CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

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:	203388
Supporting document/s:	1
Applicant's letter date:	September 8, 2011
CDER stamp date:	September 8, 2011
Product:	vismodegib (Erivedge)
Indication:	Treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and [redacted] (b) (4) [redacted] (b) (4) who are not candidates for radiation
Applicant:	Genentech, Inc.
Review Division:	Division of Hematology Oncology Toxicology
	(Division of Oncology Products 2)
Reviewer:	Dubravka Kufrin, Ph.D.
Acting Team Leader:	Todd Palmby, Ph.D.
Division Director:	John Leighton, Ph.D.
	(Patricia Keegan, M.D.)
Project Manager:	Mona Patel, D. Pharm.

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Any information or data necessary for approval of vismodegib that Genentech, Inc. 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Genentech, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of vismodegib.

Reference ID: 3076062

Labeling review for NDA 203388

Refer to the Pharmacology/Toxicology review for NDA 203388 for information from nonclinical studies conducted with vismodegib included in the package insert. This labeling review provides calculations of exposure (AUC) ratios in animals as compared to humans at the recommended dose of 150 mg/day oral vismodegib.

The following sections of the package insert for vismodegib were modified from the version proposed by the Applicant with input from the Pharmacology/Toxicology team and represent the FDA recommendations:

(b) (4)

[redacted]

5 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

DENALI D KUFRIN
01/24/2012

TODD R PALMBY
01/24/2012

MEMORANDUM

Date: January 13, 2012
From: Todd R. Palmby, Ph.D.
Acting Supervisory Pharmacologist
Division of Hematology, Oncology Toxicology
To: File for NDA 203388 vismodegib
Re: Approvability for Pharmacology and Toxicology
Indication: Treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and [redacted] (b) (4) [redacted] (b) (4) or who are not candidates for radiation

Non-clinical pharmacology and toxicology studies to support vismodegib NDA 203388 for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and [redacted] (b) (4) [redacted] (b) (4) who are not candidates for radiation were reviewed by Dubravka Kufrin, Ph.D. Information included studies conducted with orally administered vismodegib investigating the drug's pharmacology, toxicokinetics and ADME, safety pharmacology, general toxicology (mouse and dog), and genetic toxicity (*in vivo* and *in vitro*). An embryo-fetal developmental toxicology study was conducted in rats to assess the effects of vismodegib on embryo-fetal development. The studies cited in the review consist primarily of original research studies conducted by the applicant.

Pharmacology studies submitted to the NDA support that vismodegib is a hedgehog pathway inhibitor which binds to and inhibits the activity of the Smoothened 7-transmembrane domain receptor. A new Established Pharmacologic Class (EPC) of "hedgehog pathway inhibitor" was proposed by the Applicant for vismodegib. After discussion with management and review staff within the Division of Hematology, Oncology Toxicology as well as Associate Director for Pharmacology and Toxicology, Dr. Paul Brown, in the Office of New Drugs, "hedgehog pathway inhibitor" was determined to be both clinically relevant and scientifically valid.

A significant safety concern encountered in the review of NDA 203388 was the potential for teratogenicity and embryo-fetal toxicity in pregnant women exposed to vismodegib. There is extensive literature describing the critical role of the Hedgehog pathway in embryonic and fetal development. This pathway is highly conserved in many species including nematodes, insects, mammals, etc. There is also evidence that exposure of pregnant animals to Hedgehog pathway inhibitors (e.g., cyclopamine) results in severe midline defects in the offspring of multiple species. In an embryo-fetal developmental toxicity study in rats, vismodegib was teratogenic (missing and/or fused digits, open perineum and craniofacial anomalies) at a dose corresponding to an exposure of 20% of the exposure at the recommended human dose, and was embryotoxic and fetotoxic

(early resorption of 100% of the fetuses) at exposures comparable to those at the recommended human dose. A no effect level for malformations was not identified in this study. Pregnancy Category D is recommended for the use of vismodegib in this patient population.

Repeat-dose toxicology studies in rats and dogs indicate that vismodegib has the potential to impair male and female reproductive function and fertility in humans. A relative decrease in percent motile sperm was observed in rats after 26 weeks administration of oral vismodegib. In dogs, increased numbers of degenerating germ cells and hypospermia were observed in relatively young animals administered oral vismodegib for 4 weeks. A decrease in the number of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks. The reversibility of this finding is unclear. Amenorrhea was observed in clinical trials in females of reproductive potential.

Toxicities in bone (closure of epiphyseal plate) and teeth (missing teeth, degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or loss of teeth) were observed in rats administered oral vismodegib in repeat-dose toxicology studies. These toxicities are consistent with the pharmacological activity of vismodegib inhibiting the hedgehog signaling pathway, and should be considered if vismodegib is administered to pediatric patients; however effects on bone and teeth were not observed in clinical trials with vismodegib.

The most common adverse reactions observed with vismodegib in patients (≥ 10% according to Highlights section of the label) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, vomiting, and ageusia. In rats, a decrease in the number of taste buds on the tongue was observed after 26 weeks administration of oral vismodegib, which is likely related to disgeusia and ageusia observed clinically. Pilomatricoma, a benign tumor arising from the hair follicle, was noted in two rats after 26 weeks administration of oral vismodegib. Similar findings were not identified in clinical trials, and the relevance of this finding in rats is unclear. Alopecia observed in rats and dogs and muscle spasms (tremors and leg twitches) observed in rats were also seen in patients in clinical trials.

Vismodegib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human chromosomal aberration assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay. Carcinogenicity studies have not been conducted with vismodegib. However, patients in the indicated population may have an extended life expectancy and may be chronically treated with vismodegib, so studies are needed to assess the risk of carcinogenicity.

Recommendations: I concur with Dr. Kufrin's conclusion that pharmacology and toxicology data support the approval of NDA 203388 for vismodegib. There

are no outstanding nonclinical issues that would preclude the approval of vismodegib for the proposed indication.

The following information should be conveyed in the approval letter regarding the PMRs:

1. To evaluate the potential for carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

2. To evaluate the potential for carcinogenicity, conduct a long-term rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

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/s/

TODD R PALMBY
01/23/2012

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PUBLIC HEALTH SERVICE
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1 Executive Summary

1.1 Introduction

NDA 203388 was submitted to the U.S. Food and Drug Administration as a full New Drug Application (NDA) for vismodegib for the indication of treatment of adults with basal cell carcinoma that has recurred following surgery (b) (4) or who are not candidates for surgery and radiation. Vismodegib is administered orally by a once daily dose of 150 mg. Vismodegib is a new molecular entity, which inhibits the Hedgehog pathway by binding to and inhibiting the activity of the Smoothened transmembrane protein. Nonclinical pharmacology, pharmacokinetic and toxicology studies have been submitted to support the approval of vismodegib for the proposed indication.

1.2 Brief Discussion of Nonclinical Findings

Vismodegib is a small molecule inhibitor of the hedgehog (Hh) pathway. Hedgehog is a ligand that binds in the extracellular space to Patched (Ptch1), a 12-pass transmembrane, cell-surface receptor. Hedgehog bound to Ptch1 activates Smoothened (Smo), a 7-pass transmembrane domain protein. Signal transduction by activated Smo then leads to the activation and nuclear localization of Gli1 transcription factors and induction of Hedgehog target genes, such us Gli1, Ptch1, Ccnd2, FoxL1 and many others. Many of these genes are involved in cell proliferation, cell survival and angiogenesis.

Pharmacology, pharmacokinetic and toxicology studies were conducted as a part of the nonclinical evaluation of vismodegib. Pharmacology studies evaluated the binding and activity of vismodegib in murine and human cells with a luciferase expression vector linked to the Gli 1-reporter gene. Animal model studies with Ptch1$^{+/-}$ murine medulloblastoma allograft tumors together with patient derived colorectal and pancreatic adenocarcinoma xenografts in mice demonstrated vismodegib inhibition of tumor growth. Mouse hair follicles and skin tissue were also used to evaluate Hh pathway suppression as a part of pharmacology studies conducted with vismodegib. Based on primary pharmacology data submitted with this NDA and in consideration of all the pertinent information for the clinical use of vismodegib, the new Established Pharmacologic Class (EPC) of “hedgehog pathway inhibitor” was determined to be both clinically meaningful and scientifically valid for vismodegib.

Safety pharmacology studies conducted with vismodegib included *in vitro* receptor binding studies, an *in vitro* assessment of hERG channel current inhibition, and a cardiovascular safety pharmacology study in conscious, telemetered dogs. There was no significant off-target binding observed with common pharmacologic receptors *in vitro*. Vismodegib was not observed to have significant cardio-toxic potential, based on low-

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potency blocking of the hERG channel *in vitro* and the no substantial effects on ECG parameters or blood pressure in dogs.

Toxicities in bone and teeth were observed in rats administered oral vismodegib in repeat-dose toxicology studies. Effects on bone consisted of closure of the epiphyseal growth plate when oral vismodegib was administered for 26 weeks at ≥ 50 mg/kg/day. Abnormalities in growing incisor teeth (including missing teeth, degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or loss of teeth) were observed after administration of oral vismodegib for 4 weeks or longer at ≥ 15 mg/kg/day. These toxicities are consistent with the pharmacological activity of vismodegib for inhibiting the hedgehog pathway, and should be considered if vismodegib is administered to pediatric patients.

Other toxicities observed in rats and dogs administered oral vismodegib included elevations in total cholesterol, up to 3 and 5 fold, respectively, which included changes in both HDL and LDL. These elevations were generally reversible, were not considered to be adverse because there were no corresponding findings in histopathology or changes in serum triglycerides, and have not been observed clinically. In rats, a decrease in the number of taste buds on the tongue was observed after 26 weeks administration of vismodegib at ≥ 50 mg/kg/day, for which there was a trend of reversibility following an eight week recovery period. In clinical trials with vismodegib, common adverse events (incidence ≥ 10%) included dysguesia and aguesia, which are likely related to the finding of decreased taste buds in rats. Two rats administered 100 mg/kg/day oral vismodegib for 26 weeks, developed pilomatricoma, a benign tumor arising from the hair follicle. This finding was believed to represent the progression of follicular cysts that were observed at the same dose level at the end of the dosing and recovery phases. The clinical relevance of this finding is unclear. Other common adverse events that were observed in clinical trials with vismodegib that were also observed in animals were alopecia (rats and dogs) and muscle spasms (tremors and leg twitches in rats administered vismodegib for 4 weeks or longer at ≥ 50 mg/kg/day).

The major route of vismodegib elimination in rats and dogs was through biliary excretion. The exposure (C_{max} and AUC_{0-24}) of vismodegib following repeated dosing in rats and dogs did not demonstrate significant and consistent accumulation. The AUC generally increased with increasing dose, but the increase was less than dose proportional in rats and dogs. This trend is reflected in the lack of increased exposure in patients administered doses of vismodegib exceeding the recommended dose of 150 mg/day.

In a 26-week toxicology study in rats, a relative decrease in percent motile sperm was observed at ≥ 15 mg/kg/day. In dogs, increased numbers of degenerating germ cells and hypospermia were observed in relatively young animals administered oral vismodegib for 4 weeks at ≥ 50 mg/kg/day. No corresponding findings were observed in sexually mature dogs at similar doses in 13-week and 26-week toxicology studies.
A decrease in the number of corpora lutea was observed in female rats administered

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oral vismodegib for 26 weeks at 100 mg/kg/day. Repeat-dose toxicology studies in rats and dogs indicate that vismodegib has the potential to impair male and female reproductive function and fertility in humans. In addition, amenorrhea was observed in women of childbearing potential during clinical trials conducted with vismodegib.

In an embryo-fetal developmental toxicity study, vismodegib was teratogenic at a dose corresponding to an exposure of 20% of the exposure at the recommended human dose, and was embryotoxic and fetotoxic at exposures in the range achieved in patients at the recommended dose. Pregnant rats were administered oral vismodegib at doses of 10, 60, or 300 mg/kg/day during the period of organogenesis. Pre- and post-implantation loss were increased at doses of ≥ 60 mg/kg/day, which included early resorption of 100% of the fetuses. A dose of 10 mg/kg/day resulted in malformations (including missing and/or fused digits, open perineum and craniofacial anomalies) and retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws). The potential for teratogenicity due to vismodegib exposure in pregnant women is of particular concern given the understanding of the pivotal role of hedgehog signaling in early embryonic development and published reports of malformations in offspring of pregnant animals exposed to hedgehog inhibitors during pregnancy (e.g., cyclopamine).

A standard battery of genetic toxicology studies was conducted with vismodegib. Vismodegib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human chromosomal aberration assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay. Carcinogenicity studies have not been conducted with vismodegib. However, based on the proposed indicated patient population, carcinogenicity studies are required for vismodegib and will be a post marketing requirement (PMR).

1.3 Recommendations

1.3.1 Approvability

Vismodegib is recommended for approval on the basis of non-clinical studies submitted to this NDA in the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, (b) (4) or who are not candidates for radiation.

1.3.2 Additional Non Clinical Recommendations

Results of the clinical trial used to support marketing (Study SHHY476g) indicate that the median time of exposure to vismodegib was ~10 months and that patients in the indicated population will be chronically exposed to the drug for relatively long periods of time. Vismodegib is in a pharmacologic class with no other approved drugs so the carcinogenic potential is unknown. There is a concern that chronic exposure to vismodegib could cause additional cancers in patients treated with vismodegib. To

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address this concern, two rodent carcinogenicity studies, in rats and mice, need to be conducted as post-marketing requirements to assess the potential for vismodegib to cause carcinogenicity.

1.3.3 Labeling

A separate labeling review will be provided.

2 Drug Information

2.1 Drug Erivedge

Drug background

GDC 0449 is a small molecule (2-pyridyl amide), discovered by utilizing methods of a structure activity relationship (SAR) for a variety of heterocyclic replacements of a benzimidazole[1].

Table 1: Drug Information

2.1.1	CAS Registry Number	879085-55-9
2.1.2	Generic Name	vismodegib
2.1.3	Code Name	GDC-0449, GDC-0449.1, G-025897, G-025897.1, RO5450815, RG3616
2.1.4	Chemical Name	2-chloro-*N*-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonyl-benzamide
2.1.5.1	Molecular Formula	$C_{19}H_{14}Cl_2N_2O_3S$
2.1.5.2	Molecular Weight	421.3 g/mol

[1] Robarge, K.D., S.A. Brunton, G. M. Castanedo, Y. Cui, M.S. Dina, R. Goldsmith, S.E. Gould, O. Guichert, J.L. Gunzner, J. Halladay, W. Jia, C. Khojasteh, M. F. T. Koehler, K. Kotkow, H. La, R. L. LaLonde, K. Lau, L. Lee, D. Marshall, J.C. Marsters Jr., L. J. Murray, C.Qian, L.L. Rubin, L. Salphati, M.S. Stanley, J.H.A. Stibbard, D.P. Sutherlin, S. Ubhayaker, S. Wang, S. Wong, M. Xie (2009), Bioorganic & Medical Chemistry Letters, 19: 5576

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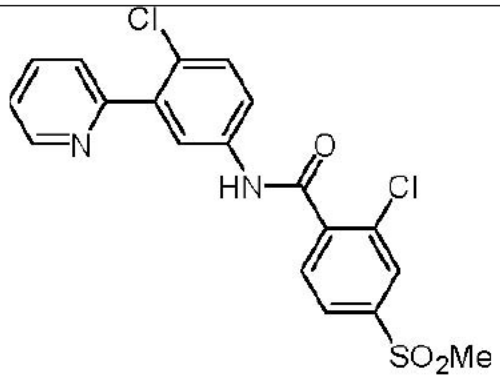
2.1.6	Structure	
2.1.7	Pharmacological Class	hedgehog pathway inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

IND (b) (4)

2.3 Drug Formulation

Vismodegib is a crystalline free, sold base of a white to tan solid color. 5 pages of draft

The solubility of vismodegib is pH dependent. 1 b li

The vismodegib Drug Product is a hard capsule of gelatinous consistency, opaque color and with a grey opaque cap. “150mg” is printed in black ink on the (b) (4) opaque body and “VISMO" is printed in black ink on the grey opaque cap.

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Table 2: Composition of vismodegib Drug Product

Ingredient	Nominal Amount per Capsule (mg)	% (w/w) (b) (4)	Function	Reference to Standard
		Capsule Fill Mass		
Vismodegib	150.0	(b) (4)	Active ingredient	In-house monograph
Microcrystalline Cellulose (b) (4)	(b) (4)		(b) (4)	USP/NF/Ph. Eur.
Lactose Monohydrate				USP/NF/Ph. Eur.
Sodium Lauryl Sulfate				USP/NF/Ph. Eur.
Povidone (b) (4)				USP/Ph. Eur.
Sodium Starch Glycolate				USP/NF/Ph. Eur.
Talc				USP/Ph. Eur.
Magnesium Stearate (non-bovine)				USP/NF/Ph. Eur.
(b) (4)				USP/NF/Ph. Eur.
Total Capsule Fill Weight			—	—
		Capsule Shell		
Body[b]				
(b) (4) Red Iron Oxide, (b) (4)	—	—	(b) (4)	(b) (4) NF, (b) (4)
Titanium Dioxide, (b) (4)	—	—		USP/Ph. Eur.
Gelatin, qs ad (b) (4)	—	—		USP/Ph. Eur.
Printing Ink[c]				USP/NF
Cap[b]				
(b) (4) Black Iron (b) (4)	—	—		(b) (4) NF, (b) (4)
Titanium Dioxide, (b) (4)	—	—		USP/Ph. Eur.
Gelatin, qs ad (b) (4)	—	—		USP/Ph. Eur.
Printing Ink[c]				USP/NF/Ph. Eur.

Ingredient	Nominal Amount per Capsule (mg)	% (w/w) (b) (4)	Function	Reference to Standard
Capsule Shell Weight	(b) (4)	—	—	—
Total Capsule Weight		—	—	—

(b) (4)

(table excerpted from Applicant's package)

2.4 Comments on Novel Excipients

No novel excipients are used in the manufacturing of vismodegib capsules.

2.5 Comments on Impurities/Degradants of Concern

[redacted] (b) (4) for vismodegib. A limit for [redacted] (b) (4) of NMT [redacted] (b) (4) has been established for the vismodegib drug substance. If the drug substance contained [redacted] (b) (4) [redacted] (b) (4) a patient administered oral vismodegib at the maximum recommended dose of 150 mg/day would receive [redacted] (b) (4) of these impurities, which is under an acceptable permitted daily exposure [redacted] (b) (4) Therefore, a specification of [redacted] (b) (4) for [redacted] (b) (4) is acceptable for vismodegib in the proposed patient population.

[redacted] (b) (4) were originally classified as potentially genotoxic due to alerting structures in DEREK and Multicase, but have been confirmed to be non-genotoxic based on Ames-negative assay results.

