**Food Consumption [twice weekly]**

Compared to controls, the average daily food consumption per animal was reduced by 20-46% and 33-53% following 10 and 30 mg/kg/day of LDE225, respectively. This effect was irreversible by the end of the recovery period.

**Physical sexual development [daily]**

Physical sexual development occurred in all animals; however, the mean day of vaginal opening in females and preputial separation in males was delayed, compared to control animals. Specifically, vaginal opening was delayed by 4 and 6 days at the 10 and 30 mg/kg/day dose levels and preputial separation was delayed by 2 and 5 days at the same dose levels. These differences may be related to overall delayed growth.

**Ophthalmoscopy [pre-dose; week 5 and 8]**

Unremarkable

**Hematology [pre-dose; week 5 and 8]**

The following changes were reversible or on a trend of reversibility by the end of the recovery period.

**Week 8 - % change in hematology parameters vs control**

	Males		Females	
	10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg
Neutrophils	+97	+310	+197	+291
Reticulocytes	+17	+43	+24	+80

**Clinical Chemistry [pre-dose; week 5 and 8]**

At the end of the recovery period, 30 mg/kg/day animals showed an approximate 50% decrease in creatine kinase levels.

**Urinalysis [pre-dose; week 5 and 8]**

Unremarkable

**Gross Pathology [at sacrifice]**

Nearly all 10 and 30 mg/kg/day animals had missing, fractured, thin, or soft teeth. A reversibly small uterus was also noted in 3/11 and 4/11 females following 10 or 30 mg/kg/day of LDE225.

**Bone measurements [at sacrifice]****% change in bone measurements vs. control**

Sex	Male					Female				
	Main study		Rec <sup>a</sup>			Main study		Rec <sup>a</sup>		
Study phase										
Dose (mg/kg/day)	1	3	10	30	30	1	3	10	30	30
<b>Bone length</b>										
Femur	-1	-1	<b>-38</b>	<b>-41</b>	<b>-51</b>	0	-2	<b>-37</b>	<b>-38</b>	<b>-45</b>
Tibia	0	-1	<b>-36</b>	<b>-38</b>	<b>-47</b>	-4	-2	<b>-37</b>	<b>-36</b>	<b>-44</b>
<b>Bone width</b>										
Femur	-4	-2	-11	-10	<b>-11</b>	-6	-4	-11	-11	-7
Tibia	2	-7	<b>-13</b>	<b>-13</b>	-16	-4	-5	<b>-14</b>	<b>-16</b>	-17

Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group -  $P \leq 0.05$ ; refer to data tables for actual significance levels and tests used.

a Rec = Recovery

**Organ Weights [at sacrifice]**

Except for decreased weight of testes and uterus, the following weight changes were reversible or on a trend of reversibility by the end of the recovery period.

**% change in organ weights (relative to brain weight) vs. control**

	Males		Females	
	10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg
Thymus	-28	-37	-40	-47
Testes	-29	-38	-	-
Ovaries	-	-	-37	-59
Uterus	-	-	x	-45

x denotes no change

**Histopathology [at sacrifice]**

Except for thinning/closure of growth plate, oligo/aspermia, degeneration/atrophy of the testis, minimal degeneration of nerve findings, and findings in teeth, the following histopathological findings were reversible or on a trend of reversibility by the end of the recovery period.