In the synthetic process for vismodegib, the following six genotoxic impurities have been identified: [redacted] (b) (4) a potential impurity [redacted] (b) (4) which was confirmed by Ames testing to be genotoxic, a known genotoxic reagent [redacted] (b) (4) and a known genotoxic by-product [redacted] (b) (4) [redacted] (b) (4) The Applicant does not propose to test for each of these impurities in the drug substance or to set a specification for each of these impurities in the drug substance. However, the Applicant provided a characterization of impurities with the NDA submission, which concluded that based on information about the manufacturing process, these genotoxic impurities would be below the level of [redacted] (b) (4) [redacted] (b) (4) in the drug substance, which is equivalent to the threshold of toxicologic concern (TTC) of [redacted] (b) (4) for an oral daily dose of 150 mg vismodegib. In addition, the proposed specification for any individual unspecified impurity in the vismodegib drug substance is [redacted] (b) (4) based on the qualification threshold described in ICH Q3A. The presence of a genotoxic impurity in the vismodegib drug substance at the TTC of [redacted] (b) (4) [redacted] (b) (4) or at the proposed impurity specification of [redacted] (b) (4) is acceptable from a Pharmacology/Toxicology perspective for the proposed patient population. If vismodegib is investigated in a patient population with less advanced disease, the proposed specifications for genotoxic impurities may need to be adjusted.

Another impurity, [redacted] (b) (4) was present in batches of vismodegib drug substance [redacted] (b) (4) The proposed specified limit for [redacted] (b) (4) in the vismodegib drug substance is [redacted] (b) (4) The specified limit for [redacted] (b) (4) was set at [redacted] (b) (4) based on the results of nonclinical toxicity studies. Specifically, the daily doses of [redacted] (b) (4) administered to rats and dogs in the chronic 6 month GLP toxicity studies (Study 07-1224 and 07-1047, respectively) were used to calculate the qualified concentration of the impurity in the API. The maximum dose of API that did not result in lethality or moribundity or other severe toxic condition in rats was 50 mg/kg/day (300 mg/m^2/day).

(b) (4) was present in the API used for this study (Lot N82695) at (b) (4) which corresponded to (b) (4) in rats, which would be equivalent to (b) (4) in humans. At the recommended therapeutic dose of 150 mg/day, (b) (4) results in a (b) (4) qualification level of (b) (4) The maximum dose of API that did not result in severe toxicity in dogs was 25 mg/kg/day (500 mg/m^2/day). (b) (4) was present in the API used for this study (Lot N82695) at (b) (4), which corresponded to (b) (4) in dogs, which would be equivalent to (b) (4) in humans. At the recommended human dose of 150 mg/day, (b) (4) results in a (b) (4) qualification level of (b) (4) Thus, the specified limit of (b) (4) is within the qualification range and is acceptable from a Pharmacology/Toxicology perspective.

2.6 Proposed Clinical Population and Dosing Regimen

Vismodegib is indicated for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and (b) (4) (b) (4) or who are not candidates for radiation. Vismodegib is administered orally by a once daily dose of 150 mg.

2.7 Regulatory Background

Genentech, Inc. filed Investigational New Drug Application (IND) 74 573 on 29 September 2006. An End-of-Phase-I meeting was held on 28 April 2008. Two SPA requests were submitted, one on 31 July 2008, and the other on 20 November 2008. A Type B pre-submission meeting was held on 11 May 2011.

3 Studies Submitted

3.1 Studies Reviewed

Study number	Study title
Pharmacology	
04-0242k	Response of subcutaneous patched heterozygous murine medulloblastoma allografts to GDC-0449.23 administered at 100 mg/kg twice a day
05-1039d	Determination of the murine efficacious dose of GDC-0449.23 in LS 180 human colorectal carcinoma xenograft model: efficacy and PK/PD
06-0636	Evaluation of GDC-0449.23 inhibition of Hh signaling in cellular GLI-luciferase reporter assay
09-0633	Characterization of the pharmacokinetic/pharmacodynamic dose response of the hedgehog pathway antagonist GDC-0449 in subcutaneous Ptch1$^{+/-}$, p53$^{+/+}$ murine medulloblastoma allograft in female CD-1 nude mice

Reference ID: 3071937

09-2968	Dose escalation study of GDC-0449 in subcutaneous Ptch$^{+/-}$, p53$^{+/+}$ murine medulloblastoma allograft
d5123-05-04	Determination of minimum effective dose of GDC-0449 to inhibit the growth of subcutaneous D5123 primary colorectal carcinoma xenografts
d5123-05-06	Pharmacokinetic/pharmacodynamic study of GDC-0449 administration in primary human colorectal carcinoma xenografts D5124
D5123-06-02	Effect of GDC-0449 at 69mg/kg twice a day alone or with gemcitabine on growth of primary human pancreatic cancer xenograft model D5124
Safety Pharmacology Studies	
04-1278-1791	Lead Profiling Screen Data Report
05-0606	Effects of GDC-0449.1 on Cloned hERG Potassium Channels Expressed in Mammalian Cells
05-1458	A oral gavage cardiovascular safety pharmacology study of GDC-0449.1 in conscious beagle dogs (GLP study)
Absorption	
04-0745	Pharmacokinetics of GDC-0449.23 following single intravenous bolus administration or oral administration to cynomolgus monkeys
05-0547	Pharmacokinetics of hedgehog (Hh) small molecule antagonist, GDC-0449.1 following intravenous or oral administration to female CD-1 mice
05-0657	Pharmacokinetics of hedgehog (Hh) small molecule antagonist, GDC-0449.1 in male Sprague-Dawley rats following daily oral dosing
05-1405	Pharmacokinetics of GDC-0449.1 single intravenous bolus administration or oral administration to male beagle dogs
Distribution	
06-0526	In vitro cross-species plasma protein binding study using 14C GDC-0449.1
08-0915	Quantitative tissue distribution of drug-related material using whole-body autoradiography following a single oral dose of 14C GDC-0449 (0.2 mg/kg) to male and female Long-Evans rats
Single-dose studies	
05-0598-1604	Pilot oral gavage dose range-finding toxicity and toxicokinetic study of GDC-0449.1 in dogs
05-1454	A single-dose oral gavage toxicity study with GDC-0449.1 in mice
05-1455	A single dose oral gavage toxicity study with GDC-0449.1 in rats
Repeat-dose studies	
05-1456	A 4-week oral gavage toxicity study with GDC-0449.1 in rats with a 4-week recovery period
05-1457	A 4-weekoral gavage toxicity study with GDC-0449.1 in dogs with a 4-week recovery period
06-1003	13-week oral gavage toxicity study with GDC-0449.1 in dogs with a 13-week recovery period
07-1047	26-week oral gavage chronic toxicity and toxicokinetic study with

Reference ID: 3071937

	GDC-0449.1 in dogs with a 13-week recovery phase
06-1202	A 13-week oral gavage chronic toxicity study with GDC-0449.1 in rats with an 8-week recovery period
07-1224	26-week oral gavage chronic toxicity and toxicokinetic study with GDC-0449.1 in Sprague-Dawley rats with an 8-week recovery phase
In vitro genotoxicity studies	
05-1451	GDC-0449.1: Salmonella-Escherichia coli/mammalian-microsome reverse assay with a confirmatory assay
05-1452	GDC-0449.1: Chromosomal aberration in cultured human peripheral blood lymphocytes
In vivo genotoxicity studies	
05-1453	In vivo rat micronucleus assay with GDC-0449.1
Reproductive and developmental toxicity study	
09-2778	RO5450815-000: Dose-range finding study with oral administration for effects on embryo-fetal development in the rat

3.2 Studies Not Reviewed

Study number	Study title
Pharmacology	
04-0242k	Response of subcutaneous patched heterozygous murine medulloblastoma allografts to GDC-0449.23 administered at 100 mg/kg twice a day
d5123-05-06	Pharmacokinetic/pharmacodynamic study of GDC-0449 administration in primary human colorectal carcinoma xenografts D5124
D5123-06-02	Effect of GDC-0449 at 69mg/kg twice a day alone or with gemcitabine on growth of primary human pancreatic cancer xenograft model D5124
Analytical methods and validation reports	
05-107	Quantitative determination of GDC-0449 in rat plasma by LC/MS/MS
05-218	Quantitative determination of GDC-0449 in dogs plasma by LC/MS/MS
Absorption	
05-0523	5-day pilot toxicokinetic study for GDC-0449.1 in male and female Sprague-Dawley rats following daily oral dosing
05-0944	14-day toxicokinetic (TK) study with GDC-0449.1 in male and female Sprague-Dawley rats following daily oral dosing
07-1366	Pharmacokinetics of GDC-0449.1 following single intravenous bolus administration or oral administration to male beagle dogs
07-1366	Pharmacokinetics of GDC-0449.1 following intravenous oral administration as a 25 mg dose in the presence or absence of

Reference ID: 3071937

	activated charcoal to male beagle dogs
Distribution	
06-0599	In vitro cross-species blood-plasma partitioning study using 14C GDC-0449.1
10-2576	In vitro protein binding determination of GDC-0449 to human a-1 acid glycoprotein (AAG) and human serum albumin (HAS) using micro-equilibrium dialysis device (HTD 96)
Metabolism	
06-0500	Preliminary identification of in vitro and in vivo metabolites of GDC-0449
06-0638	Reaction phenotyping of GDC-0449.21 using human recombinant cytochrome P450
07-1010a	Metabolite profiling and identification of 14C GDC-0449.1 in rat plasma, urine, feces, and bile
09-0830	Metabolite radioprofiling and identification in plasma, bile, urine, and feces from dogs following oral administration of 14C GDC-0449
Excretion	
06-0261	Determination of radiolabeled mass balance, routes of excretion, and metabolic profiles of 14C GDC-0449
08-0768	Assessments of rat and human hepatic uptake and biliary excretion of GDC-0449 in vitro using sandwich-cultured hepatocytes (B-CLEAR)
09-0357	A study to evaluate the pharmacokinetics, excretion, and metabolism of 14 C-GDC-0449 in intact and bile duct cannulated dogs after a single oral administration
Nonclinical pharmacokinetic drug interactions	
05-1528	In vitro analysis of GDC-0449.1 inhibition of cytochrome P450 enzyme, calculation of IC<50> and determination of time dependent inhibition of CYP3A4/5
08-1880	MDR1-MDCK permeability
08-1983	CYP450 K<i> and mechanism of inhibition, GDC-0449.1-38
08-1984	CYP450 inhibition – IC<50>
08-1985	Evaluation of cytochrome P450 induction potential by GDC-0449.1 using human cryopreserved hepatocytes for IC50 determination
09-0054	PXR competitive binding TR-FRET assay of GDC-0449 for IC50 determination
09-0806	BCRP substrate and inhibitor assessment of customer test compound, GDC-0449.1 in appropriate cell monolayer systems
09-2611	Inhibitory potential of GDC-0449 and G-025698 in MDCKII-BCRP monolayer and parental control
Single-dose studies	
05-0598-1604	Pilot oral gavage dose range-finding toxicity and toxicokinetic study of GDC-0449.1 in dogs
05-1454	A single-dose oral gavage toxicity study with GDC-0449.1 in mice
05-1455	A single dose oral gavage toxicity study with GDC-0449.1 in rats

Reference ID: 3071937

Repeat-dose studies	
05-0479	5-day pilot toxicity study for GDC-0449.1 in Sprague-Dawley rats following daily oral dosing
05-0943	14-day pilot toxicity study of a hedgehog antagonist (GDC-0449) in male and female SD rats following daily oral dosing and a 14-day recovery period
05-1061	A 7-day oral gavage toxicity study of GDC-0449.1 in beagle dogs followed by a 7-day recovery period
Safety Pharmacology Studies	
04-1008-1791	Hit profiling screen data report

3.3 Previous Reviews Referenced

Two non clinical pharmacology/toxicology reviews were used as reference to this NDA submission:

1) IND 74,573 non clinical pharmacology/toxicology review by Dr. P. Myers, dated 10/20/06
2) IND 103 846, non clinical pharmacology/toxicology review by Dr. Margaret Brower, dated November 10, 2008.

Below is an "overall summary and drug history" as cited from Dr. Brower's review:

"Starting dose of GDC-0449 for IND 74 573 was daily dose of 900 mg/m^2 for 28 days, for the treatment of locally advanced or metastatic tumors in adults. Neurotoxicity, body and limb tremors, axonal degeneration, was observed in the 4-week pivotal rat study, together with decreased motor activity, and grip strength at doses of 900 and 3000 mg/m^2/day. Non-recoverable necrosis and degeneration of the teeth and bones of the upper incisors were also observed at doses of > 300 mg/m^2. The same findings were lacked in dog observations, although degeneration of the male reproductive tract was indicated.
In vitro studies suggested that GDC-0449 may be associated with a risk for delayed ventricular repolarization and prolongation of QT; with the exception of mild QTc prolongation in one pilot study, these findings were not observed in 28 day studies."

OVERALL SUMMARY:
Previous clinical studies have identified a Phase 2 dose of 150mg/day(D) (92.5mg/m^2) GDC-0449. In addition, a single pediatric patient has been administered the drug at daily doses of 62.5mg/m^2 for a 28D cycle. The proposed dose for the current pediatric study is 85mg/m2/day for a continuous 28D cycle duration up to 13 cycles. Clinical signs of neurotoxicity in treated patients included anxiety, dyspnea, and confusion. CNS and peripheral neurotoxicity was observed in rodents administered GDC-0449 for 28D. In addition, necrosis and degradation of the teeth and bones of the upper incisors were observed at doses of ≥300mg/m^2 through recovery in rodents. The single pediatric patient experienced headache and anxiety following dosing.

Reference ID: 3071937

Published studies in 10-14 day old mice administered a hedgehog pathway inhibitor (Kimura, H. et al. Cancer Cell. 2008, Mar; 13(3):249-60) resulted in permanent defects in bone growth. In a separate publication, Tavella, S. et al. J Bone Miner Res. 2004, Oct; 19(10):1678-88) noted that craniorachischisis and skeletal defects in ribs, sternum, and long bones were observed following overexpression of human sonic hedgehog (SHH) in chondrocytes of transgenic mouse embryos.
Based on disease severity of the pediatric patient population (recurrent/refractory medulloblastoma), and previous clinical administration in adults and a medulloblastoma pediatric patient, the study was reviewed as "may proceed at the proposed dose". However, data on neurotoxicity, dental bone necrosis, and long bone defects in rodents should be included in the Patient's Informed Consent.
In addition, pediatric patients should be monitored for signs of CNS/peripheral neurotoxicity, and bone defects.

4 Pharmacology

4.1 Primary Pharmacology

Vismodegib binds to and inhibits smoothened (Smo), a 7-transmembrane protein that is a part of the hedgehog (Hh) signaling pathway[2]. Secreted proteins of the Hh family are evolutionary conserved and frequently reported in the literature. An essential morphogen[3], hedgehog is expressed during embryogenesis when it is critical in forming dorsal-ventral patterning. In adult tissues, Hh modulate homeostasis mechanisms either by genetic or epigenetic[4] inactivation of the hedgehog pathway, or components of the pathway receptors, such us patched and/or smoothened. A study by Yauch et al, showed that a heterozygous mutation in Smo, D473H (Asp to His substitution at amino acid position 473), located in the central binding cavity of the protein, was necessary for vismodegib to inhibit Smo[5] activity. Specifically, ^{14}C-labeled vismodegib bound *in vitro* to human embryonic kidney–293 cells transfected with SMO WT, but did not show specific binding to cells transfected with a control vector or SMO-D473H. This finding was supported by a mouse model with medulloblastoma allografts in which the D477G

[2] Yauch, R.L., G.J.P. Dijkgraaf, B. Alicke, T. Januario, C.P. Ahn, T. Holcomb, H. Pujara, J. Stinson, C.A. Callahan, T. Tang, J.F. Bazan, Z. Kan, S. Seshagiri, C.L. Hann, S.E. Gould, J.A. Low, C.M. Rudin, F.J. de Sauvage (2009), Science, 326:572

[3] Morphogen is a protein that controls pattern formation by emanating from a localized source and creating a concentration gradient that regulates cell fate (proliferation, survival or differentiation) depending on the cell's position in the gradient (Crompton, T. Outram S.V, Hager-Theodorides A.L. (2007), Nature Reviews Immunology, 7:726

[4] Epigenetics is the study of heritable chages in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. Examples might ebbe DNA methylation or histone deacetylation, both suppresses gene expression without altering DNA sequence of the silenced gene.

[5] Yauch, R.L.; G.J.P. Dijkgraaf; B. Alicke;T. Januario;C.P. Ahn; T. Holcomb; K. Pujara; J. Stinson; C.A. Callahan; T.Tang; J.F. Bazan; Z. Kan; S. Seshagiri; C. H. Hann, S.E. Gould; J. A. Low; C. M. Rudin; F. J. deSauvage (2009) Science, 326:572

Reference ID: 3071937

mutation, homologous to position 473 of the human Smo protein, was sufficient to confer resistance to Hh pathway inhibition by vismodegib.

Regulation of the hedgehog pathway in early embryogenesis, specifically in stem cell function and tissue patterning, is balanced by a critical threshold level of Hh pathway accumulated signaling. The differences in the level of the Hh signal are often measured by Gli 1 expression rate or the potency of Patched (Ptc) inhibition of Smo activity. Binary analysis of this network, done by Lai, Robertson and Schaffer[6], showed that an increase in Gli 1 expression or decrease in the potency of Ptc inhibition of Smo leads to an irreversible switch, where once the Hh signaling network is turned on, it is incapable of accessing the off state again. Therefore, the system results in an irreversible state of cell proliferation. It has been hypothesized that colorectal and pancreatic cancer are the results of paracrine signaling, which originate between the tumor and surrounding stroma that supports tumor growth and ligand-dependent activation of the Hh signaling pathway. Additionally, hedgehog pathway activation within the tumor epithelium has been documented in human tumors, such us medulloblastoma and basal cell carcinoma[7] . Subsequent studies in mice[7] with allografted human tumors showed that Hh exhibits' stromal and paracrine signaling and that vismodegib was capable of suppressing both of these signaling mechanisms.

A naturally occurring Smo antagonist, cyclopamine, has been shown to cause teratogenic effects in lambs; specifically cephalic defects including cyclopia in the most severe cases[8].

05-1039 D **Determination of the Minimum Efficacious Dose of GDC-0449.23 in LS180 Human Colorectal Carcinoma Xenograft Model: Efficacy and PK/PD**

Experiment was performed with GDC-0449.23-17 (hydrochloride salt of GDC-0449.1, Lot 17) and a vehicle consisting of 0.5% methylcellulose/0.2% Tween-80 was used as a negative control.
GDC-0449 was administered on a twice daily schedule at decreasing dose levels. The maximum inhibition of LS180 colorectal cancer xenograft growth was observed with 75 mg/kg twice daily (60.2% inhibition, as seen on the Figure 1; excerpted from sponsor's submission), similar to the 50% inhibition using 100 mg/kg twice daily.
Both 75 and 100 mg/kg twice daily dosing caused significant inhibition compared with the vehicle at Day 18, while 25 and 50 mg/kg twice daily doses did not show the same inhibitory potential.

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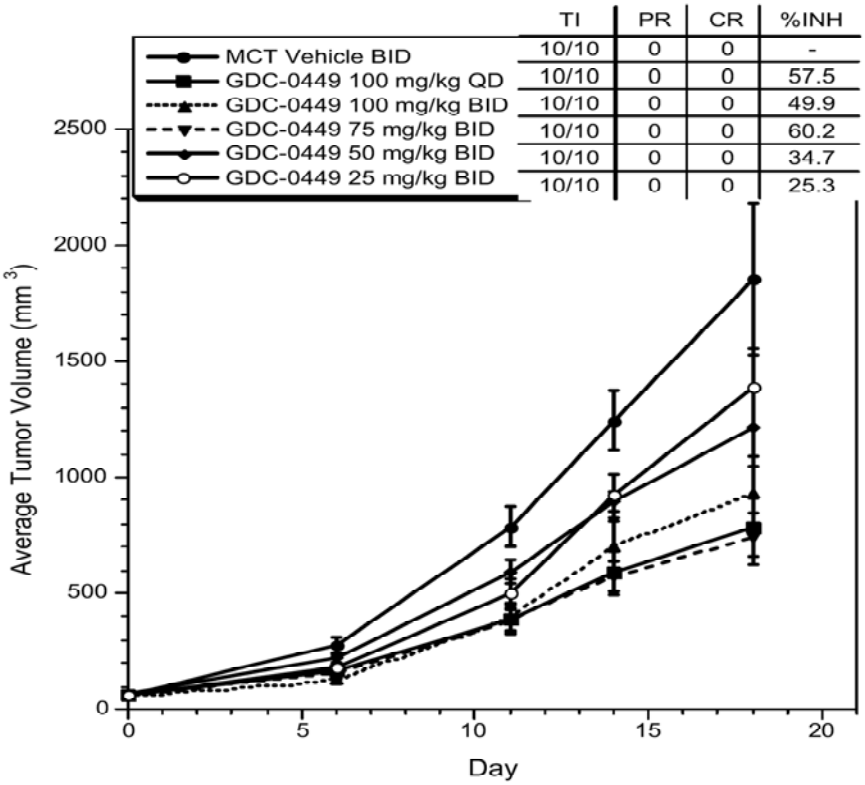
[6] Lai, K., M.J. Robertson, D.V. Schaffer 2004; Biophysical Journal (86): 2748

[7] Yauch, R.L., S.E. Gould, S.J. Scales, T. Tang, H. Tian, C.P. Ahn, D. Marshall, L. Fu, T. Januario, D. Kallop, M. Nannini-Pepe, K. Kotkow, J.C. Marsters, Jr., L.L. Rubin, F.J. de Sauvage (2008) Nature (455):406

[8] Chen, J.K., J. Taipale, M.K. Cooper, P.A. Beachy (2002), Genes and Development (16):2743

Reference ID: 3071937

Figure 1: GDC-0449 delayed the growth of LS180 CRC xenografts subcutaneously implanted in nude mice



BID=twice a day; CR=complete regression; % INH=percent of tumor inhibition; MCT=0.5% methylcellulose/0.2% Tween-80; PR=partial regression; QD=once a day; TI=tumor incidence.

The figure depicts oral dosing of GDC-0449 QD (Group 2) and BID (Groups 3, 4, 5,and 6) for 18 days.

(figure excerpted from Applicant's package)

06-0636 **Evaluation of GDC-0449.23 Inhibition of Hh Signaling in Cellular GLI−Luciferase Reporter Assays**

Testing material in this experiment was hydrochloride salt of GDC-0449.1, Lots 8, 9, 10, 14, and 15.

The IC_{50} values of GDC-0449 are presented in Table 1. GDC-0449 inhibited hedgehog (Hh)-mediated transcriptional activation of the Luc reporter gene in the Hh-responsive cell lines S12 GLI−Luc and HEPM GLI−Luc at IC_{50} values of 12.7 and 2.8 nM, respectively. GDC-0449 did not inhibit transcription of the Luc reporter gene in the control cell lines S12 SV40–Luc or HEK293 NFκB–Luc.

Table 3: Activity of GDC-0449 in Luc reporter cells

GDC-0449 Lot No.	S12 GLI–Luc IC_{50} (μM)	HEPM GLI–Luc IC_{50} (μM)	S12 SV40–Luc IC_{50} (μM)	HEK293 NFκB–Luc IC_{50} (μM)
8	0.00627	0.0026	NM	NM
9	0.00601	0.0023	>50	>50
10	0.0687	0.0036	NM	NM
14	0.032	NM	NM	NM
15	0.013	NM	NM	NM
Mean	0.0127	0.0028	—	—
SD	0.0109	0.00072	—	—

IC_{50}=the concentration of GDC-0449 that resulted in 50% inhibition of activity; Luc=luciferase; NM=not measured; SD=standard deviation.

(table excerpted from Applicant's package)

This experiment shows that GDC-0449 is an inhibitor of Hh signaling in human and murine cell lines, with mean IC_{50} values ranging from 2.8 to 12.7 nM. GDC-0449 inhibited Hh pathway but not TNFα and SV40-mediated transcription (IC_{50}: >50 μM).

09-0633 **Characterization of the Pharmacokinetic/Pharmacodynamic Dose Response of the Hedgehog Pathway Antagonist GDC-0449 in Subcutaneous *Ptch1*$^{+/}$, *p53*$^{+/+}$ Murine Medulloblastoma Allograft in Female CD-1 Nude Mice**

Test material**:** GDC-0449.23-22 (HCl salt of GDC-0449, Lot 22).

Female CD-1 nude mice were injected subcutaneously with 5 × 106 *Ptch1*$^{+/-}$ murine medulloblastoma cells in a volume of 0.1 mL in the right lateral thorax. Mice with tumors in the range of 300−1000 mm^3 were divided into four groups of 21 mice each and given either MCT or vismodegib at 1, 10, or 50 mg/kg. Three animals in each group were euthanized and then, plasma and tumor samples were collected at 2, 4, 8, 12, 16, 24, and 32 hours following drug administration. Two hours following dosing, average vismodegib concentrations in plasma were 0.097, 2.99, and 13.3 μM in the 1, 10, and 50 mg/kg dose groups, respectively (see Table 4: Plasma concentration of vismodegib after a single oral dose of 1, 10, or 50 mg/kg (Study 09-0633)Table 4).
Plasma concentrations of vismodegib were below the lower limit of quantitation (LLOQ) in all animals from both the 1 and 10 mg/kg dose groups by 12 and 16 hours post-dosing, respectively. Dosing at 50 mg/kg resulted in peak plasma concentrations of vismodegib that persisted at approximately the same levels for 8 hours and then decreased to less than the LLOQ by 32 hours (Please see Table 4).

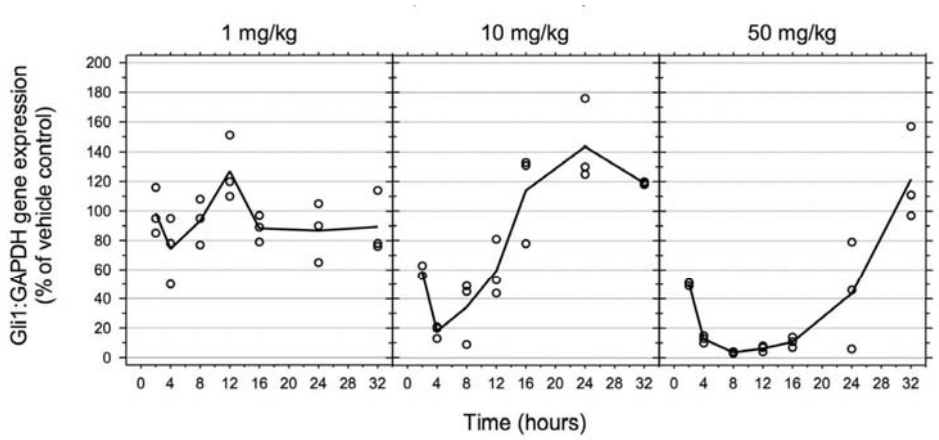
Table 4: Plasma concentration of vismodegib after a single oral dose of 1, 10, or 50 mg/kg (Study 09-0633)

	Dose (mg/kg) [a, b]		
Time (hr)	1	10	50
2	0.097 ± 0.038	2.990 ± 1.467	13.300 ± 2.606
4	0.037 ± 0.014	1.009 ± 0.237	7.760 ± 0.269
8	0.006 ± 0.007	0.392 ± 0.069	11.843 ± 5.821
12	< LLOQ [c]	< LLOQ [c]	3.170 ± 1.581
16	< LLOQ [c]	< LLOQ [c]	1.250 ± 0.331
24	< LLOQ [c]	< LLOQ [c]	0.478 ± 0.679
32	< LLOQ [c]	< LLOQ [c]	< LLOQ [c]

[a] Doses are expressed as free-base equivalents.
[b] Plasma concentrations represent mean ± SEM for n = 3 group.
[c] The lower limit of quantitation (LLOQ) was 0.0023 μM for some samples and 0.0475 μM for others. Mean and SEM were not calculated for a group if the plasma level for at least one mouse was < LLOQ.

The PD effect of vismodegib was assessed by assaying *Gli1* mRNA levels and plotting them in relation to the housekeeping gene *GAPDH* relative to control-treated samples. Figure 2, below, shows Gli1 expression levels in response to time and three different concentrations of GDC-0449.

Figure 2: Gli1 gene expression over time by dose



Notes: Trellis plot of *Gli1* gene expression levels (relative to *GAPDH* and expressed as a percentage of vehicle control) in individual subcutaneous *Ptch1*$^{+/-}$ murine medulloblastoma allografts following a single oral dose of GDC-0449 by gavage at 1, 10, or 50 mg/kg. Tumors were collected from 3 animals at 2, 4, 8, 12, 16, 24, and 32 hours postdosing for each dose group. Open circles indicate individual values. Solid black lines connect the mean at each timepoint.

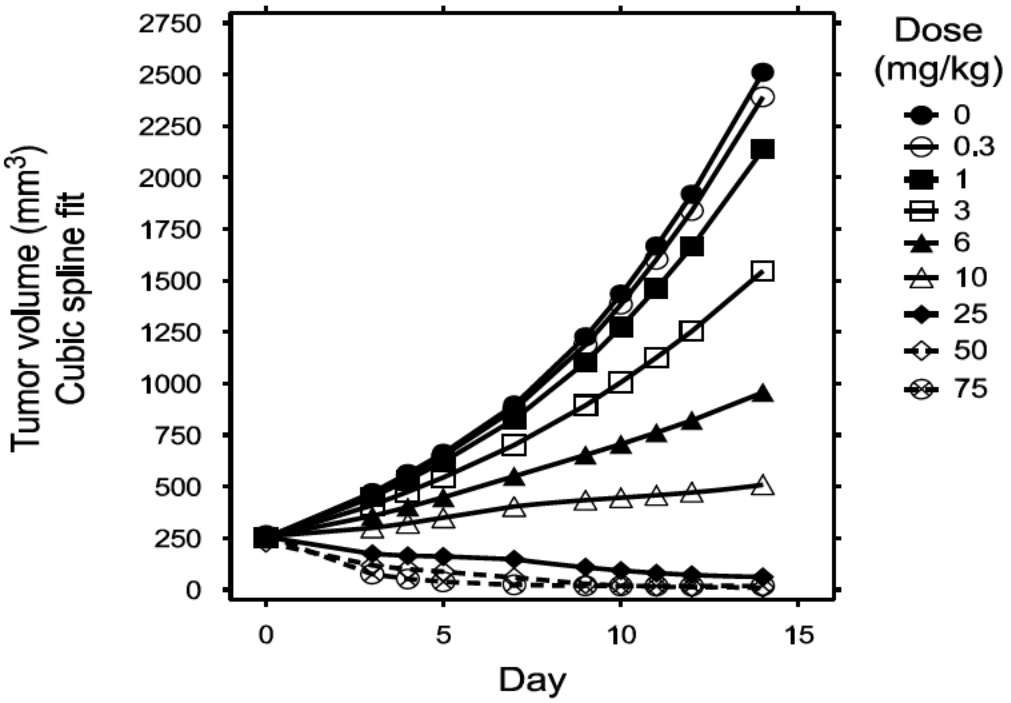
(excerpted from Applicant's package)

Gli1 expression levels varied in response to vismodegib by time and dose. In the 1 mg/kg dose group, there was significant variability in *Gli1* expression levels and no clear effect of vismodegib administration. In the 10 mg/kg dose group, *Gli1* expression levels were reduced to 60% of control by 2 hours, decreased to as low as 20% by 4 hours, and rebounded to roughly control values by 16 hours following vismodegib administration. The decrease in *Gli1* expression levels was most pronounced and exhibited the longest duration in response to 50 mg/kg vismodegib. *Gli1* expression levels were at 50% by 2 hours, < 5% by 8 hours, and returned to control levels by 32 hours. Correlation between vismodegib concentrations in plasma and *Gli1* levels in tumor was noted. Maximal repression of the Hh pathway was observed at vismodegib plasma concentrations greater than 1 mM.

09-2968 **Dose Escalation Study of GDC-0449 in Subcutaneous *Ptch1*$^{+/-}$, *p53*$^{+/+}$ Murine Medulloblastoma Allografts**

The growth of subcutaneous Ptch1$^{+/-}$, p53$^{+/+}$ murine medulloblastoma allografts were evaluated in female CD-1 nude mice when GDC-0449 was given in a range of doses (as visible in Figure 3):

Figure 3: Effect of twice-daily oral dose of vismodegib on the growth of Ptch1$^{+/-}$ medulloblastoma allografts



MB = medulloblastoma; 0 mg/kg dose = vehicle.
Cubic spline fits of tumor volumes after twice daily PO administration of vismodegib for 14 days are depicted by dose group. Doses are expressed as free-base equivalents in mg/kg BID (10 mg/kg BID = 20 mg/kg/day).

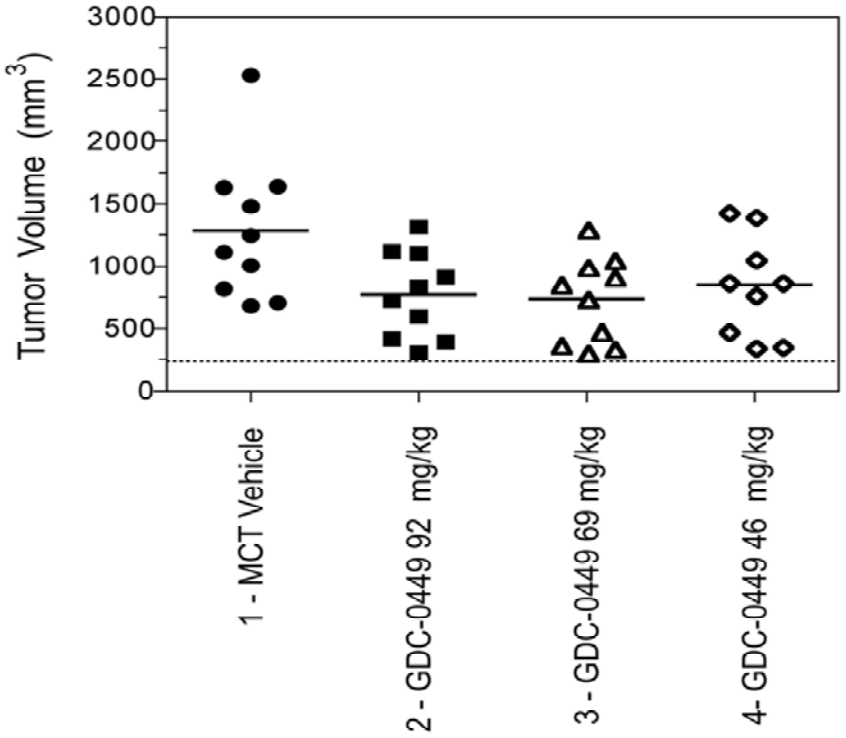
(Excerpted from Applicant's package)

GDC-0449 had shown anti-tumor activity in this animal model. Tumor stasis (calculated by formula that results with a percentage of tumor growth inhibition values as being the percentage of the area under the curve (AUC) on the linear scale for the specific dose group (daily) in relation to the vehicle) was estimated to occur at 15.6 mg/kg, while ED_{50} was calculated to 5.8 mg/k, and an ED_{90} of 29 mg/kg.

D5123-05-04 **Determination of the Minimum Effective Dose of GDC-0449 to Inhibit the Growth of Subcutaneous D5123 Primary Colorectal Carcinoma Xenografts**
TEST MATERIALS: Active: GDC-0449.23-9 (hydrochloride salt of GDC-0449, Lot 9)
Vehicle: 0.5% methylcellulose, 0.2% Tween-80.

Figure 4, below shows data points of measured individual tumor volume at day 18, while solid lines represent mean tumor volume for each group on day 18.

Figure 4: Tumor volume at end of study (Day 18)



(figure excerpted from Applicant's package)

Maximum repression of Hh signaling in tumors occurred 6 hours after oral administration of GDC-0449. The minimum dose of GDC-0449 that results in maximum Hh pathway suppression in tumors is 69 mg/kg. This is also a dose that results in maximum inhibition of tumor growth rates in D5123 tumor-bearing mice.

4.2 Secondary Pharmacology

06-0690 **Pharmacokinetic (PK) and Pharmacodynamic (PD) Study Using vismodegib (GDC-0449) to Determine the Role of Hedgehog Signaling in Hair Follicle Morphogenesis in Female C57Bl/6 Mice**

Oral administration of 100 mg/kg vismodegib twice daily for five total doses during anagen hair follicle phase resulted in significant suppression of mouse *Gli1* RNA in hair follicles and skin biopsies harvested 4 hours after the final dose on day 3. A 9.3-fold reduction in *Gli1* expression was detected during anagen phase, while 3.6-fold reduction was noted in telogen phase of mouse skin. *Gli1* was repressed similarly

during telogen and anagen in hair follicles (1.5-fold). Drug exposure was measured at 93.8 µM and 140.4 µM for anagen and telogen mice, respectively. The relative expression of *Gli1* and vismodegib plasma levels is summarized in Table 5 and Table 6.

Table 5: Relative expression of mouse Gli1 in hair follicles and vismodegib levels in plasma four hours post-dose

Group (n=4)	Age (weeks)	Test Material	Gli1	Change vs. Vehicle	Vismodegib Plasma Conc. (∝M) [a]	p-Value [b]
1	4	MCT vehicle	79±3.7	|	|	|
2	4	Vismodegib (100 mg/kg)	53.9±8.4	1.5-fold	93.8±17.7	0.034
4	7	MCT vehicle	78.9±12.2	|	|	|
5	7	Vismodegib (100 mg/kg)	52.5±10.3	1.5-fold	140.4±20.7	0.149

Conc.=concentration; MCT=methylcellulose with Tween-80.

[a] Plasma concentrations were determined 4 hours after the fifth dose of twice daily dosing (Day 3).

[b] The p-value was calculated versus MCT vehicle using a two-tailed Student t test.

Table 6: Relative expression of mouse Gli1 in skin and vismodegib levels in plasma four hours post-dose

Group (n=4)	Age (weeks)	Test Material	Gli1	Change vs. Vehicle	Vismodegib Plasma Conc. (∝M) [a]	p-Value [b]
1	4	MCT vehicle	33.6±2.9	|	|	|
2	4	Vismodegib (100 mg/kg)	3.6±0.8	9.3-fold	93.8±17.7	0.00006
4	7	MCT vehicle	14.8±1.8	|	|	|
5	7	Vismodegib (100 mg/kg)	4.1±0.7	3.6-fold	140.4±20.7	0.0014

Conc.=concentration; MCT=methylcellulose with Tween-80.