Tissue and finding	Grade	Males		Females	
		10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg
Bone (femur)					
- <i>thinning/closure of growth plate</i>	4-5	11/12	15/15	12/12	14/14
- <i>hyperostosis: periosteal</i>	1-3	10/12	12/15	10/12	9/14
Bone (tibia)					
- <i>thinning/closure of growth plate</i>	4-5	11/12	15/15	12/12	14/14
- <i>hyperostosis: periosteal</i>	1-2	6/12	8/15	9/12	9/14
Cecum					
- <i>necrosis: cryptal</i>	1-3	1/12	2/15	0/12	5/14
Colon					
- <i>necrosis: cryptal</i>	1	0/12	2/15	0/12	3/14
Duodenum					
- <i>necrosis: cryptal</i>	1	3/12	5/15	5/12	3/14
Ileum					
- <i>necrosis: cryptal</i>	1	6/12	10/15	6/12	6/14
Jejunum					
- <i>necrosis: cryptal</i>	1	6/12	11/15	4/12	6/14
Rectum					
- <i>necrosis: cryptal</i>	1	0/12	4/15	0/12	5/14
Sciatic Nerve					
- <i>degeneration</i>	1-3	10/12	13/15	6/12	7/14
Skin					
- <i>hair follicle atrophy</i>	3-4	10/12	15/15	10/12	14/14
Spleen					
- <i>increased hematopoiesis</i>	2	2/12	2/15	6/12	9/14
Thoracic spinal cord					
- <i>degeneration</i>	1	2/12	3/15	0/12	1/14
Thymus					
- <i>depletion</i>	1-2	2/12	4/15	4/12	5/14
Teeth					
- <i>atrophy</i>	5	12/12	13/15	12/12	12/12
- <i>fracture</i>	5	2/12	5/15	2/12	1/12
Epididymis					
- <i>oligo/aspermia*</i>	1-5	10/12	15/15	-	-
- <i>inflammation</i>	1	2/12	5/15	-	-
Prostate					
- <i>partial glandular development</i>	1	3/12	5/15	-	-
Seminal vesicle					
- <i>partial glandular development</i>	1	1/12	4/15	-	-
Testis					
- <i>degeneration/atrophy</i>	1-3	12/12	13/15	-	-
- <i>necrosis</i>	1-4	7/12	1/15	-	-
Ovary <sup>#</sup>					
- <i>degeneration/necrosis</i>	1	-	-	2/12	10/14

Tissue and finding	Grade	Males		Females	
		10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg
Uterus - atrophy	1-2	-	-	8/12	11/14
Vagina - atrophy	1-2	-	-	4/12	10/14

Grade 1, 2, 3, 4, 5 refers to minimal, slight, moderate, marked, severe, respectively

Severity of findings was generally correlated with dose

\*oligo/aspermia in the epididymis was also noted in 3/12 males following 3 mg/kg/day of LDE225

#degeneration/necrosis in the ovary was also noted in 2/12 females following 3 mg/kg/day of LDE225

### Toxicokinetics [0.5, 1, 3, 7, and 24 hrs post-dose on day 1 and week 5]

- LDE225 exposure (AUC) was greater than dose-proportional from 1 to 3 mg/kg/day.
- Drug accumulation was apparent following 30 mg/kg/day of LDE225.
- Sex differences were limited to greater accumulation in females.
- Details are shown in Table 21.

**Table 21: Summary of Toxicokinetic Parameters from 5-week Toxicity Study in Juvenile Rats**

Gender	Study Day	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	C <sub>max</sub> /dose (ng/mL/mg/kg/day)	AUC <sub>(0-24h)</sub> (ng-h/mL)	AUC <sub>(0-24h)</sub> /dose (ng-h/mL/mg/kg/day)	SE (ng-h/mL)	Co (ng/mL)
Dose: 1 mg/kg/day								
Male	1	1.00	178	178	930	930	98.1	0
	week 5	1.00	98.6	98.6	443	443	62.2	0
Female	1	1.00	116	116	1100	1100	59.7	0
	week 5	0.500	110	110	635	635	102	0
Dose: 3 mg/kg/day								
Male	1	3.00	421	140	5220	1740	811	0
	week 5	1.00	456	152	4120	1370	172	16.9
Female	1	3.00	526	175	6480	2160	777	0
	week 5	3.00	384	128	4510	1500	501	61.1
Dose: 10 mg/kg/day								
Male	1	3.00	1360	136	17800	1780	1610	0
	week 5	3.00	1580	158	15400	1540	2220	218
Female	1	3.00	1600	160	22600	2260	1900	0
	week 5	7.00	2210	221	38400	3840	1980	930
Dose: 30 mg/kg/day								
Male	1	3.00	3610	120	43000	1430	2890	0
	week 5	7.00	3900	130	61300	2040	4360	1210
Female	1	1.00	2660	88.7	50100	1670	3370	0
	week 5	3.00	5530	184	90900	3030	NA	2400

SE: Standard error of Composite AUC (b) (4)

NA: not applicable (not calculable since only one animal at 7h was available)

(table excerpted from Applicant's NDA)

## 10 Special Toxicology Studies

**Study title:** Neutral Red Uptake Phototoxicity Test

Study no.: 0770120

Study report location: 4.2.3.7.7

Conducting laboratory and location: Safety Profiling & Assessment  
Novartis Pharma AG  
Basel Switzerland

Date of study initiation: March 19, 2007

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: LDE225/1/99%

The objective of this study was to evaluate the phototoxicity of sonidegib (LDE225) in murine (Balb/c 3T3) fibroblasts when cultured in the presence or absence of 5J/cm<sup>2</sup> ultraviolet (UVA) irradiation from a solar simulator (SOL500) equipped with a filter (H1) to attenuate UVB for 50 minutes. The positive control agent was chlorpromazine. The negative control was DMSO. Uptake of neutral red was used as a measure of cell viability. The photoirritancy factor (PIF) was calculated using the EC<sub>50s</sub> ± irradiation. A PIF of greater than 2 was considered to predict probable phototoxic potential.

Under the conditions used LDE225 did not demonstrate potential for phototoxicity, based on a PIF of 0.9-1.5 in two assays. The PIF for chlorpromazine, in comparison, was between 29 and 31.

The assay met the criteria for a valid test (OD<sub>540</sub> in solvent-treated cells was ≥ 0.2; the radiation sensitivity of solvent-treated cells was > 80%, and all survival and sensitivity parameters of chlorpromazine-treated cells were within the range of historical control data.

## 11 Integrated Summary and Safety Evaluation

Nonclinical pharmacology studies demonstrated that sonidegib is an antagonist of smoothed (Smo), a transmembrane protein involved in hedgehog signal transduction. In vitro, sonidegib showed an IC<sub>50</sub> of 11 nM in an agonist displacement assay using human Smo. Supporting this finding, sonidegib inhibited Gli-dependent downstream hedgehog signaling with at a similar concentration (IC<sub>50</sub>=12.7 nM).

Since hair follicles have active hedgehog signaling, hair growth can serve as a pharmacodynamic surrogate of hedgehog signaling. Therefore, utilizing a hair growth model in mice, the Applicant demonstrated that daily administration of a 1% topical solution of sonidegib for 14 days inhibits hair growth and the expression of various genes involved in hedgehog signaling in skin samples.

Embryonic skin punches derived from Ptch+/- -LacZ heterozygous mice form basaloid nest lesions when cultured and stimulated with recombinant hedgehog protein or small

molecule Smo agonists. Thus, these skin punches may be utilized as a mouse model of basal cell carcinoma to evaluate the efficacy of Smo inhibitors. In this model, sonidegib inhibited basaloid lesion formation and regression of pre-formed basaloid lesions.

Sonidegib was assessed for its off-target activity across a panel of 150 receptors, enzymes, ion channels, and transporters. Sonidegib showed an  $IC_{50}$  of  $\leq 10 \mu\text{M}$  for human melatonin MT1 receptor ( $IC_{50} = 1.1 \mu\text{M}$ ), human cannabinoid CB2 receptor ( $IC_{50} = 9.7 \mu\text{M}$ ), human acetylcholinesterase enzyme ( $IC_{50} \sim 10 \mu\text{M}$ ), rat brain sodium channel type II ( $IC_{50} = 0.82 \mu\text{M}$ ), and rabbit vesicular monoamine transporter VMAT2 ( $IC_{50} = 10 \mu\text{M}$ ). Based on a total sonidegib human mean steady state  $C_{\text{max}}$  of  $1.5 \mu\text{M}$ , the only potentially clinically relevant off-target activity of sonidegib identified in this screen is on the melatonin MT1 receptor. To date, no toxicities have been noted clinically in humans directly related to melatonin MT1 receptor inhibition.