[a] Plasma concentrations were determined 4 hours after the fifth dose of twice daily dosing (Day 3).

[b] The p-value was calculated versus MCT vehicle using a two-tailed Student t test.

(tables excerpted from Applicant's package)

Increased inhibitory activity of GDC-0449, as measured by a decrease in mouse Gli1 expression in hair follicles and skin biopsies, was detected during the anagen base of the hair cycle of the skin biopsies.

Based on the sponsor's conclusions, this particular assay has been noted as a potentially useful pharmacodynamic assay for assessing vismodegib activity in skin biopsies.

4.3 Safety Pharmacology

04-1278-1791 **Lead Profiling Screen Data Report**

In this *in vitro*, non-GLP, receptor binding assay, vismodegib was evaluated for its ability to inhibit radioligand binding of a panel of 43 receptors (isolated from recombinant and non-recombinant cells) identified as potential mediators of unintended pharmacologic activity. The levels of radioligand binding in the presence of vismodegib were denoted in the following Table 7:

Reference ID: 3071937

Table 7: Receptor binding assay

PT#: 1052374
CODE: GEN-365, G-25897.23-10

December 30, 2004 7:07 AM
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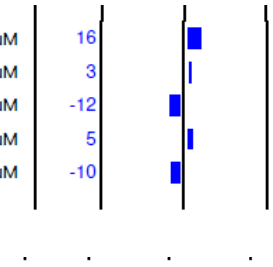
EXPERIMENTAL RESULTS - BIOCHEMICAL ASSAYS

Cat. #	TARGET	BATCH*	SPP.	n=	CONC.	†% INHIBITION % (-100 -50 0 50 100)	IC_{50}	K_I	n_H	R
200720	Adenosine A_3	125643	hum	2	10 μM	6				
203400	Adrenergic α_{1D}	125607	hum	2	10 μM	7				
212510	Bradykinin B_1	125472	hum	2	10 μM	10				
212610	Bradykinin B_2	125473	hum	2	10 μM	-3				
214510	Calcium Channel L-Type, Benzothiazepine	125650	rat	2	10 μM	5				
216000	Calcium Channel N-Type	125652	rat	2	10 μM	7				
219800	Dopamine D_3	125616	hum	2	10 μM	-2				
219900	Dopamine $D_{4.2}$	125617	hum	2	10 μM	30				
224010	Endothelin ET_A	125654	hum	2	10 μM	0				
224110	Endothelin ET_B	125655	hum	2	10 μM	-2				
225500	Epidermal Growth Factor (EGF)	125656	hum	2	10 μM	-2				
226010	Estrogen ERα	125480	hum	2	10 μM	2				
228510	$GABA_B$, Non-Selective	125620	rat	2	10 μM	4				
232010	Glucocorticoid	125660	hum	2	10 μM	-13				
232700	Glutamate, Kainate	125570	rat	2	10 μM	-2				
232810	Glutamate, NMDA, Agonism	125571	rat	2	10 μM	5				
232910	Glutamate, NMDA, Glycine	125572	rat	2	10 μM	-12				
239710	Histamine H_2	125662	hum	2	10 μM	1				
239810	Histamine H_3	125663	hum	2	10 μM	-10				
243510	Interleukin IL-1	125665	mouse	2	10 μM	6				
250460	Leukotriene, Cysteinyl $CysLT_1$	125575	hum	2	10 μM	27				
252600	Muscarinic M_1	125522	hum	2	10 μM	-10				
257010	Neuropeptide Y_1	125667	hum	2	10 μM	1				
257110	Neuropeptide Y_2	125668	hum	2	10 μM	7				
260110	Opiate δ (OP1, DOP)	125624	hum	2	10 μM	19				
260210	Opiate κ (OP2, KOP)	125625	hum	2	10 μM	-3				
265010	Platelet Activating Factor (PAF)	125627	hum	2	10 μM	6				
268700	Purinergic P_{2X}	125485	rabbit	2	10 μM	-6				
268810	Purinergic P_{2Y}	125486	rat	2	10 μM	-7				
271110	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1A}$	125527	hum	2	10 μM	37				
271910	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_3$	125531	hum	2	10 μM	-5				

255510	Tachykinin NK_1	125621	hum	2	10 µM	16
285010	Testosterone	125676	rat	2	10 µM	3
220320	Transporter, Dopamine (DAT)	125648	hum	2	10 µM	-12
226400	Transporter, GABA	125568	rat	2	10 µM	5
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	125649	hum	2	10 µM	-10



* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.
♦ Denotes item meeting criteria for significance
† Results with ≥ 50% stimulation or inhibition are highlighted. (Negative values correspond to stimulation of binding or enzyme activity)
R=Additional Comments
hum=human

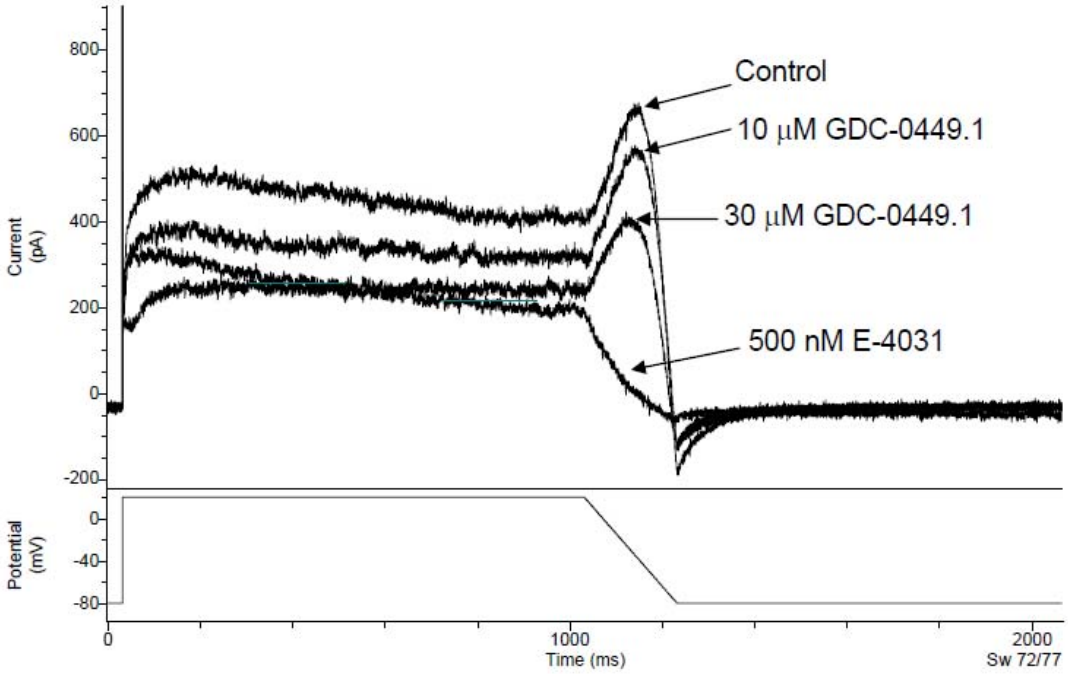
(table excerpted from Applicant's package)

These results show that a concentration of 9.2 µM of vismodegib did not have a biologically significant effect on radioligand binding to any of the off-target receptors tested.

05-0606 **Effects of GDC-0449.1 on Cloned hERG Potassium Channels Expressed in Mammalian Cells**

Four concentrations of vismodegib were used to measure inhibition of Human Ether-a-go-go Related Gene, 3, 10, 30 and 80 µM (potassium channels in voltage-clamped human embryonic kidney cells, HEK293). Typical hERG potassium current traces are seen in Figure 5 below:

Figure 5: Typical hERG potassium current traces



Upper panel [Current (pA); Time (ms)] shows superimposed, records of hERG potassium currents obtained in a single cell during application of control, test article and reference substance. HERG potassium currents were evoked by the voltage protocol shown in the lower panel [Voltage (mV)]. Cell ID: E 4 KMS 060413_0000.abf.

(figure excerpted from Applicant's package)

GDC-0449.1 at 3, 10, 30 and 80 μM inhibited hERG potassium current by ~ 4.9; ~14.4; ~ 40 and ~77%, respectively, while 60 nM terfenadine, used here as a positive control, inhibited hERG potassium current by ~71.8%. The IC_{50} for hERG inhibition by GDC-0449.1 was > 30 μM, which makes GDC-0449.1 a low-potency blocker. All concentrations of GDC-0449.1 used in the experiment were within 15% of nominal formulations, thereby the experiment meet the acceptance criteria.

05-1458 **A Oral Gavage Cardiovascular Safety Pharmacology Study of GDC-0449.1 in Conscious Beagle Dogs (GLP study)**

GDC-0449.1 was found not to have toxicologically-relevant effect on the cardiovascular system on four male and four female dogs given 600 or 2000 mg/kg vismodegib by gavage.

Electrocardiograph results show that there were no substantial changes between control and vismodegib-administered animals in blood pressure measurements including heart rate, systolic, diastolic and mean arterial pressure and systolic-diastolic pulse pressure, or on body temperatures. All animals were placed back to their respective colonies when the experiment ended.

5 Pharmacokinetics/ADME/Toxicokinetics

A summary of the results obtained from pharmacokinetic studies is provided in this section.

Absorption

Study # 05-0547	Mice plasma clearance (PC) is 23.0 mL/min/kg, based on <25% of hepatic blood flow
Study # 05-0657	Rats PC is 4.65 mL/min/kg,
Study # 05-1405	Dogs PC 0.338 mL/min/kg
Study 04-0745	Cynomolgus monkey PC is 19.3 mL/min/kg, approximately 43% of hepatic blood flow

Vismodegib terminal half life ranged from ~1 hour in the mouse to ~41 hours in the dog. The bioavailability ranged from 13% in monkeys to 53% in rat, following oral dosing in 0.5% methylcellulose with 0.2% Tween-80 (MCT). Oral absorption was approximately 42.6% in male and 41.6% in female rats, and approximately 31% in male dogs, as examined from the mass-balance studies.

Vismodegib toxicokinetics was evaluated in female rats to support a GLP dose range-finding study for effects on embryo-fetal development on gestation Days 6 (referred to as study Day 1) and 15 (referred to as study Day 10) at daily PO doses of 10, 60, and 300 mg/kg of vismodegib. Exposure (AUC and C_{max})) increased less than proportional to the increase in dose on study Day 1. On study Day 10, AUC increased greater than dose proportionally in the 60 mg/kg group and less than dose proportionally in the 300 mg/kg/day group. Accumulation was noted in the 60 and 300 mg/kg dose groups. The time to the maximum plasma concentration (t_{max}) was variable and ranged from 1 to 7 hours following dosing.

Similar toxicokinetic parameters were evaluated in dogs administered vismodegib twice daily in repeat-dose GLP studies lasting 28 days, 13 weeks, and 26 weeks. No differences in exposure (AUC and C_{max}) were observed between male and female dogs in these studies. Vismodegib accumulation was observed in dogs as exposures were higher following multiple doses when compared to exposures after a single dose. Less than dose-proportional increases in exposure were observed over the range of doses

Reference ID: 3071937

tested in multiple studies suggesting that vismodegib may exhibit a plateau in its pharmacological activity. The t_{max} was variable in all studies.

Distribution

Vismodegib pharmacokinetics is highly dependent on apha-1-acid glycoprotein (AAG) concentration. *In vitro,* vismodegib was protein-bound in plasma from mice, rats, rabbits, dogs, monkeys, and humans. Vismodegib binds to α1-acid glycoprotein in a concentration-dependent manner. In contrast, binding to human serum albumin was independent of drug concentration but dependent on protein concentrations. Vismodegib did not appear to preferentially distribute to red blood cells, with blood-plasma partition ratios ranging from 0.608 to 0.881 in all species tested.

The *in vitro* plasma protein binding of vismodegib was evaluated by equilibrium dialysis using [$_{14}$C] vismodegib (Study 06-0526). Protein binding was assessed at vismodegib concentrations of 1, 10, and 100 μM in mouse, rat, rabbit, dog, cynomolgus monkey, and human pooled plasma. Vismodegib appeared to be highly protein bound, approximately ~ 95% in all species. Protein binding appeared to have no dependence on concentration in any species over the concentration range tested. The exception was cynomolgus monkey plasma, which appeared to have an approximately 2-fold increase in the unbound fraction (from approximately 3% to 6% between 1 and 100 μM).

An additional tissue-distribution study (08-0915) followed radioactive traces of [$_{14}$C] vismodegib following a single oral administration (2 mg/kg) to male and female pigmented Long Evans rats using quantitative whole-body autoradiography. Drug-derived radioactivity was distributed to tissues through 24 hours. Maximum tissue concentrations for most tissues were at 1 hour post-dose in male and at 4 hours in female rats. The highest concentrations of radioactivity in tissues at t_{max} were found in: liver, eye uvea, adrenal gland, white adipose, Harderian gland, kidney cortex and medulla, aorta, ovary, and small intestine. The highest concentrations of radioactivity at t_{max} were found in the contents of the alimentary canal (21.396–432.881 μg equiv/g), and bile (10.837–45.939 μg equiv/g). Much lower concentrations were found in the urinary bladder contents (3.369–4.131 μg equiv/g), suggesting that biliary excretion was the major route of elimination compared to renal excretion. Radioactivity in the blood was highest at 1 hour post-dose (1.677 and 2.592 μg equiv/g in male and female, respectively). Radioactivity in blood from males was no longer detectable at 24 hours, whereas concentrations in blood from females remained measurable through 144 hours.

The association of [^{14}C] vismodegib-derived radioactivity with melanin-containing tissues appeared to be reversible and was expected to be eliminated if the study had been conducted for a longer time because radioactivity in pigmented skin and uveal tract decreased steadily.

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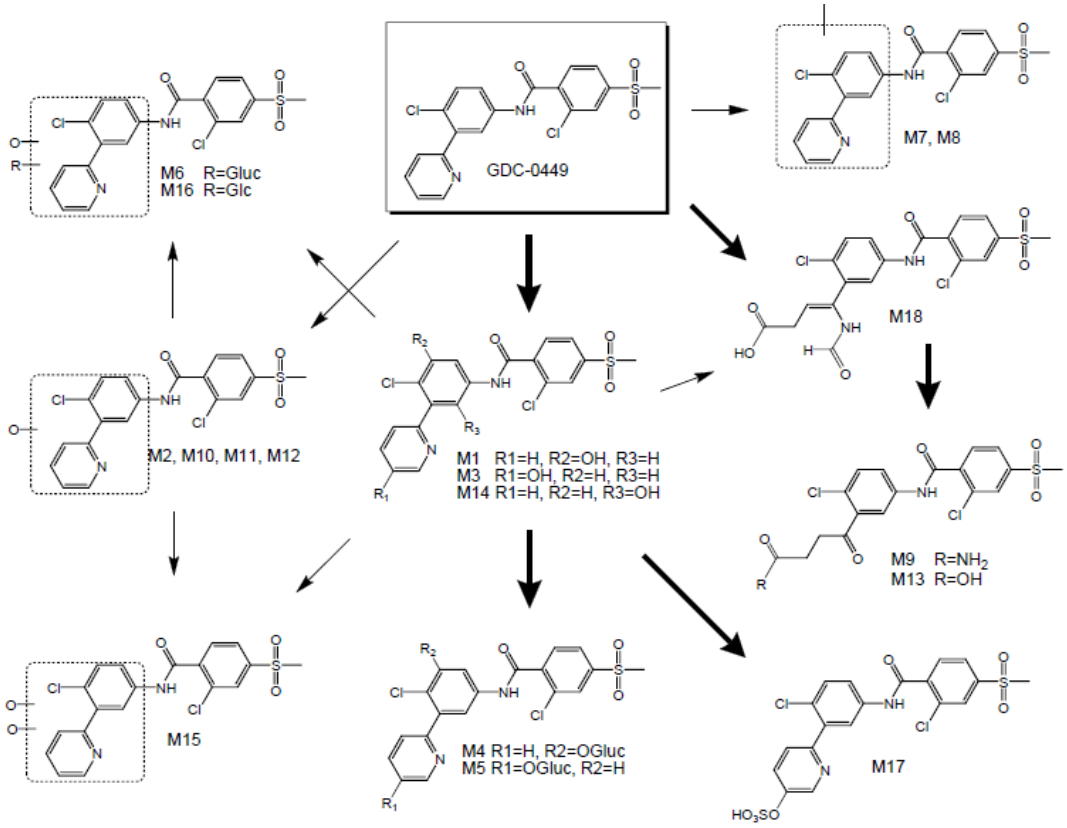
Metabolism

In vitro studies using rat, dog, and human liver microsomes, and *in vivo* studies in rat and dog were used to identify major metabolic pathways for vismodegib. Primary oxidations followed by sequential glucuronidation or sulfation were two major metabolic pathways identified. Major metabolic pathways proposed in either rats or dogs are depicted in the following figure (excerpted from the Applicant's submission):

Figure 6: Proposed metabolic pathways for the biotransformation of vismodegib



(figure excerpted from Applicant's package)

Three additional metabolites were identified from *in vivo* studies that resulted from an uncommon pyridine ring opening. Two minor glutathione (GSH) conjugates were also identified in rat bile, but not in dog bile.

In vitro studies did not identify human-specific metabolites.

Human recombinant P450 isoforms 3A4, 3A5, and 2C9 produced the greatest quantity of the two oxidative metabolites identified in microsomes.

Excretion

Mass-balance studies in rat and dog showed drug-derived radioactivity recovered primarily in feces (~90% and 75.5%, respectively), followed by bile (93% and 83.5%, respectively). In feces, unchanged vismodegib was one of the main components of the drug-derived radioactivity recovered. In contrast, radioactivity recovered in bile was mainly in the form of metabolites. Recovery of drug-derived radioactivity in urine from both species occurred to a lesser extent (< 9% of dose).

Pharmacokinetic drug interactions

Vismodegib was not a potent inhibitor of P450 isoforms 1A2, 2B6, 2C19, 2D6, and 3A4/5 with 50% inhibitory concentration (IC_{50}) values > 15 μM.
The inhibition constant (K_i) for P450s 2C8 and 2C9 were 6.0 and 5.4 μM, respectively. Considering the high degree of plasma protein binding (> 99% *ex vivo* in humans), vismodegib does not appear likely to act as a potent inhibitor of P450s. Vismodegib was not a potent time-dependent inhibitor of P450 3A4/5 activity.

Vismodegib appears to be a P-glycoprotein substrate, but not an inhibitor in MDR1-MDCK cells. Vismodegib does not appear to be a breast cancer resistance protein (BCRP) substrate. In MDCKII-BCRP cells, vismodegib inhibited the efflux ratio of prazosin efflux with an IC_{50} of 2.4 μM. Based upon a high degree of plasma protein binding in patients (> 99%) and the low confirmed clinical occurrence of BCRP-based drug-drug interactions, there is a low likelihood that vismodegib will be a clinically relevant inhibitor of BCRP.