Safety pharmacology studies consisted of an in-vitro evaluation of hERG (human ether-á-go-go-related gene) channel interaction, a combined functional observational battery (FOB) neurological and respiratory assessment in rats, and a cardiovascular safety pharmacology study in dogs. No sonidegib-induced adverse effects were seen in any of these studies. Sonidegib was a weak hERG blocker with a low potential to induce QT prolongation. Due to test-article stability issues in the hERG assay and lack of ECG analysis software validation in the cardiovascular safety pharmacology study in dogs, the validity of these results are unclear; however, stand-alone safety pharmacology studies are not absolute requirements to support the safety assessment of drugs intended for the treatment of advanced cancer. Cardiovascular safety endpoints were included in the non-rodent general toxicology studies to address the need for an assessment. Considering the lack of remarkable ECG changes in the repeated-dose toxicity studies in dogs, and the lack of adverse cardiac findings in humans, there is no significant cardiac risk predicted for patients taking sonidegib.

In regard to the pharmacokinetics in animals, the oral absorption of sonidegib was high in the rat (78%) and moderate in the dog (37.9%). Sonidegib was highly bound to plasma proteins in the mouse, rat, dog, and human (97-99%). The tissue distribution of sonidegib was widespread with the highest concentrations observed in the uveal tract, hardierian gland, fat, liver, small intestine, adrenal cortex, and adrenal medulla. Sonidegib crossed the blood:brain barrier at moderate levels and was detectable greater than 300 hours following a single dose in rats. The metabolism of sonidegib was qualitatively similar but quantitatively different across species. Oxidations and oxidative cleavages (N/O dealkylation) in the morpholine ring appeared to be major metabolic pathways of sonidegib in all species. Among these oxidative metabolites, the most abundant metabolite was M31 in rat and M37 in dog. Amide hydrolysis was another minor pathway in rat and dog, which led to the M48 (LGE899) metabolite. Oxidations in the pyridine ring and in the biphenyl moiety, N-dearylation at the amide nitrogen, glutathione conjugation at the pyridine ring with follow-up reactions, and other biotransformations appeared to be additional minor pathways. Glucuronidation after oxidation or amide hydrolysis was also observed. No unique metabolites were identified

in human plasma. The majority of sonidegib was excreted via feces in rats, dogs, and humans.

The toxicity of daily doses of oral sonidegib was assessed by conducting repeat-dose toxicity studies of up to 26-weeks in duration in rats and dogs. The main target organs of toxicity noted in both species were the skin, bone, and gastrointestinal tract. Skin toxicity consisted of alopecia with histopathological atrophy of hair follicles. Considering hair follicles have active hedgehog signaling, alopecia was an expected pharmacodynamic effect of sonidegib. Consistent with this finding, alopecia was noted clinically in humans treated with sonidegib. Bone toxicity consisted of thinning/closure of the growth plate in various bones. Teeth abnormalities including missing or fractured teeth and histopathological atrophy were also noted in rats. These findings are unlikely to be a significant clinical issue for the intended adult patient population for ODOMZO®; however, they may be a concern if the drug is used in a pediatric population. Gastrointestinal toxicity, characterized by inflammation and necrosis, occurred at doses approximately  $\geq 2$  times the recommended human dose based on AUC. These adverse gastrointestinal findings may be related to the abdominal pain and diarrhea observed clinically.

Additional sonidegib-induced toxicity noted in both species consisted of uterus atrophy and increased cholesterol levels. Since these adverse findings occurred at doses  $\geq 10$  mg/kg/day (approximately  $\geq 2$  times the recommended human dose based on AUC), the relevance to humans is unknown.

Generally increased plasma levels of creatine kinase were also noted in both species and appear to be related to a muscle toxicity class effect of hedgehog inhibitors. In humans creatine kinase elevations and musculoskeletal adverse reactions including spasms, pain, and myalgia were noted following treatment with sonidegib. The underlying pharmacology driving this muscle toxicity is hypothesized to be related to hedgehog signaling in satellite cells. As a precursor to skeletal muscle, satellite cells proliferate and differentiate in response to growth or muscle injury (Hawke and Garry, et al., 2001). Koleva et al., demonstrated that hedgehog signaling contributes to proliferation and survival of satellite cells in adult muscle that can be reversed with the Smo antagonist, cyclopamine (Koleva et al., 2005). Through the same mechanism of action, sonidegib may inhibit the proliferation and survival of satellite cells resulting in musculoskeletal adverse reactions.

Tremors occurred at the high dose levels in both species used for toxicological assessment of sonidegib. This finding, along with the occasional elevations in creatine kinase, is included in Section 13.2 - Animal Toxicology and/or Pharmacology of the ODOMZO® label. This toxicity was consistently seen in rats at doses  $\geq 10$  mg/kg/day (approximately  $\geq 2$  times the recommended human dose based on AUC). Although body tremors were also noted in dogs administered 50 mg/kg/day of sonidegib, this dose exceeded the maximum tolerated dose and resulted in overt toxicity; thus the pharmacological relevance of these tremors is uncertain. The off-target activity of sonidegib on rat sodium brain channel type II provides evidence that body tremors in

rats may be unrelated to the muscle issues (including muscle spasms) reported clinically.

Species-specific adverse findings following exposure to sonidegib included lymphoid depletion and ovarian atrophy in rats. Consistent with these findings, lymphopenia and amenorrhea occurred clinically in humans. Additional species-specific adverse findings consisted of prostate inflammation in rats and adrenal vacuolation in dogs. Since these findings occurred at doses  $\geq 10$  mg/kg/day (approximately  $\geq 2$  times the recommended human dose based on AUC), the relevance to humans is unknown.

In a 5-week juvenile rat toxicity study, the bones, teeth, reproductive tissues, and nerves demonstrated findings of sonidegib-induced toxicity at doses  $\geq 10$  mg/kg/day (approximately 1.2 times the recommended human dose based on AUC). Bone findings included thinning/closure of bone growth plate, decreased bone length and width, and hyperostosis. Findings in teeth consisted of missing or fractured teeth, and atrophy. Reproductive tissue toxicity was evidenced by atrophy of testes, ovaries, and uterus, partial development of the prostate gland and seminal vesicles, and inflammation and aspermia of the epididymis. Nerve degeneration was also noted.

Sonidegib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) and was not clastogenic or aneugenic in an in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus test. Carcinogenicity studies were not conducted with sonidegib; however in consideration of the life expectancy of the intended patient population, the Applicant will need to assess carcinogenicity, as a post-marketing requirement.

The effect of sonidegib on fertility was evaluated in rats. Sonidegib resulted in a lack of fertility when administered to female rats at  $\geq 20$  mg/kg/day (approximately 1.3 times the recommended human dose based on body surface area (BSA)). A reduction in the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day (approximately 0.12 times the recommended human dose based on BSA). Based on fold-exposure levels, these adverse findings on fertility are expected to manifest clinically and were noted in the ODOMZO® label. No adverse effects on male fertility were noted when rats were administered sonidegib at doses up to 20 mg/kg/day, the highest dose tested.

Embryo-fetal toxicity studies with sonidegib were conducted in rabbits. Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at doses  $\geq 5$  mg/kg/day (approximately 0.05 times the recommended human dose based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection. Based on the severity of these adverse findings, a boxed-warning on embryo-fetal toxicity was included in the ODOMZO® label.

In conclusion, the Applicant has conducted sufficient non-clinical studies to support the use of sonidegib (ODOMZO®) in patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4) [REDACTED]. From a Pharmacology/Toxicology perspective, approval for sonidegib (ODOMZO®) is recommended.