5.2 Toxicokinetics

Toxicokinetic evaluations that were conducted as a part of single or repeat-dose toxicology studies are included as a part of specific reviews of the toxicity studies under Sections 6.1 and 6.2 of this review.

6 General Toxicology

6.1 Single-Dose Toxicity

05-0598-1604 **Pilot Oral Gavage Dose Range-Finding Toxicity and Toxicokinetic Study of GDC-0449.1 in Dogs** (b) (4) (b) (4) (b) (4)

Male beagle dogs were used to evaluate the toxicity of GDC-0449.1 when administered as a single dose via oral gavage for a period of 7 days. Six groups of dogs were observed to assess the reversibility, persistence or delayed occurrence of effects. Number of animals, dose levels and concentrations are depicted in following table:

Reference ID: 3071937

Group	No. of Animals Male	Dose Day	Dose Level (mg/kg)	Dose Concentration (mg/mL)
1	2	1	0	0
2	2	1	75	15
3	2	2	225	45
4	2	3	700	140
5	2	4	1400	280
6 [a]	2	1	2000	400

a Group 6 was added to the study following the observation period for Groups 1 through 4, and, therefore, the first day of dosing for Group 6 animals was designated Day 1 of the dosing phase.

GDC-0449.1 administration-effects included increased (~85%) serum cholesterol in animals given 225 mg/kg, which was greater at 7 days post-dose than at 48 hours post-dose. No lethality occurred. Notable other findings were fluctuations in food consumption, which possibly translated to findings in fluctuation of body weight and body weight gain.

05-1454 **A Single-Dose Oral Gavage Toxicity Study with GDC-0449.1 in Mice**

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

The toxicity of GDC-0449.1 was evaluated in twenty male Crl: CD1 (ICR) mice for a period of 14 days. Four groups of mice received GDC-0449.1 orally, by gavage. The number of animals, dose levels and concentrations are depicted in following table:

Group	No. of Males	Dose Level[b] (mg/kg)	Dose Concentration (mg/mL)
1 (Control)[a]	5	0	0
2 (Low)	5	200	40
3 (Mid)	5	600	120
4 (High)	5	2000	400

a Group 1 received the control article only.
b Dose level (mg/kg) and dose concentration (mg/mL) are expressed as the free base of GDC-0449.1.

Microscopic changes in the kidney were observed at all dose levels of GDC-0449.1 treated mice. Specifically, the finding was noted as “scattered, individual proximal tubules that were minimally to slightly dilated and lined with some hyperplastic epithelium”. There were no additional notable findings described in this study.

05-1455 **A Single-Dose Oral Gavage Toxicity Study with GDC-0449.1 in Rats**

(b) (4)

Twenty male Crl: CD (SD) rats were used to evaluate the toxicity of a single dose of GDC-0449.1 given by oral gavage for a period of 14 days. The number of animals, dose levels and concentrations are depicted in following table:

Group	No. of Males	Dose Level[b] (mg/kg)	Dose Concentration (mg/mL)
1 (Control)[a]	5	0	0
2 (Low)	5	200	40
3 (Mid)	5	600	120
4 (High)	5	2000	400

a Group 1 received the control article only.
b Dose level (mg/kg) and dose concentration (mg/mL) are expressed as the free base of GDC-0449.1

Single-dose evaluation of GDC-0449.1 in rats resulted in minimal signs of toxicity. One animal dosed with 2000 mg/kg of GDC-0449.1 had too few feces, while one additional male dosed 200 mg/kg had one abdominal sore. No other notable observation for this single dose rat study was attributed to GDC-0449 administration.

6.2 Repeat-Dose Toxicity

(This study review is summarized from Dr. Dorothy W. Pease's pharmacology/toxicology review dated August 7, 2006, for IND 074573).

Study title: **A 4-Week Oral Gavage Toxicity Study with GDC-0449.1 in Rats with a 4-Week Recovery Period** [redacted] (b) (4) **Sponsor Study # 05-1456).**

Key Study Findings (as described in the review): Dose dependent decrease in body weight, body and/or limb tremors which increased during recovery period, dental toxicity, dose dependant increase in cholesterol (total, LDL, HDL), dose dependent decrease in ALP, that did not recovered in high dose treated males.

The review follows with: "GDC-0449 is readily absorbed by oral administration and has a relatively short half life in the rodent (~1 hour). Different absorption profiles were observed in dog and monkey studies. The dog has a higher AUC and higher half life (~42 hrs) and the monkey has a smaller AUC and shorter (~0.5 hr) half life. Two metabolites have been identified in studies with human microsomes as well as in animal studies. GDC-0449 did not appear to inhibit any of the major CYP p450 enzymes tested.
The most notable toxicity observed was an increase in body and limb tremors that occurred in rats (but not dogs) and was unexplained. This could be related to CNS or PNS toxicity. It is also possible (but less likely) that it is an effect related to muscle toxicity of the compound. A decrease in motor activity occurred at the high and mid dose as well as a decrease in grip strength, and was observed even during a four-week cessation of the drug treatment.
Other toxicities include dental toxicity in the rodent which was verified by several histopathology indicators. The inhibition of the necrosis and degradation of the teeth and bone of the upper incisor were severe and remained throughout recovery."

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"Serum cholesterol (total, LDL, and HDL) all increased with dose in the rat and the dog. The cholesterol increase appeared to plateau after 2-3 weeks of dosing. After cessation of treatment, levels returned to normal.
Lastly, reproductive toxicity was noted with male reproductive tissues in the dog. Both the testes and epididymis had toxicities associated with decreased development as well as hypospermia."

Based on the summary review above, the potential for adverse effects on bones should be considered if this drug is used in children or other patients with developing bones.

Study title**: A 13 Week Oral Gavage Toxicity Study with GDC-0449.1 in Rats with an 8-Week Recovery Period**

Study no.:	06-1202
Study report location:	Bullet 4. Nonclinical Study Reports of the electronic submission, specifically bullet 4.2.3.2 Repeat-Dose Toxicity
Conducting laboratory and location:	(b) (4)
Date of study initiation:	14 November 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1, Lot P188-10-3, 99.7%

Key Study Findings

- Substantial body weight loss, hunched and thin appearance at high dose of 500 mg/kg/day resulted to discontinuation of the dosing and sacrifice.
- Malocclusion in 50 mg/kg/day males and 150 mg/kg/day females; missing incisors in 150 mg/kg/day males and 500 mg/kg/day females.
- Tremors and/or leg twitching in all animals; reversible.
- Increased total and HDL-cholesterol and decreased alkaline phosphatase activity in high-dose rats; reversible.
- Histopathologic effects on teeth in ≥ 50 mg/kg/day animals.
- The no-observable-adverse-effect level under the conditions of this study is 10 mg/kg/day, which corresponded to group mean C_{max} and AUC values of 3190 ng/mL and 37600 ng·hr/mL, respectively.

Methods

Doses:	0, 5, 25, 75, 250 mg/kg/dose; 0 (control), 10 (Low), 50 (Mid), 150 (Mid-High), and 500 (High) mg/kg/day
Frequency of dosing:	Twice-daily
Route of administration:	Oral Gavage

Reference ID: 3071937

Dose volume:	5 mL/kg
Formulation/Vehicle:	GDC-0449.1 in vehicle: 0.5% (w/v) Hydroxypropyl methylcellulose (Dow Chemicals Methocel K100 premium LV) and 0.2% (v/v) polysorbate 80 [Tween 80 (Spectrum)] in reverse osmosis (RO) water
Species/Strain:	Sprague Dawley Rat
Number/Sex/Group:	15/sex/group; 6/sex/group for toxicokinetic assessment
Age:	46 to 52 days old
Weight:	Not mentioned
Satellite groups:	Toxicokinetic group
Unique study design:	Male reproductive assessment
Deviation from study protocol:	Some study deviations were noted, but found to not compromise the integrity of the study

Observations and Results

Mortality

10 /15 males and 9/15 females given the high dose of 500 mg/kg/day resulted to discontinuation of the dosing on Study day 44. These animals were euthanized on Study day 51, after a week-long observation period. Microscopic pathology evaluations of these animals did not reveal the cause of death. General debilitation was observed in two additional males that were administered 150 mg/kg/day of GDC-0449, which were necropsied on study day 67 and 71. Microscopic assessment did not reveal the cause of moribundancy.

Clinical Signs

The high dose given animals had hunched and thin appearance, clear oral discharge, and rough haircoat. Dose-related, and irreversible (except for the lowest dose tested) teeth toxicities were observed in most study animals. An increased incidence of malocclusion was noted for males and females administered 50 or 150 mg/kg/day.

Missing incisors were noted for 150 or 500 mg/kg/day animals and 50 mg/kg/day females. Reversible, neurological signs such us leg-twitching and body and limb tremors were observed in animals administered 50 or 150 mg/kg/day and to the lesser extent in animals administered 500 mg/kg/day, in which dosing was discontinued on study day 44.

Body Weights and Feed Consumption

Severe body weight loss in animals administered 500 mg/kg/day (main study and toxicokinetic animals) resulted in discontinuation of the dosing on study day 44, or 45

Reference ID: 3071937

respectively. Decreases in mean body weights, body weight gains, and food consumption were observed in animals administered 150 mg/kg/day. Mean food consumption for treated female groups was comparable with that of control animals. Mean food consumption was decreased during the recovery phase for males and females administered 150 or 500 mg/kg/day vismodegib. This finding possibly corresponds to the test article-related decreases in mean body weight and body weight gains.

Ophthalmoscopy

No test article-related ophthalmic findings were noted.

Hematology, Urinalysis

No test article-related findings were noted.

Clinical Chemistry

Minimally to mildly increased total cholesterol and high-density lipoprotein (HDL) cholesterol was noted in animals administered 500 mg/kg/day. Minimally to mildly lower alkaline phosphatase activity was noted in animals administered 500 mg/kg/day and males administered 150 mg/kg/day of vismodegib.

Gross Pathology, Organ Weights

No test article-related findings were noted.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

Toxicologically relevant test article-related effects were seen in the upper incisor teeth of male and female rats at dose levels of 50, 150, and 500 mg/kg/day. Microscopic changes consisted of loss/atrophy of odontoblasts and ameloblasts, degradation of dentin with scattered sequestra, formation of fluid-filled cysts in the dental pulp, hyperplasia of the periodontal ligament, ossification of the root canal, regeneration of the dental organ, occasional fibrometaplasia, and scattered hemorrhage and subacute inflammation. These changes were generally more pronounced in males, and the primary microscopic changes appeared to be centered on the odontoblasts, ameloblasts, and dentin, while the other lesions were considered secondary. These changes increased in incidence and severity with increased dose. Odontoblasts appeared more resilient at lower doses. The majority of these changes persisted in

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recovery animals and were generally dose-responsive; fibrometaplasia was more frequent in both main study and recovery males. Ossification of the root canal was occasionally more severe in the recovery animals given 150 mg/kg. Regeneration of the dental organ consisted of normal tooth bud and/or early tooth formation arranged in an orderly progression, with normal-appearing accompanying cellular and acellular components.

A few recovery animals administered 500 mg/kg, which were necropsied after a 14-week recovery period, had substantial regenerative tooth growth, but the severity of secondary space filling changes (i.e., ossification) prevented the regenerative teeth from growing in a normal manner. The findings in the incisor teeth support the clinical sign of malocclusion and likely contributed to the observed reduction in food consumption and body weight decreases.

No histologic abnormalities were observed in any of the examined upper molar teeth. Occasional findings of lymphocyte infiltrates in tissues such tongue, liver, lung, thymus, kidney, and eye was noted in treated animals. These findings were not dose related or present in recovery animals. Therefore, they were considered spontaneous findings.

Special Evaluation

Sperm Analysis
The mean percent sperm motility, caudal epididymal sperm count, and sperm morphology were not affected by treatment with GDC-0449.1 at dosage levels of 10, 50, and 150 mg/kg/day. No biologically meaningful differences were observed between the study groups.

Toxicokinetics

Dose associated increase in AUC $_{0\text{-}24}$ and C_{max} in male and female rats was observed in this study. However, the increase in AUC $_{0\text{-}24}$ and C_{max} levels were less than dose proportional.
No large or consistent differences were noted in AUC $_{0\text{-}24}$ or C_{max} among male and female rats, as visible in Table 8 below.

Table 8: Toxicokinetics following 13-week administration in rats

Daily Dose (mg/kg):	0 (Control)		10 (Low)		50 (Mid)		150 (Mid-High)		500 (High)	
Number of Animals:	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Toxicokinetics: AUC_{0-24} (ng • hr/mL)										
Day 1	—	—	46400	28300	172000	124000	260000	212000	277000	318000
Day 45	—	—	35400	27000	87800	94700	267000	269000	189000	400000
Day 91	—	—	39900	35200	169000	164000	203000	425000	—	—

(table excerpted from Applicant's package)

Study title: **26-Week Oral Gavage Chronic Toxicity and Toxicokinetics Study with GDC-0449.1 in Sprague-Dawley Rats with an 8 Week Recovery Phase**

Study no.:	07-1224
Study report location:	Module 4. Nonclinical Study reports; 4.2.3 Toxicology; 4.2.3.2. Rat-Oral-Long
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15 November 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1, P195-69-5, 98.7%

Key Study Findings

- Two males and one female administered 100 mg/kg/day were euthanized due to general debilitation.
- Decrease weight gain and food consumption in ≥ 50 mg/kg/day males.
- Clinical signs included malocclusion/missing incisors, red ocular discharge, red skin and haircoat, squinted or protruding eyes.
- Decreased alkaline phosphatase activity and increased total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol in animals administered ≥50 mg/kg/day.
- Pilomatricoma was observed in two animals administered 100 mg/kg/day at the recovery necropsy.
- Decrease in the number of taste buds in animals administered ≥50 mg/kg/day; reversible.
- Decrease in the percent of motile sperm observed at terminal and recovery necropsies in ≥ 15 mg/kg/day males.
- Decrease in number of corpora lutea was observed in the female rats administered 100 mg/kg/day at terminal and recovery necropsies.

Methods

Doses:	0, 7.5, 25, 50 mg/kg/dose; 0, 15, 50 and 100 mg/kg/day
Frequency of dosing:	twice daily dosing with 6 hours between the daily doses
Route of administration:	oral
Dose volume:	5 mL/kg
Formulation/Vehicle:	GDC-0449.1 in the following vehicle: 0.5% (w/v) Hydroxypropyl methylcellulose and 0.2% (w/v) polysorbate 80 (Tween 80) in reverse osmosis water
Species/Strain:	Rat/ Crl: CD(SD)
Number/Sex/Group:	20/sex/group

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Age:	6-7 weeks
Weight:	M 205-291g; F 147-214 g
Satellite groups:	Toxicokinetic group
Unique study design:	Neurobehavioral study and male/female reproductive assessments
Deviation from study protocol:	Some study deviations were noted, but found to not compromise the integrity of the study.

Group	No. of Animals Male	No. of Animals Female	Dose Level[a] (mg/kg/day)	Dose Level[a] (mg/kg/dose)	Dose Concentration[a] (mg/mL)
Toxicity Animals[b]					
1 (Control)[c]	20	20	0	0	0
2 (Low)	20	20	15	7.5	1.5
3 (Mid)	20	20	50	25	5
4 (High)	20	20	100	50	10
Toxicokinetic Animals[d]					
5 (Control)[c]	3	3	0	0	0
6 (Low)	9	9	15	7.5	1.5
7 (Mid)	9	9	50	25	5
8 (High)	9	9	100	50	10

a Dose level (mg/kg/dose) and dose concentration (mg/mL) are expressed as the free base of GDC-0449.1. Animals were dosed twice daily (6 hours ± 30 minutes apart).
b After 26 weeks of dosing, up to 10 animals/sex/group in Groups 1 through 4 were euthanized, with the remaining animals subsequently entering an 8-week recovery phase.
c Groups 1 and 5 received control article [0.5% (w/v) hydroxypropyl methylcellulose and 0.2% (w/v) polysorbate 80 in reverse osmosis water, pH 3.0 ± 0.2] only.
d Toxicokinetic animals were included solely for the purpose of blood sample collections and were euthanized and disposed of without necropsy after the final blood collection.

(table excerpted from Applicant's package)

Observations and Results

Mortality

Five animals died or were sacrificed in moribund condition. Two males (B61497 and B61504) and one female (B61629) were administered the highest dose of vismodegib of 50 mg/kg/dose (100 mg/kg/day; B61497 and B61504) and one female (B61629) was given the same dose. One additional male dosed with 25 mg/kg/dose (50 mg/kg/day) was euthanized due to lymphosarcoma that was not considered to be associated with the vismodegib administration. One female control animals (B61636) was also euthanized due to paw injury on day 180.

Clinical Signs

A dose-related increase in the incidence of malocclusion was observed during the dosing period. Malocclusion has been observed in all mid and high dose males, and all high dose females. Additionally, 85% males and 80% females in the low dose group had an increased incidence of malocclusion. Malocclusion was also observed in control animals in 60% of males and 50% of females. All evaluated recovery animals had

malocclusion. The number of evaluated animals in recovery was equal to the number of animals with malocclusion at the end of dosing, which indicates malocclusion was not reversible.
Mild tremors were observed in all animals at the mid and high dose, except one female at the mid dose. Mild, moderate and severe tremors were consistently present in high dose animals. Other notable clinical signs mostly in the high dose animals were protruding eyes, red discharge and squinted eyes; mouth, perioral or periorbital alopecia. Irreversible red haircoat and skin were observed in all animals. Myoclonus jerking of the limbs together with excessive lacrimation was noted in approximately 30% of the animals administered 100 mg/kg/day of vismodegib in study week 13 and 26.

Body Weights and Feed Consumption

Decreased mean body weight and body weight gain was noted in males (as it is depicted in Table 9 below), with a statistically significant decrease observed in males administered given 50 or 100 mg/kg/day of vismodegib. Although mean body weight was lower for females administered given 50 or 100 mg/kg/day,, these findings were not statistically significant.

Table 9: Mean body weights and body weight changes in rats after 26 weeks of vismodegib administration

	0 mg/kg/day		15 mg/kg/day		50 mg/kg/day		100 mg/kg/day	
	M (20)	F(20)	M(20)	F (20)	M (20)	F(20)	M (20)	F(20)
Body Weight (g)[f] – Study Day 182	600	318	-2	4	-9*	-3	-19*	-3
Body Weight Change (g)[g] – Study Days 1–182	354	136	346	150	304*	130	239*	129
Food Consumption (g)[f] – Study Days 176–181	161	114	1	4	-5	1	-9*	-3
Recovery Evaluation								
Number Evaluated	10	9	10	10	9	10	9	10
Body Weight (g)[i] – Study Day 238 (Recovery Day 56)	611	322	1	9	-3	-1	-16*	0
Body Weight Change (g)[g] – Study Days 183–238 (Recovery Days 1–56)	53	30	60	44*	64	28	61	30
Food Consumption (g) – Study Days 232–237 (Recovery Days 50–55)	157	111	-3	2	-3	3	-6	3

(table excerpted from Applicant's package)

Decreased body weight correlated with lower food consumption, specifically in males administered 50 and 100 mg/kg/day of vismodegib.