## 12 References

- Hawke TJ and Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl. Physiol.* (2001) 91: 534-551
- Koleva M, et al. Pleiotropic effects of sonic hedgehog on muscle satellite cells. *Cell Mol. Life Sci.* (2005) 62: 1863-1870
- Namba D, et al. Role of sonic hedgehog signaling in epithelial and mesenchymal development of hair follicles in an organ culture of embryonic mouse skin. *Develop. Growth Differ.* (2003) 15: 231-239
- Oro AE and Higgins K. Hair cycle regulation of Hedgehog signal reception. *Dev. Biol.* (2003) 255: 238-248
- Slominski A, et al. Hair cycle-associated changes in splenocyte proliferation. *In Vivo.* (1997) 11(1): 101-102
- Williams JA, et al. Identification of a small molecule inhibitor of the hedgehog signaling pathway: Effects on basal cell carcinoma-like lesions. *Proc. Natl. Acad. Sci.* (2003) 100(8): 4616-4621

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/s/  
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ALEXANDER H PUTMAN  
05/28/2015

WHITNEY S HELMS  
05/28/2015

## MEMORANDUM

**Date:** May 28, 2015  
**From:** Whitney S. Helms, PhD.  
Pharmacology Team Leader  
Division of Hematology Oncology Toxicology for Division of Oncology Products 2  
**To:** File for NDA #205266  
Sonidegib (ODOMZO)  
**Re:** Approvability of Pharmacology and Toxicology

Non-clinical studies examining the pharmacology and toxicology of sonidegib provided to support NDA 205266 for the treatment of patients with locally advanced basal cell carcinoma were reviewed in detail by Alexander H. Putman, PhD. The submission included studies of orally administered sonidegib in mice, rats, and dogs that investigated the drug's pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (*in vivo* and *in vitro*), and reproductive toxicity.

The pharmacology studies submitted to this NDA demonstrate that sonidegib is a Smoothed (Smo) antagonist. Smoothed is a transmembrane protein that is an integral part of the Hedgehog signaling pathway. Binding of hedgehog ligands to the Patched receptor results in release of Patched-mediated inhibition of Smo signaling and downstream nuclear translocation of the active Gli transcription factor with subsequent Gli-responsive transcriptional activation. Sonidegib inhibited Gli-dependent transcription with  $IC_{50}$ s of between 4 and 13 nM in various *in vitro* assays. As binding of hedgehog ligands to Patched initiates the downstream events leading to Smo activation, the activity of sonidegib is consistent with labeling the drug as a hedgehog pathway inhibitor as its established pharmaceutical class.

Sprague Dawley rats and Beagle dogs were the primary models used to investigate the toxicology of sonidegib in studies of up to 26 weeks. Major target organs identified in both species included the bone (growth plate closure), gastrointestinal tract, and hair follicles. Gastrointestinal toxicity and alopecia are reported clinically. In the rat the teeth were an additional major target. Findings in the teeth included atrophy of the root, malocclusion, and tooth loss. The tooth findings were associated with declining clinical condition and led to humane euthanasia of some rats at the high dose level, a dose that resulted in male exposures only slightly higher than clinical exposures at the recommended dose, in the 26-week study.

While not required to support the use of sonidegib in the current indication, the Applicant also conducted a juvenile animal study in rats. In general findings in the juvenile animals were similar to those seen in adult rats, with the bones, teeth, gastrointestinal tract, and hair follicles being major target organs in these animals. Juvenile rats presented with delays in sexual maturation compared to controls and limited signs of nerve damage as well. The bone findings correlated with significant decreases in bone length and width at the end of the treatment period that were enhanced at the end of an 8 week recovery period. These findings are likely to be relevant to a pediatric patient population and are recommended for inclusion in the ODOMZO label in the Pediatric Use section, Section 8.4.

Musculoskeletal toxicity was the major toxicity associated with sonidegib in clinical trials. This toxicity was characterized by reports of musculoskeletal pain, myalgia, and muscle spasms preceding significant increases in creatine kinase (CK). Published reports describe a role for hedgehog signaling in the proliferation and survival of satellite cells present in skeletal muscle that proliferate and differentiate in response to growth or muscle injury, providing a potential pharmacological basis for this toxicity<sup>1-2</sup>. While no histopathological signs of muscle degeneration or atrophy occurred in the repeat dose toxicology studies conducted in either rats or dogs, continuous or intermittent full body tremors occurred at the highest dose level in each species as well as in the juvenile rats. In addition, transient increases of greater than 100% in creatine kinase occurred in rats. The elevations in CK along with tremors are included in the ODOMZO label and are suggestive of the musculoskeletal events of muscle spasms and elevations in CK reported clinically. Sonidegib did, however, have some off target activity on the rat sodium brain channel type II which could be a factor in rat tremors at high dose levels. In addition, minimal findings of nerve degeneration occurred in juvenile rats. These observations along with sonidegib's ability to cross the blood brain barrier make some direct effect on the central nervous system another possible explanation for the tremors, although the Applicant proposes that the peripheral nerve degeneration observed in juvenile rats may be related to closures of growth plates in bones preventing nerve growth.

Sonidegib was negative in assays for genotoxicity. Carcinogenicity studies were not conducted to support the use of sonidegib in patients with locally advanced basal cell carcinoma. Since the natural history of this disease is highly variable and patients may be taking sonidegib for long periods of time, carcinogenicity studies in rats and mice are recommended as postmarketing requirements.

The Applicant investigated the potential reproductive toxicity of sonidegib in dedicated fertility and embryofetal development studies in rats. Treatment with sonidegib resulted in a lack of fertility in female rats at doses resulting exposures approximately 1.3 times the exposure in humans at the recommended dose of 200 mg. In the same study, increases in the number of early resorptions and decreases in the number of viable fetuses occurred at exposures as low as 0.12 times the clinical exposure. Supporting these findings, histopathological findings in female rats in the 6 month adult toxicology study included atrophy of the uterus and ovaries at twice the exposure in humans and similar disturbances occurred in a juvenile animal study. Sonidegib may, therefore, affect female fertility. Sonidegib did not appear to affect male fertility in adult animal studies, though degeneration and atrophy of the testis and delayed preputial separation were reported in a juvenile animal study.

Sonidegib is a powerful teratogen in animals. In an embryofetal development study conducted in rabbits, sonidegib administration resulted in abortion, complete resorption of fetuses, or severe malformations including vertebral, distal limb and digit, and severe craniofacial defects, at doses resulting in exposures of approximately 0.05 times the exposure in humans at the recommended dose of 200 mg. Skeletal variations were observed even when maternal exposure to sonidegib was below the limit of detection for the drug. Due to the severe findings in rabbits, an embryofetal development study in a second species was not required, consistent with the recommendations in ICH S9. Because of the severity of the findings a black box warning for

embryofetal risk is included in the ODOMZO label. The half-life of ODOMZO in clinical trials was approximately 28 days. In distribution studies the drug accumulated multiple tissues and was present at least 23 days in white fat. Because of the severe teratogenic findings and long half-life of the drug, the label includes a recommendation for females of reproductive potential to use effective contraception during and for at least 20 months following the final dose of ODOMZO. While sonidegib is not genotoxic and had no clear effect on adult male fertility, because of the teratogenic risk of the drug at even very low concentrations, the label includes the recommendation that males who are taking ODOMZO and have female partners of reproductive potential use effective contraception during and for at least 8 months following the final dose of the drug. This recommendation is based on the half-life of the drug in combination with an estimated distribution in semen of approximately 10-20%.

**Recommendations:** I concur with the conclusion of Dr. Putman, that the pharmacology and toxicology data support the approval of NDA 205266 for ODOMZO. Because the life expectancy of patients with locally advanced basal cell carcinoma varies widely, carcinogenicity studies in mice and rats are recommended for this drug as postmarketing requirements. There are no outstanding nonclinical issues that would prevent the approval of ODOMZO for the proposed indication.

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<sup>1</sup> Hawke TJ and Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl. Physiol.* (2001) 91: 534-551

<sup>2</sup> Koleva M, et al. Pleiotropic effects of sonic hedgehog on muscle satellite cells. *Cell Mol. Life Sci.* (2005) 62: 1863-1870

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WHITNEY S HELMS  
05/28/2015

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

**BLA Number:** 205266

**Applicant:** Novartis

**Stamp Date:** 9/26/2014

**Drug Name:** Sonidegib

**NDA Type:** Standard

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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		
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		Appears to be acceptable.
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		Appears to be acceptable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		Appears to be acceptable.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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	This is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	Not applicable		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	Not applicable		

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

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

None

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