Ophthalmoscopy, hematology and urinalysis

No test article-related findings were noted.

Clinical Chemistry

A significant increase (29-39%) in total cholesterol was noted in 50 mg/kg/day females and all 100 mg/kg/day animals, which persisted in females to observation day 183. The same trend was observed in HDL and LDL levels.
Statistically significant dose-related decreases in alkaline phosphatase levels, ranging from 13 to 39%, were noted in all vismodegib dose groups.

Gross Pathology

Alopecia was noted in one low dose and one mid dose female, and in males and females at the high-dose. Discolored and missing incisors were observed in mid and high dose animals.

Organ Weights

No differences in organ weight were observed in rats administered GDC-0449.1.

Histopathology

Adequate Battery: Yes.
Peer Review: Yes.

Histological Findings

Microscopic findings were noted in bone, teeth, skin/subcutis, and taste buds with the majority of effects occurring in animals administered $\geq$50 mg/kg/day.

Alteration of the proximal femoral epiphyseal plate was noted at the terminal necropsy in 3/11 and 8/11 males at 50 and 100 mg/kg/day, respectively, and 1/10 and 5/10 females at 50 and 100 mg/kg/day, respectively (including animals that died or were euthanized at unscheduled intervals). Femoral epiphyseal plate alteration is characterized by loss and disorganization of chondrocytes and cartilaginous matrix making up the epiphyseal plate and loss of spongiotic and trabecular bone, resulting in partial to complete closure of the epiphysis.

Adverse effects on incisors was observed in males administered 15, 50, or 100 mg/kg/day and in females administered 50 or 100 mg/kg/day. They consisted of loss/atrophy of odontoblasts and ameloblasts, with secondary degradation of dentin with scattered sequestra, formation of fluid-filled cysts in the dental pulp, hyperplasia of the periodontal ligament, ossification of the root canal, and subacute inflammation.

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Table 10: Histopathology findings in rats after 26 weeks administration of oral vismodegib

Dose (mg/kg/day)	0		15		50		100	
Observation	Number of observations*							
	M	F	M	F	M	F	M	F
	10	9	10	10	9	10	9	10
Root canal ossification					7	8	9	5
Periodontal ligament hyperplasia					4	7	4	6
Dentin degradation					9	9	9	10
Ameloblast loss/atrophy					9	8	9	10
Odontoblast loss/atrophy					9	8	9	10
Dentin sequestra	1		1		6	8	7	10

*same animal may have multiple observations

The finding of pilomatricoma, a benign tumor arising from the hair follicle, was observed in two animals administered 100 mg/kg/day at the recovery necropsy. This finding was believed to represent the progression of follicular cysts that were observed at the same dose level at the end of the dosing and recovery phases.

Decreased incidence of identification of taste buds in the examined tongue sections was observed at all dose levels at the terminal and recovery necropsies. Although a consistent dose-response relationship was not apparent in all cases, this finding was considered test article-related in animals given ≥50 mg/kg/day. There was a trend of reversibility of this change at the recovery necropsy.

Special Evaluation

Male reproductive assessment showed irreversible loss (13-26%) of motile sperm in animals administered vismodegib at 15 mg/kg/day.

Female reproductive assessment
Females administered vismodegib at the dose of 100 mg/kg/day had decreased numbers of corpora lutea (~45%) compared to the control females (~30%)

A decrease in the number of corpora lutea in females at terminal and recovery necropsies and a decrease in motile sperm in males at terminal and recovery necropsies may represent test article-related effects on fertility.

Neurotoxicity assessment test
Males and females administered 100 mg/kg/day showed lacrimation during hand-held observations. Males administered 100 mg/kg/day had a low carriage, and myoclonic jerking during home cage observations. Decreased forelimb and hindlimb grip strength were observed during the dosing and recovery phases in 100 mg/kg/day males.

Toxicokinetics

An increase in vismodegib dose was associated with an increase in AUC_{0-24} and C_{max} in male and female rats. However, the AUC_{0-24} and C_{max} were not consistently proportional to the increase in dose from 15 to 50 mg/kg/day on study days 1, 91, and 182. When the dose was increased from 50 to 100 mg/kg/day, mean C_{max} and AUC_{0-24} estimates were dose-proportional, with the exception of C_{max} estimates on study day 1 (Table 11). Gender differences were observed in AUC_{0-24} and C_{max} , but there was no consistent trend among dose groups or time points. Mean AUC_{0-24} and C_{max} estimates on study day 1 were comparable to those estimated for study days 91 and 182, with the exception of the 100-mg/kg/day group, in which the study day 91 mean AUC_{0-24} and C_{max} estimates were increased. There was no significant accumulation from study day 1 to study day 182. The mean time of maximum observed concentration (t_{max}) estimates ranged from 1 to 10 hours after the first dose.

Table 11: Toxicokinetics in rats after 26 weeks administration of vismodegib

Daily Dose (mg/kg)[a]:	0 (Control)		15		50		100	
Number of Animals:	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Toxicokinetics[b]								
Study Day 1								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	67400	65600	138000	77400	192000	152000
C_{max} (ng/mL)	NC	NC	4730	4790	10500	9940	13900	10300
Study Day 91								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	91100	92500	183000	131000	234000	589000
C_{max} (ng/mL)	NC	NC	6560	8240	15300	20200	19400	46400
Study Day 182								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	110000	45200	152000	99200	239000	251000
C_{max} (ng/mL)	NC	NC	8920	3980	10000	6700	23100	19200

(table excerpted from Applicant's package)

Study title: **A 4-Week Oral Gavage Toxicity Study with GDC 0449.1 in Dogs with a 4-Week Recovery Period**

Study no.: 05-1457
Study report location: Original electronic application, 4.2.3. Toxicology; 4.2.3.2.1 Legacy Study Report Section
Conducting laboratory and location: (b) (4)
Date of study initiation: 20 February 2006
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: GDC-0449.1; P182-46-2; 99.5%

Key Study Findings

- One 100 mg/kg/day male was sacrificed due to moribund condition.
- Reversible emesis and mucoid feces, reversible effects on platelets and cholesterol, and potentially reversible testicular degeneration.
- NOAEL in females = 50 mg/kg/day; NOAEL was not established in males.

Methods

Doses:	0, 25, 75, 200 mg/kg/dose; 0, 50, 150, and 400 mg/kg/day
Frequency of dosing:	twice daily dosing with 6 hours between the daily doses
Route of administration:	oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% (w/v) Hydroxypropyl Methylcellulose and 0.2% (v/v) Polysorbate 80 in reverse osmosis water, pH 3 ± 0.2
Species/Strain:	Beagle dogs
Number/Sex/Group:	5/sex/group
Age:	6-7 months
Weight:	M: 7.4-12.1 kg; F:6-9 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Some study deviations were noted, but found to not compromise the integrity of the study.

Observations and Results

Mortality

One 400 mg/kg/day male was euthanized on Day 11 due to poor health and body weight loss. This animal had a two-fold higher plasma–drug concentration than other animals in the same dose group, suggesting that the higher exposure may have caused the moribund condition.

Body Weights and Feed Consumption

No test article-related findings were noted.

Clinical signs

Emesis and mucoid feces were observed during the dosing period, particularly in the 150 or 400 mg/kg/day animals.

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Ophthalmoscopy; electrocardiography

No test article-related findings were noted.

Hematology

Transient, moderate (counts < 100,000/µL) to marked (counts < 60,000/µL) decreases in platelet counts were observed in some dogs at 150 or 400 mg/kg/day. These values returned to predose levels prior to the end of treatment and were not associated with changes in coagulation parameters.

Clinical Chemistry

Reversible, three-fold increase in cholesterol was noted in all animals receiving vismodegib. HDL amounts were increased approximately two-fold in all dosed animals, while LDL increases were proportional to the dose of vismodegib. Animals at 400 mg/kg/day had LDL levels increased by ~70 mg/dL compared to control animals.

Urinalysis, Gross Pathology and Organ Weights

No test article-related findings were noted.

Histopathology

Histopathology findings were limited to the testes and epididymides and were observed in the majority of vismodegib–treated males at all doses (see Table 12 below). Findings were characterized by the appearance of increased numbers of degenerating germ cells within the seminiferous tubules and were generally reflected in the epididymides by a relative paucity of spermatozoa and abnormal accumulation of cellular debris. These findings were reversible.

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Table 12: Histopathology findings in dogs after 4 weeks administration of vismodegib

Daily Dose (mg/kg/day):	0 (Control)		50		150		400	
Number of Animals:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Noteworthy Findings (cont'd)								
Histopathology (Terminal) [d]								
Number evaluated	3	3	3	3	3	3	4[e]	3
Testes								
Degenerating germ cells	0	NA	++(3/3)	NA	+(1/3)	NA	+++(4/4)	NA
Epididymides								
Increased cellular debris	+(1/3)	NA	++(3/3)	NA	+++(3/3)	NA	+++(4/4)	NA
Hypospermia	++(1/3)	NA	++(2/3)	NA	+(2/3)	NA	+++(4/4)	NA
Histopathology (Recovery) [e]								
Number evaluated	2	2	2	2	2	2	1	2
Testes								
Degenerating germ cells	0	NA	+(1/2)	NA	+(1/2)	NA	0	NA
Epididymides								
Increased cellular debris	0	NA	+(1/2)	NA	+(1/2)	NA	0	NA
Hypospermia	0	NA	++(1/2)	NA	++(1/2)	NA	0	NA

—=No noteworthy findings. + Minimal ++ Slight +++ Moderate

* $p \leq 0.05$; BID=Twice Daily; NA=Not Applicable; PO=Oral Gavage.

[a] The number of animals evaluated was 5/sex/group during the dosing phase and 2/sex/group during the recovery phase, with the exception of group 4 (400 mg/kg) males where 4 and 1 male dogs, respectively, were evaluated during the dosing (after Day 11) and recovery phases.

[b] At end of dosing or recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown and were calculated as followed: [(treated – control)/control]*100. Statistical significance is based on actual data (not on the percent differences).

[c] Numerics signifies the number of animals affected.

[d] Number in parentheses reflects the incidence; approximate mean severity grade indicated using +, ++ or +++.

[e] Includes unscheduled euthanasia.

(Table excerpted from Applicant's package)

Toxicokinetics

Mean exposures ($AUC_{0\text{-}tlast}$ and C_{max}) were similar for 150 and 400 mg/kg/day animals (as depicted in Table 13). The increase in exposure from 50 mg/kg/day to the two higher dose groups was less than proportional to the increase in dose. No differences in exposure between male and female animals were observed.

Table 13: Toxicokinetics in rats after 4 weeks administration of vismodegib

Daily Dose (mg/kg/day):	0 (Control)		50		150		400	
Number of Animals [a]:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Toxicokinetics: $AUC_{0\text{-}tlast}$ (ng • hr/mL)								
Day 1	—	—	156000	159000	284000	324000	358000	294000
Day 14	—	—	649000	740000	969000	1060000	1650000	1070000
Day 28	—	—	479000	527000	648000	861000	738000	757000

(table excerpted from Applicant's package)

Stability and Homogeneity

The results of homogeneity and concentration verification of the middle samples indicated that formulations were generally within 10% of normal concentrations and homogeneously mixed.

Study title: **13-Week Oral Gavage Study with GDC-0449.1 in Dogs with a 13-Week Recovery Period**

Study no.:	06-1003
Study report location:	Original electronic application, 4.2.3. Toxicology; 4.2.3.2.1 Legacy Study Report Section
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	16 November 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1; P175-191-3; 99.4%

Key Study Findings

- One 150 mg/kg/day female was sacrificed moribund on Day 15 in association with thrombocytopenia and hemorrhage.
- Decreased food consumption and body weight, alopecia, fecal changes, increased cholesterol at ≥ 50 mg/kg/day; decreased platelet counts at 150 mg/kg/day. Findings were reversible.
- A NOAEL was not determined due to the presence of localized alopecia with microscopic correlates of skin inflammation in all vismodegib-treated groups; however, no severe or dose-limiting toxicities were observed at the 15 mg/kg dose level.

Methods

Doses:	0, 7.5, 25, 75 mg/kg/dose; 0, 15, 50, 150 mg/kg/day
Frequency of dosing:	Twice daily dosing with six hours between the daily doses
Route of administration:	oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% (w/v) Hydroxypropyl Methylcellulose and 0.2% (v/v) Polysorbate 80 in reverse osmosis water, pH 3 ± 0.2
Species/Strain:	Beagle dog
Number/Sex/Group:	5/sex/group
Age:	10 to 12 months
Weight:	M: 8.5-10.3 kg; F:6.3-8.9 kg
Satellite groups:	No
Unique study design:	Cardiovascular and respiratory assessment
Deviation from study protocol:	Some study deviations were noted, but found to not compromise the integrity of the study.

Observations and Results

Mortality

One female dosed at 150 mg/kg/day was sacrificed moribund on Day 15 with acute multi-organ hemorrhage that was associated with a severe decrease in platelet count.

Clinical Signs

Observed clinical signs included mostly alopecia on the paws or/and muzzle, which persisted in a small number of recovery animals. An increased incidence of discolored (black) liquid and/or mucoid feces was observed during the dosing phase in males and females at ≥ 50 mg/kg/day; however, this observation was not correlated with gross or microscopic pathology findings.

Body Weights

Vismodegib-treated dogs showed a small (the highest was 6% decrease in males at 150 mg/kg/day) decrease in mean body weight when compared to control animals, which was not reversible.

Feed Consumption

Dogs administered ≥50 mg/kg/day had a decreased food consumption of approximately ≤ 80% less than control animals. Dogs in recovery consumed about 62% less of food when compared to control animals.
The decrease in food consumption was likely not reflected in remarkable decreased weight gain because dogs in the 50 and 100 mg/kg/day groups were supplemented with canned dog food beginning on Day 13 until the end of dosing. .

Ophthalmoscopy

One male dosed with 150 mg/kg/day twice daily developed posterior suture line cataract on both eyes.

ECG

No vismodegib-related changes were noted in electrocardiographic parameters.

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Hematology

Lower platelets counts were noted in treated animals when compared to control animals. Significantly lower platelet count was noted in the animals treated with 150 mg/kg/day. This finding was not present at the end of the treatment.

Clinical Chemistry

Cholesterol, HDL and specifically LDL levels were dose-dependently increased in animals administered vismodegib. Serum chemistry findings in dogs at ≥ 15 mg/kg/day included dose-dependent increases in LDL and HDL cholesterol that resulted in approximately 2- to 5-fold increases in total cholesterol. Increases in cholesterol values were observed at all intervals during the dosing phase; however, values decreased progressively during the recovery phase.

Urinalysis

No test article-related findings were noted.

Gross Pathology

Vismodegib-related macroscopic findings observed at all dose levels were reversible and associated with findings of alopecia on the paws, muzzle, or dorsal area.

Organ Weights

No test article-related findings were noted.

Histopathology

Adequate Battery: Yes.

Peer Review: Yes.

Histological Findings

Focal hyperkeratosis and/or inflammation were noted as microscopic correlates of alopecia.
Other vismodegib-related microscopic findings were present in the kidney and adrenal glands. In the kidneys, increased vacuolation of tubular epithelium was observed in females at all dose levels persisting to the end of the recovery period. Reversible decrease in vacuolation of the adrenal cortex was observed in animals at all dose levels, although not correlated with any changes in clinical pathology parameters.
No microscopic changes were observed in the testes or epididymides in sexually mature dogs in this study.

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Table 14: Histopathology findings in dogs after 13 weeks administration of vismodegib - Terminal sacrifice

Daily Dose (mg/kg/day):	0 (Control)		15		50		150	
Number of Animals:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Noteworthy Findings (cont'd)								
Terminal Body Weight (%)[a] Terminal	9500 g	7667g	2	-2	2	-4	4	4
Number evaluated	3	3	3	3	3	3	3	2
Organ Weights (%)	-	-	-	-	-	-	-	-
Gross Pathology								
Alopecia	0	0	3	3	3	3	3	2
Histopathology[c]								
Adrenal, Cortex								
Mineralization	0	0	0	0	1	0	0	0
Cyst	0	0	0	1	0	0	0	0
Vacuolation, decreased	0	0	3	1	3	2	3	2
Kidney								
Mineralization, tubule/collecting duct	2	2	2	1	3	1	1	1
Vacuolation, Tubule Cell	0	3	0	3	0	3	0	2
Vacuolation, mesangial cell	0	1	1	1	0	0	0	0
Skin/Subcutis								
Hyperkeratosis, follicle, paw	0	0	3	3	3	3	3	2
Inflammation, chronic-active, paw	0	0	3	2	1	1	3	0
Inflammation, pyogranulomatous, paw	0	0	0	1	2	2	0	2
Bacteria, intrafollicular, paw	0	0	0	1	0	0	0	0
Acanthosis, paw	0	0	3	3	3	3	3	2

Table 15: Histopathology findings in dogs after 13 weeks administration of vismodegib - Recovery sacrifice

Daily Dose (mg/kg/day):	0 (Control)		15		50		150	
Number of Animals:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Postdose Evaluation								
Terminal Body Weight (%)[b] Recovery	10300 g	7550 g	-4	1	-4	15	-6	5
Number evaluated	2	2	2	2	2	2	2	2
Histopathology								
Adrenal, Cortex								
Vacuolation, decreased	0	0	0	0	0	0	0	1
Kidney								
Vacuolation, Tubule Cell	0	2	0	2	0	2	0	1

- No noteworthy findings.

* $p \leq 0.05$.

[a] At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[b] At period indicated. For controls, group means are shown. For treated groups, percent differences from controls are shown and were calculated as followed: [(treated – control)/control]*100. Statistical significance is based on actual data (not on the percent differences).

[c] Number affected.

BID=twice daily; NA=not applicable; PO=oral gavage.

(Tables excerpted from Applicant's package)

Toxicokinetics

Although mean exposures ($AUC_{0-tlast}$ and C_{max}) were within approximately 2-fold for all dose groups, there was a trend towards increased exposure with increased dose. There were no differences in TK parameters between male and female animals.

Table 16: Group mean TK parameters in dogs after 13 weeks administration of vismodegib

Daily Dose (mg/kg/day):	0 (Control)		15		50		150	
Number of Animals:	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Toxicokinetics: AUC_{0-24}(ng • hr/mL)								
Day 1	-	-	61600 ±5630	65800 ±11700	133000 ±16500	147000 ±34600	186000 ±33200	241000 ±54500
Day 44	-	-	366000 ±40400	317000 ±71700	372000 ±47800	381000 ±50600	575000 ±94600	649000 ±73200
Day 90	-	-	372000 ±59300	317000 ±76500	485000 ±108000	501000 ±56600	441000 ±88800	548000 ±77200

(Table excerpted from Applicant's package)

Study title: **26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with GDC-0449.1 in Dogs with a 13-Week Recovery Phase**

Study no.:	07-1047 (sponsor) 6281-847 (testing facility)
Study report location:	Electronic Submission, Nonclinical Study Reports, 4.2.3. Toxicology; 4.2.3.2. Dog – Oral- Long; 4.2.3.2.1.Legacy Study Report
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2 Nov 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1, P195-69-5, 98.7%

Key Study Findings

- One animal in the low and mid dose groups were sacrificed due to swelling of the paws that limited dosing. One 50 mg/kg/day animal was sacrificed due to moribund condition.
- Paw swelling was observed in all GDC-0449.1 groups and correlated with follicular hyperkeratosis and granulomatous inflammation in the skin or subcutis, which were reversible.
- Fever was observed in some animals at ≥15 mg/kg/day; alopecia at ≥5 mg/kg/day; increase in serum LDL- and HDL-cholesterol at ≥5 mg/kg/day; increase in adrenal weight at 50 mg/kg/day. All findings were reversible.
- NOAEL was not determined due to the effects on the skin and paws at all dose levels.

Methods

Doses:	0, 1, 7.5, 25 mg/kg/dose; 0; 2; 15; and 50 mg/kg/day
Frequency of dosing:	Twice daily, 6 hours ±30 min apart
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	vehicle [0.5% (w/v) hydroxypropyl methylcellulose and 0.2% (w/v) polysorbate 80 (Tween 80) in reverse osmosis (RO) water, pH = 3.0 + 0.2]
Species/Strain:	Purebred beagle dogs
Number/Sex/Group:	Six/sex/group
Age:	12.6 to 14.5 months
Weight:	M: 7 to 13.4 kg; F: 5.4 to 9.3 kg
Satellite groups:	No
Unique study design:	No
Deviation from study protocol:	Some study deviations were noted, but found to not compromise the integrity of the study.

Observations and Results

Mortality

Three dogs were moribund due to vismodegib ingestion, one at each dose tested (8%). One animal in the low and mid dose groups had paw discomfort, and the animal in the high dose group was moribund at study day 159.

Clinical Signs

Clinical signs that were more pronounced or observed more frequently are listed in tabulated form below.

Table 17: Clinical signs in dogs after 26 weeks administration of vismodegib

Dose (mg/kg/day)	0	5	15	50
Findings (below):	# at end of dosing / # at recovery			
Swollen all paws	0	6/4	6/3	6/4
Swollen front paws	1/0	5/1	6/0	3/0
Thin appearance	1/0	3/0	1/0	1/1
Hypoactive behavior	0	0	1	2
Vomitus (cont. food)	1/0	6/0	5/1	4/2
Vomitus* (discolored, foamy, red in color, white in color, yellow)	4/1	5/0	4/0	6/0
Nonformed feces	5/1	5/2	6/2	4/4

Reference ID: 3071937

Eyes: Clear and cloudy discharge*	0/1	6/2	3/1	5/1
All paws alopecia	0/0	6/4	6/3	6/4
Hind legs alopecia	0/0	2/3	4/0	2/3
Muzzle alopecia	0/0	6/4	6/3	6/4
Red skin (all paws)	0/0	5/4	6/1	6/2
Red skin on muzzle	0/0	1/1	2/0	5/0
Red skin (testes)	0	3	0	4
Swollen, all paws	0/0	6/2	6/1	6/2
Discharge (appears to be cycling)	4/1	2/1	3/1	3/1

* number of observations; i.e., may have been observed several times in the same animal, and not observed at all in the another animal.

- Discolored and liquid feces continued in the recovery period at three times in low, and two times in the high dose treated animals.

- Signs of inflammation in foot, particularly front paws, were present at the end of the recovery period.

Body Weights and Feed Consumption

No significant findings were noted.

Ophthalmoscopy

Slit Lamp biomicroscope observations did not reveal any changes in eyes of treatment or recovery animals.

ECG

All the ECG parameters, systolic/diastolic blood pressures, and heart rates were considered within normal limits and were not significantly different from controls.

Hematology

No significant findings were noted.

Clinical Chemistry

Table 18: Clinical chemistry findings in dogs after 26 weeks administration of vismodegib

Dose	0		5 mg/kg/day		15 mg/kg/day		50 mg/kg/day	
	M	F	M	F	M	F	M	F
	Observed value		Change compared to control					
Albumin (g/dL)								
D 99	3.7	3.5	-2.7	2.9	-2.7	-2.9	-16.2	-5.7

D 184	3.6	3.4	-2.8	5.9	-2.8		-13.9	
Globulin (g/dL)								
D 99	2.3	2.2	-4.3	13.6	8.7	4.5	13	18.2
D 184	2.5	2.4	-4.0	4.2		4.2	12.0	8.3
Albumin to globulin ration								
D 99	1.7	1.8		-16.7	-11.8	-16.7	-29.4	-27.8
D 184	1.5	1.5		-6.7	-6.7	-6.7	-20.0	-13.3
Total Cholesterol (mg/dL)								
D 99	152	188	70	44	163	66	120	127
D 184	156	230	54	27	133	57	104	73
HDL Cholesterol (mg/dL)								
D 99	128	156	34	23	65	31	36	52
D 184	130	183	32	13	62	28	48	25
LDL Cholesterol (mg/dL)								
D 99	8	11	338	136	1125	300	775	791
D 184	8	26	263	31	913	135	750	281

Vismodegib administration was associated with increased total cholesterol and LDL-cholesterol, specifically in males at 15 mg/kg/day (~140%), and similarly between sexes in animals at 50 mg/kg/day (~87%). Dose-dependent response was not seen, but the findings persisted in recovery animals, although a trend of reversibility was observed.

Urinalysis

No significant findings were noted.

Gross Pathology

No test article-related findings were noted.

Organ Weights

Increased adrenal gland organ weight was more pronounced in males than females in the low and mid dose animals.

Histopathology
Adequate Battery: Yes
Peer Review: Yes

Histological Findings

Table 19: Histopathology findings in dogs after 26 weeks administration of vismodegib

Dose (mg/kg/day)	**0**	**5**	**15**	**50**
Findings (below):	# animals with observation/# evaluated			

Follicular hyperkeratosis:				
Total incidence	0/8	7/7	7/7	7/7
Moderate and marked skin incidence	0/8	0/7	2/7	2/7
Moderate and marked footpad incidence	0/8	6/7	12[1]/7	11[1]/7
Recovery findings:				
Incidence	1/4	4/4	3/3	4/4
Moderate and marked skin incidence	0/4	0/4	0/3	1/4
Moderate and marked footpad incidence	0/4	2/4	1/3	1/4
Granulomatous inflammation:				
Total Incidence	6/8	7/7	7/7	6/7
Moderate and marked footpad inflammation	2/8	6/7	5/7	5/7
Recovery findings:				
Incidence	4/4	3/4	3/3	2/4
Moderate and marked footpad inflammation	0/4	1/3	2/3	0/4

[1] One animal had more than a single observation in a different location on the footpad

Toxicokinetics

Table 20: Toxicokinetics in dogs after 26 weeks administration of vismodegib

Daily Dose (mg/kg)[a]:	0 (Control)		5		15		50	
Number of Animals:	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Toxicokinetics								
Study Day 1								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	43300	37400	97600	80700	188000	203000
C_{max} (ng/mL)	NC	NC	2350	2000	5340	4240	10100	11400
Study Day 29								
C_{min} (ng/mL)	NC	NC	6550	4710	13200	9080	24900	25500
Study Day 92								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	162000	116000	302000	259000	456000	483000
C_{max} (ng/mL)	NC	NC	7750	5620	14600	12100	21200	22500
Study Day 183								
AUC_{0-24hr} (ng • hr/mL)	NC	NC	179000	127000	289000	227000	445000	449000
C_{max} (ng/mL)	NC	NC	8450	6070	13000	10400	20700	21600

(table excerpted from Applicant's package)

Stability and Homogeneity

Analysis of GDC-0449.1 concentration met the specification of 97% to 104% of theoretical specification (within 10% of the target concentration). One sample of GDC-0449.1 administered on Day 7 was 86.6% of the target concentration. GDC-0449.1 was determined to be stable when stored refrigerated up to 35 days, or up to 6 months when stored frozen (-60 to -80^{0}C). All formulations met the homogeneity specification, of the overall mean of the top, middle and bottom levels tested.

7 Genetic Toxicology

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

Study title: **GDC-0449.1: Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay**

Study no.:	05-1451
Study report location:	Original electronic application, 4.2.3. Toxicology; 4.2.3.2.1 Legacy Study Report Section
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 March 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1; P182-46-2; 99.5%

Methods

Strains: *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* tester strain WP2uvrA

Concentrations in definitive study: 10, 33.3, 100, 333, 1000, 2000, 5000 µg/plate

Basis of concentration selection: Results of dose range-finding study

Negative control: DMSO

Positive control:

Tester	S9	Positive	Concentration
TA98	+	benzo[a]pyrene	2.5
TA98		2-nitrofluorene	1.0
TA100	+	2-	2.5
TA100		sodium azide	2.0
TA1535	+	2-	2.5
TA1535		sodium azide	2.0
TA1537	+	2-	2.5
TA1537		ICR-191	2.0
WP2*uvr*A	+	2-	25.0
WP2*uvr*A		4-nitroquinoline-	1.0

Formulation/Vehicle: DMSO

Incubation & sampling time: 52+4 hours at 37°C; sampling time immediately followed the incubation period

Study Validity

GDC-0449 was initially tested on TA100 strain at concentrations up to 5000 µg/plate. The Ames assay was conducted in both the presence and absence of S9 mix, along with appropriate vehicles and positive control using three plates per dose. S9 mix ranged from 33.3 to 5000 ug/plate. No positive increases in the mean number of revertants per plate were observed with any of the tester strains.
Based on the result analysis, all experiments were well-replicated and had valid negative and positive control results.

Results

Results of the dose-range-finding study were found acceptable and no positive increases in the mean number of revertants per plate were observed with tester strains with or without S9. These results were used for the definitive mutagenicity assay.

Reference ID: 3071937

Table 21: Ames assay results

Test Article: Vismodegib

Test for Induction of: Reverse mutation in bacterial cells Strains: *Salmonella typhimurium* and *Escherichia coli* Metabolizing System: Aroclor™-induced rat liver S9 Vehicles: For Test Article: dimethylsulfoxide (DMSO) For Positive Controls: Water (sodium azide only); DMSO (all other positive controls) Treatment: Plate incorporation for 52 ± 4 hr.	Cytotoxic Effects: No findings attributed to test article Genotoxic Effects: No findings attributed to test article No. of Independent Assays: 2 No. of Replicate Cultures: 3 No. of Cells Analyzed/Culture: $0.5x10^9$ Date of Treatment: 28-Mar-06 (Assay 1 of 2)	Study No.: 05-1451 Study Title: GDC-0449.1: *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay GLP Status: GLP

Metabolic Activation	Test Article	Dose Level (µg/Plate)	Revertant Colony Counts (Mean ± Standard Deviation)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without	DMSO	50 µL/Plate	16 ± 3	82 ± 5	14 ± 5	8 ± 1	13 ± 2
Activation	GDC-0449	10.0[a]	13 ± 4	86 ± 6	16 ± 5	5 ± 3	NA
(Initial Assay)		33.3	17 ± 2	83 ± 11	12 ± 2	5 ± 3	16 ± 9
		100	16 ± 1	78 ± 14	10 ± 4	11 ± 5	16 ± 5
		333	20 ± 6	70 ± 2	11 ± 2	8 ± 1	14 ± 4
		1000	18 ± 2	58 ± 7	15 ± 3	7 ± 1	11 ± 4
		3330	NA	NA	NA	NA	5 ± 3
		5000[b]	14 ± 2	23 ± 2	3 ± 2	6 ± 4	4 ± 2
	2-nitrofluorene	1.0	405 ± 38				

Metabolic Activation	Test Article	Dose Level (µg/Plate)	Revertant Colony Counts (Mean ± Standard Deviation)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without	Sodium azide	2.0		1122 ± 55	1008 ± 69		
Activation	ICR-191	2.0				347 ± 31	
(cont'd)	4-nitroquinoline-N-oxide	1.0					335 ± 18
With Activation	DMSO	50 µL/Plate	28 ± 4	97 ± 7	12 ± 3	7 ± 4	17 ± 8
(Initial Assay)	GDC-0449	10.0[a]	21 ± 3	94 ± 7	9 ± 3	10 ± 5	NA
		33.3	19 ± 2	97 ± 2	14 ± 5	7 ± 6	19 ± 5
		100	30 ± 4	92 ± 5	17 ± 3	9 ± 0	18 ± 8
		333	26 ± 7	103 ± 7	13 ± 3	13 ± 2	15 ± 3
		1000	18 ± 7	54 ± 5	9 ± 5	7 ± 4	17 ± 4
		3330	NA	NA	NA	NA	4 ± 3
		5000[b]	12 ± 1	27 ± 7	4 ± 1	3 ± 2	6 ± 2
	Benzo[a]pyrene	2.5	313 ± 49				
	2-aminoanthracene	2.5		849 ± 35	116 ± 6	192 ± 138	
	2-aminoanthracene	25.0					369 ± 68

NA=Not applicable.
[a] 10 µL/Plate tested in *S. typhimurium*, not *E.Coli*
[b] Test article precipitated in agar.

Metabolic Activation	Test Article	Dose Level (µg/Plate)	Revertant Colony Counts (Mean ± Standard Deviation)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without	Sodium azide	2.0		1012 ± 32	664 ± 35		
Activation	ICR-191	2.0				251 ± 44	
(cont'd)	4-nitroquinoline-N-oxide	1.0					189 ± 47
With Activation	DMSO	50 µL/Plate	22 ± 8	92 ± 3	10 ± 3	7 ± 2	23 ± 0
(Confirmation	GDC-0449	10.0 [a]	19 ± 1	88 ± 12	10 ± 2	4 ± 2	–
Assay)		33.3	24 ± 2	89 ± 13	11 ± 2	7 ± 3	18 ± 8
		100	19 ± 2	87 ± 2	14 ± 2	12 ± 4	13 ± 3
		333	23 ± 4	91 ± 9	11 ± 5	7 ± 4	26 ± 5
		1000	18 ± 5	70 ± 10	9 ± 4	4 ± 2	20 ± 4
		2000 [b]	11 ± 2	37 ± 2	9 ± 2	3 ± 2	14 ± 2
		5000 [b]	4 ± 2	21 ± 2	4 ± 1	1 ± 0	9 ± 1
	Benzo[a]pyrene	2.5	166 ± 18				
	2-aminoanthracene	2.5		671 ± 54	78 ± 9	93 ± 9	
	2-aminoanthracene	25.0					132 ± 6

NA=Not applicable.
[a] 10 µL/Plate tested in *S. typhimurium*, not *E.Coli*
[b] Test article precipitated in agar.

(table excerpted from Applicant's package)

Conclusion

GDC-0449.1 did not cause an increase in the mean number of revertants per plate with the tester strains in the presence or absence of microsomal enzymes prepared from Aroclor-induced rat liver (S9) under the conditions tested.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title: **GDC-0449: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes**

Study no.: 05-1452
Study report location: Original electronic application, 4.2.3. Toxicology; 4.2.3.2.1 Legacy Study Report Section
Conducting laboratory and location: (b) (4)
Date of study initiation: 8 March 2006
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: GDC-0449.1; P182-46-2; 99.5%

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	14.7, 19.6, 26.0, 34.6, 46.1, 61.3, 81.5, 108, 144, 192, 255, 339, 451, and 600 µg/mL without metabolic activation; and 14.7, 26.0, 46.1, 81.5, 144, 255, 339, 451, and 600 µg/mL with metabolic activation.
Basis of concentration selection:	Evaluation of mitotic index from the negative control, vehicle control and a range of test article concentrations in an initial assay
Negative control:	RPMI 1640 culture medium
Positive control:	Mitomycin C (MMC) for the assay without metabolic activation, cyclophosphamide (CP) in the assay with metabolic activation
Formulation/Vehicle:	DMSO
Incubation & sampling time:	3 hours & 22 hours after the initiation of the treatment

Results

In the confirmatory assay with metabolic activation, a precipitate was observed after dosing at >144 ug/mL.

Table 22: Chromosomal aberration assay results

Test Article: Vismodegib

Test for Induction of: Chromosomal aberrations Strains: Primary human lymphocytes Metabolizing System: Aroclor™-induced rat liver S9 Vehicles: For Test Article: DMSO For Positive Controls: Water Treatment: Pulse treatment 3 hours and recovery time 19 hours without S9	Cytotoxic Effects: Reduction in the mitotic index Genotoxic Effects: No findings attributed to test article No. of Independent Assays: 2 No. of Replicate Cultures: 2 No. of Cells Analyzed/Culture: 100 Date of Treatment: 8 March 2006 (Assay 1 of 2)	Study No.: 05-1452 Study Title: GDC-0449.1: Chromosomal Aberrations Assay in Cultured Human Peripheral Blood Lymphocytes GLP Status: GLP

Metabolic Activation	Test Article	Concentration (µg/mL)	Cytotoxicity (% of control)	Aberrant Cells Mean -g	Aberrant Cells Mean +g	% Poly-ploid	% Endo-reduplicate
Without Activation	Vehicle Control	DMSO 10.0 µL/mL	100	0.0	1.5	0.0	0.0
(Initial Assay)	Negative Control	RPMI 1640	—	0.0	0.0	0.0	0.0
	GDC-0449	101	100	0.0	1.0	0.5	0.0
		144	100	0.0	0.5	0.0	0.0
		294 [a]	100	0.0	2.5	0.5	0.0
		600 [a]	50	0.5	2.5	0.0	0.0
	Positive Control	MMC 1.00 [b]	—	49.0 *	59.0	0.0	0.0

Metabolic Activation	Test Article	Concentration (µg/mL)	Cytotoxicity (% of control)	Aberrant Cells Mean -g	Aberrant Cells Mean +g	% Poly-ploid	% Endo-reduplicate
With Activation	Vehicle Control	DMSO 10.0 µL/mL	100	0.0	0.5	0.0	0.0
(Initial Assay)	Negative Control	RPMI 1640	—	0.0	1.5	0.0	0.0
	GDC-0449	24.2	100	0.0	1.0	0.0	0.0
		49.4	86	1.0	2.5	0.0	0.0
		101	56	1.0	2.0	0.0	0.0
		206 [a]	56	0.0	0.5	0.5	0.0
	Positive Control	CP 20.0 [b]	—	36.0 *	40.0	0.5	0.0
Without Activation	Vehicle Control	DMSO 10.0 µL/mL	100	0.0	0.5	0.0	0.0
(Confirmatory Assay)	Negative Control	RPMI 1640	—	0.0	1.0	0.0	0.0
	GDC-0449	34.6	78	0.5	2.0	0.5	0.0
		61.3	72	0.0	0.5	1.0	0.0
		81.5	55	0.5	1.5	0.0	0.0
		108	45	0.0	1.0	0.0	0.0
	Positive Control	MMC 0.300 [a]	—	19.3 *	25.3	0.0	0.0

Metabolic Activation	Test Article	Concentration (µg/mL)	Cytotoxicity (% of control)	Aberrant Cells Mean -g	Aberrant Cells Mean +g	% Poly-ploid	% Endo-reduplicate
With Activation	Vehicle Control	DMSO 10.0 µL/mL	100	0.5	1.0	0.0	0.0
(Confirmatory Assay)	Negative Control	RPMI 1640	—	0.0	1.0	0.0	0.0
	GDC-0449	81.5	100	0.5	2.0	0.0	0.0
		144	100	1.0	2.0	0.0	0.0
		255 [b]	100	0.5	1.0	0.0	0.0
		451 [b]	61	0.5	1.0	0.5	0.0
	Positive Control	CP 25.0 [c]	—	34.0 *	40.8	0.0	0.0

RPMI 1640=culture medium; DMSO=dimethyl sulfoxide; MMC=mitomycin C; CP=cyclophosphamide.
* Significantly greater in -g than the vehicle control, $p \leq 0.01$.
[a] 75 cells/culture analyzed.
[b] Precipitate observed in culture.
[c] 50 cells analyzed from A culture; 53 cells analyzed from B culture.

(table excerpted from Applicant's package)

The high dose analyzed, 600 ug/mL, had a reduction in mitotic index of 50% when compared to vehicle controls, although there were no significant increases in chromosomal aberrations, polyploidy or endoreduplication found at any dose tested.

Conclusion

Vismodegib was not clastogenic in the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes under the conditions tested.

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

Study title: ***In vivo* Rat Micronucleus Assay With GDC-0449**

Study no.:	05-1453
Study report location:	Original electronic application, 4.2.3. Toxicology; 4.2.3.2.1 Legacy Study Report Section
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 March 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0449.1; P182-46-2; 99.5%

Methods

Doses in definitive study:	0; 500; 1000; and 2000 mg/kg
Frequency of dosing:	Single administration
Route of administration:	Oral gavage
Dose volume:	10 mL/kg (positive control) all other samples as 5 mL/kg
Formulation/Vehicle:	0.5% (w/v) hydroxypropylmethylcellulose (HPMC) and 0.2% (v/v) polysorbate 80 in reverse osmosis water, pH 3 ± 0.2
Species/Strain:	rat / CD (SD) IGS BR
Number/Sex/Group:	5 male rats/group
Satellite groups:	No
Basis of dose selection:	Based on acute toxicology data in rats with vismodegib
Negative control:	Vehicle
Positive control:	Cyclophosphamide

Study Validity

Based on the information provided, the assay has been found to be valid.

Results

Male rats were administered either vehicle, cyclophosphamide (60 mg/kg, as a positive control) or vismodegib at a dose of 500, 1000, or 2000 mg/kg. All animals were euthanized 24 hours after dose administration.
Animals in an additional two groups of 5 males each, were administered either vehicle or vismodegib at a dose of 2000 mg/kg and were euthanized 48 hours after administration.

Bone marrow was extracted and at least 2000 PCEs per animal were analyzed for micronuclei. Cytotoxicity was assessed by scoring the number of PCEs and

Reference ID: 3071937

normochromatic erythrocytes (NCEs) in at least the first 500 total erythrocytes for each animal.

Table 23: Micronucleus assay results

Test Article: Vismodegib

Test for Induction of: Bone-marrow micronuclei Species/Strain: Rat, CD®(SD)IGS BR Age: approximately 8 weeks Cell Evaluated: Polychromatic erythrocytes No. of Cells Analyzed/Animal: 2000 Special Features: None Toxic/Cytotoxic Effects: There were no cytotoxic effects to the bone marrow at any dose. Genotoxic Effects: No findings attributed to test article Evidence of Exposure: There were no cytotoxic effects to the bone marrow at any dose.	Treatment Schedule: One dose Sampling Time: 24 and 48 hours after dosing Method of Administration: Oral gavage Vehicle/Formulation: 0.5% (w/v) Hydroxypropyl Methylcellulose and 0.2% (v/v) Polysorbate 80 in reverse osmosis water, pH 3±0.2 Date of Dosing: 06-Mar-06	Study No.: 05-1453 Study Title: *In Vivo* Rat Micronucleus Assay with GDC-0449.1 GLP Status: GLP

Test Article	Dose (mg/kg)	Number of Animals	Harvest Time (hours)	% Micronucleated PCEs Mean of 2000 per Animal ±Standard Error	Ratio PCE:NCE Mean±Standard Error
Vehicle Control	VC 5 mL/kg	5	24	0.09±0.03	0.96±0.05
		5	48	0.05±0.02	0.92±0.02
GDC-0449	500	5	24	0.06±0.02	0.94±0.06
	1000	5	24	0.05±0.02	0.97±0.03
	2000	5	24	0.03±0.02	1.06±0.06
		5	48	0.02±0.01	0.93±0.05
Positive Control	Cyclophosphamide 60 mg/kg	5	24	1.90±0.12 *	0.74±0.04 **

Dunnett Test: * Significantly greater than the corresponding vehicle control, p≤0.01.

** Significantly less than the corresponding vehicle control, p≤0.05.

VC=0.5% (w/v) Hydroxypropyl Methylcellulose and 0.2% (v/v) Polysorbate 80 in reverse osmosis water, pH 3±0.2

(table excerpted from Applicant's package)

Conclusion

Vismodegib did not induce clinical toxicity at doses up to 2000 mg/kg.
No statistically significant increases in micronucleated PCEs were observed at any dose examined. Vismodegib was not cytotoxic to the bone marrow (i.e., no statistically significant decreases in the PCE to NCE ratios) at any doses tested. Therefore, vismodegib was not clastogenic in the *in vivo* micronucleus assay under the conditions tested.

8 Carcinogenicity

No carcinogenicity studies have been conducted with vismodegib.

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9 Reproductive and Developmental Toxicology

9.2 Embryonic Fetal Development

Study title**: Dose-Range Finding Study with Oral Administration for Effects on Embryo-Fetal Development in the Rat**

Study no.:	RO5450815-000/ GLP-Study No. 3036R09
Study report location:	Electronic Submission,
Conducting laboratory and location:	Roche Pharma Research; F. Hoffmann-La Roche Ltd. Basel, Switzerland
Date of study initiation:	3 May 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RO5450815-000 (GDC-0449), 0909L053, 98.4% (by HPLC)

Key Study Findings

Methods

Doses:	vehicle, 10, 60, and 300 mg/kg/day
Frequency of dosing:	Once daily on days 6-17 of gestation
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose, 0.2% Tween 80 at pH 3
Species/Strain:	Wistar rats
Number/Sex/Group:	6 mated females per group
Satellite groups:	2 mated females per dose group for toxicokinetic
Study design:	Followed the ICH S5 (R2) guidance
Deviation from study protocol:	Two minimal deviations were noted, but found to compromise the integrity of the study.

Observations and Results

Mortality and Clinical Signs
No deaths and no clinical signs attributed to vismodegib were noted.

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Body Weight
High dose females (300 mg/kg/day) had decreased weight gain while on the study and had resorbed their entire litters. Decreased weight gain was present in the dams after additional calculations for body weight on day 6 was subtracted from carcass weight without the uterus. Weight gain was reduced 5 % in the females after it was normalized for litter resorption.

Feed Consumption
Food consumption was decreased in the high dose animals (13%) when compared to controls.

Toxicokinetics

Rats were continuously exposed to RO5450815-000 at all dose levels for the duration of the dosing period. Maximum plasma concentrations were reached between 1 to 7 hr post doses. On day 1, exposure increased less than dose proportionally. On day 10, $AUC_{0\text{-}24hr}$ increased greater than dose proportionally in the 60 mg/kg/day group and less than dose proportionally in the 300 mg/kg/day group. As a result, the exposure increased less than two fold between the 60 mg/kg and the 300 mg/kg dose level on day 10. After multiple dosing, accumulation was noted in the 60 mg/kg and 300 mg/kg dose group.

Table 24: Toxicokinetics in pregnant female rats

Dose	10 mg/kg/day		60 mg/kg/day		300 mg/kg/day	
Day	1	10	1	10	1	10
T_{max} (hours)	3	1	7	7	7	1
C_{max} (ng/mL)	6 540	7 220	17 400	50 200	36 700	75 400
AUC $_{(0\text{-}24h)}$ ng*hr/mL	63 600	50 500	250 000	620 000	506 000	1 030 000

Stability and Homogeneity

RO5450815-000 at concentrations of 10 and 400 mg/mL were stable (within 10% of theoretical value) for at least 35 days when stored protected from light under refrigerated conditions (2-8 °C). Samples were stable after 6 months protected from light in frozen conditions.
Homogeneity of the RO5450815-000 was within 7% of the overall mean (n=6) when compared with the mean value measured at each sample location, top, middle, and bottom.

Necropsy

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No abnormal findings were noted in the dams.

Fertility Parameters

According to the observed parameters, vismodegib crossed the placenta and was severely toxic to the conceptus.

Table 25: Fertility parameters in pregnant rats administered vismodegib

Dose (mg/kg/day)	0	10	60	300
Implantation sites	82	73	59	74
Pre-implantation loss	1	3	11	5
% of implantation loss per animal	1.7	3.8	17.7	5.8
No of fetuses	75	70	0	0
% of fetuses alive	100	100	0	0
Live fetuses	75	70	0	0
Malformed fetuses	0	17	0	0
Early resorptions (%)	6 (7.7%)	3 (4%)	59 (100%)	74 (100%)

There were 6 pregnant females each in the control and high dose group and 5 pregnant females each in the low and mid dose group. No remarkable differences were observed between male or female offspring loss from low dose females compared to control females. Vismodegib administered at 60 mg/kg/day (corresponding to 2.4 times the steady-state exposure at the recommended human dose of 150 mg/day) was embryolethal to all conceptus.

Structural alterations

Table 26: Structural alterations in offspring of pregnant rats administered vismodegib

	Control/ 0 mg/kg/day		Low dose/ 10 mg/kg/day	
	Fetuses evaluated/ Affected (%)	Litters evaluated/ Affected	Fetuses evaluated/ Affected (%)	Litters evaluated/ Affected
Morphology				
Anomaly	75/0	6/0	70/21 (30%)	5/4
Retardation	75/29 (39%)	6/6	70/50 (71%)	5/5
Variation	75/15/ (20%)	6/5	70/19 (27%)	5/5
External incidences				
Anomaly	75/0	6/0	70/17 (24%)	5/4
Retardation	75/0	6/0	70/0	5/0
Variation	75/0	6/0	70/0	5/0
Fetal Visceral incidence				
Anomaly	39/0	6/0	36/1	5/1
Retardation	39/0	6/0	36/16 (44%)	5/4
Variation	39/4 (10%)	6/3	36/15 (42%)	5/4

Fetal Skeletal Incidence				
Anomaly	36/0	6/0	34/9 (26%)	5/2
Retardation	36/29 (80%)	6/6	34/34 (100%)	5/5
Variation	36/11 (30%)	6/5	34/4 (12%)	5/3

Malformations noted in Table 26 above included absent and/or fused digits on the hind limb; one fetus had an open perineum; one fetus had multiple craniofacial anomalies; The incidence of fetal retardations and variations were increased in fetuses of females given the low dose of vismodegib, 10 mg/kg/day (corresponding to an exposure of 20% of the recommended human dose of 150 mg/day). These retardations and variations included dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws.

11 Integrated Summary and Safety Evaluation

Vismodegib is a small-molecule inhibitor of the hedgehog (Hh) signaling pathway and has been evaluated in a battery of nonclinical, pharmacology and toxicology studies for the proposed indication of adults with basal cell carcinoma that has recurred following surgery (b) (4) or who are not candidates for surgery and radiation. De-regulation of the Hh pathway has been documented in basal cell carcinoma and other cancers.

Vismodegib will be administered orally at 150 mg/day.

Vismodegib has been found to bind to plasma proteins *in vitro* in plasma from humans and multiple animal species. No human-specific metabolites were found in *in vitro* metabolism studies with rat, dog, and human liver microsomes. Rat and dog species were found acceptable for nonclinical evaluation of vismodegib, based on adequate exposures of the drug in these species.

Vismodegib administrations to rat and dogs exhibited toxicities that include:

- Teratogenicity, embryotoxicity and fetotoxicity in rats at subclinical exposures (AUC)
- Germ cell degeneration in younger dogs treated for 4 weeks, but not found in sexually mature male dogs treated for 13 or 26 weeks
- Decreased percent motile sperm was observed in the 26-week rat toxicity study, without corresponding effects on sperm count or morphology or microscopic testicular findings
- A decrease in the number of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks at 100 mg/kg/day
- Toxicities in teeth and bone (alteration/loss of incisors and closure of the femoral epiphysis) in rats
- Alopecia in rats and dogs, follicular cysts in rats, and reversible swelling of

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the paws in dogs with histopathology correlate of follicular hyperkeratosis and granulomatous inflammation
- Reduced number of taste buds in the 26-week rat study
- Reversible tremors, myoclonic jerking, or ataxia in rats
- 1 dog euthanized as moribund in association with thrombocytopenia in the 13-week toxicity study at 150 mg/kg/day
- Reversible increases in serum cholesterol in rats and dogs, but with no effects on serum triglycerides
- Pilomatricoma, a rare, benign subcutaneous neoplasm, was observed in 100-mg/kg/day treated-recovery group animals in the 26-week rat study

Based on the results of a *hERG* safety study and a cardiovascular safety pharmacology study conducted in telemetry instrument-implanted dogs, it is not predicted that vismodegib treatment would induce effects on cardiac function.

Likely pharmacological effects of Hh inhibition were found in skin, growing teeth and bones, and taste buds of treated animals, in addition to the effects on male and female reproductive systems, reversible neurologic effects, platelets findings, and effects on cholesterol.

Effects on growing teeth and bones have not been observed clinically, and they are not expected to affect adult patients. Additionally, predictability of fertility-related reproductive findings in animals to humans remains uncertain.

Overall, vismodegib is considered relatively safe to be used at the dose of 150 mg/day in patients with advanced BCC from nonclinical perspective.

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/s/

DENALI D KUFRIN
01/13/2012

TODD R PALMBY
01/13/2012

MEMORANDUM

Date: January 13, 2012
From: Todd R. Palmby, Ph.D.
Acting Supervisory Pharmacologist
Division of Hematology, Oncology Toxicology
To: File for NDA 203388 vismodegib
Re: Approvability for Pharmacology and Toxicology
Indication: Treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, (b) (4) or who are not candidates for radiation

Non-clinical pharmacology and toxicology studies to support vismodegib NDA 203388 for the treatment of renal cell carcinoma after failure of one prior systemic therapy were reviewed by Dubravka Kufrin, Ph.D. Information included studies conducted with orally administered vismodegib investigating the drug's pharmacology, toxicokinetics and ADME, safety pharmacology, general toxicology (mouse and dog), and genetic toxicity (*in vivo* and *in vitro*). An embryo-fetal developmental toxicology study was conducted in rats to assess the effects of vismodegib on embryo-fetal development. The studies cited in the review consist primarily of original research studies conducted by the applicant.

Pharmacology studies submitted to the NDA support that vismodegib is a hedgehog pathway inhibitor which binds to and inhibits the activity of the Smoothened 7-transmembrane domain receptor. A new Established Pharmacologic Class (EPC) of "hedgehog pathway inhibitor" was proposed by the Applicant for vismodegib. After discussion with management and review staff within the Division of Hematology, Oncology Toxicology as well as Associate Director for Pharmacology and Toxicology, Dr. Paul Brown, in the Office of New Drugs, "hedgehog pathway inhibitor" was determined to be both clinically relevant and scientifically valid.

A significant safety concern encountered in the review of NDA 203388 was the potential for teratogenicity and embryo-fetal toxicity in pregnant women exposed to vismodegib. There is extensive literature describing the critical role of the Hedgehog pathway in embryonic and fetal development. This pathway is highly conserved in many species including nematodes, insects, mammals, etc. There is also evidence that exposure of pregnant animals to Hedgehog pathway inhibitors (e.g., cyclopamine) results in severe midline defects in the offspring of multiple species. In an embryo-fetal developmental toxicity study in rats, vismodegib was teratogenic (missing and/or fused digits, open perineum and craniofacial anomalies) at a dose corresponding to an exposure of 20% of the exposure at the recommended human dose, and was embryotoxic and fetotoxic (early resorption of 100% of the fetuses) at exposures comparable to those at the recommended human dose. A no effect level for malformations was not

identified in this study. Pregnancy Category D is recommended for the use of vismodegib in this patient population.

Repeat-dose toxicology studies in rats and dogs indicate that vismodegib has the potential to impair male and female reproductive function and fertility in humans. A relative decrease in percent motile sperm was observed in rats after 26 weeks administration of oral vismodegib. In dogs, increased numbers of degenerating germ cells and hypospermia were observed in relatively young animals administered oral vismodegib for 4 weeks. A decrease in the number of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks. The reversibility of this finding is unclear. Amenorrhea was observed in clinical trials in females of reproductive potential.

Toxicities in bone (closure of epiphyseal plate) and teeth (missing teeth, degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or loss of teeth) were observed in rats administered oral vismodegib in repeat-dose toxicology studies. These toxicities are consistent with the pharmacological activity of vismodegib inhibiting the hedgehog signaling pathway, and should be considered if vismodegib is administered to pediatric patients; however effects on bone and teeth were not observed in clinical trials with vismodegib.

The most common adverse reactions observed with vismodegib in patients (≥ 10% according to Highlights section of the label) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, vomiting, and ageusia. In rats, a decrease in the number of taste buds on the tongue was observed after 26 weeks administration of oral vismodegib, which is likely related to disgeusia and ageusia observed clinically. Pilomatricoma, a benign tumor arising from the hair follicle, was noted in two rats after 26 weeks administration of oral vismodegib. Similar findings were not identified in clinical trials, and the relevance of this finding in rats is unclear. Alopecia observed in rats and dogs and muscle spasms (tremors and leg twitches) observed in rats were also seen in patients in clinical trials.

Vismodegib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human chromosomal aberration assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay. Carcinogenicity studies have not been conducted with vismodegib. However, patients in the indicated population may have an extended life expectancy and may be chronically treated with vismodegib, so studies are needed to assess the risk of carcinogenicity.

Recommendations: I concur with Dr. Kufrin's conclusion that pharmacology and toxicology data support the approval of NDA 203388 for vismodegib. There are no outstanding nonclinical issues that would preclude the approval of vismodegib for the proposed indication.

The following information should be conveyed in the approval letter regarding the PMRs:

1. To evaluate the potential for carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

2. To evaluate the potential for carcinogenicity, conduct a long-term rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

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/s/

TODD R PALMBY
01/13/2012

MEMORANDUM

Erivedge (vismodegib)

Date: January 13, 2012
To: File for NDA 203388
From: John K. Leighton, PhD, DABT
Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting review of Dr. Kufrin and secondary memorandum and labeling provided by Dr. Palmby. I concur with Dr Palmby's conclusion that Erivedge may be approved and that no additional nonclinical studies are needed for approval of Erivedge for the proposed indication.

As discussed by Dr Palmby, the review team concluded that a carcinogenicity evaluation for vismodegib should be provided. I concur with this assessment.

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/s/

JOHN K LEIGHTON
01/13/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203388 **Applicant: Genentech** **Stamp Date:**

Drug Name: Vismodegib **NDA/BLA Type: NDA** **September 8, 2011**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		X	Rodent carcinogenicity assessment is needed; the NDA is still fileable.
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		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	No, see the response under 4, above.

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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	This will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes.____

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

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

Denali Dubravka Kufrin October 3, 2011

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

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/s/

DENALI D KUFRIN
10/04/2011

TODD R PALMBY
10/04/2011