CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	January 23, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	203388
Applicant Name	Genentech, Inc.
Date of Submission	September 8, 2011
PDUFA Goal Date	March 8, 2012
Proprietary Name / Established (USAN) Name	Erivedge vismodegib
Dosage Forms / Strength	hard gelatin capsules/ 150 mg
Proposed Indication	Vismodegib as treatment for patients with advanced basal cell carcinoma for whom surgery is inappropriate.
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Mona Patel
Medical Officer Review	Michael Axelson
Statistical Review	Xiaoping Jiang
Pharmacology Toxicology Review	Dubravka Kufrin
CMC (DP) and Biopharmaceutics Review	Zedong Dong
CMC Review (DS)	Anne Marie Russell
Product Quality Microbiology Review	John Metcalfe
Facilities (EES) Review	Mahesh Ramanadham
Clinical Pharmacology Review	Jian Wang & Hong Zhao (TL)
Clinical Pharmacometrics Review	Bahru Habetemariam
Clinical Pharmacogenomics Review	Christian Grimstein
IRQT Consultant Review	Qianyu Dang; Joanne Zhang; Justin Earp
OPDP	Carole Broadnax (PI) Sharon Mills (Med Guide)
OSI	Lauren Iaconno-Conners
CDTL Review	Jeff Summers
OSE/DMEPA Review	Richard Abate
OSE/DRISK Review	Amarylis Vega
MHT Consult	Tammie Brent Howard

OND=Office of New Drugs
IRQT+
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

On September 8, 2011, Genentech Inc., submitted an NDA for a new molecular entity, vismodegib (ERIVEDGE capsules), with a novel mechanism of action (inhibition of hedgehog pathway signaling). Vismodegib was studied in patients with recurrent locally advanced or metastatic basal cell carcinoma (BCC) following surgery, with disease progression after radiation or in whom radiation is contraindicated. There is no FDA-approved treatment for patients with metastatic BCC; the most commonly unapproved systemic treatment cited in the published literature is platinum-based chemotherapy. FDA-approved topical therapies (5-FU and Imiquimod creams) for localized lesions have been shown to be effective in patients with small lesions (i.e., < 2 cm in diameter) and their efficacy in patients with recurrent disease and large tumor burden is not known.

The recommendation for approval is based on demonstration of clinically important tumor shrinkage as evidenced by durable overall response rates (ORR) in patients with locally advanced (ORR 43%, median duration 7.6 months) or metastatic (ORR 30%, median duration of response 7.6 months) BCC with an acceptable safety profile (e.g., Grade 3 toxicities occurring in ≤7% of patients which resolved after discontinuation of ERIVEDGE). The benefits of ERIVEDGE outweigh its risks in this patient population, for whom there is no FDA-approved treatment for metastatic disease or where FDA-approved local therapy (Imiquimod or 5FU cream) has not been adequately studied. Regular approval should be granted for this application based on the long duration of responses, which provide both cosmetic improvement as well as the potential for symptomatic relief, in a population with a serious and potentially life-threatening disease. FDA has previously considered durable objective tumor responses as sufficient to support regular approval in cutaneous T-cell lymphoma.

In the clinical trial providing evidence of efficacy, patients were required to have basal cell carcinoma that recurred following surgery and radiation therapy or who were not candidates for surgery or radiation (e.g., patients with Gorlin's syndrome). Central pathologic review of archival or baseline tissue was conducted to confirm the diagnosis of BCC. All thirty three patients with metastatic disease (mBCC) had histologically-confirmed BCC and 63 patients of the 71 with locally advanced disease (laBCC) had histologically-confirmed BCC, by central review. These 96 patients constituted the efficacy-evaluable population. The median age was 62 years, 98% of patients were White, 60% were male, and 97% had an ECOG performance status of 0 or 1. Sixty eight percent of patients had locally advanced disease and 32% had metastatic disease; 21% of the efficacy population carried a diagnosis of Gorlin's syndrome. Among patients with mBCC, 97% were previously treated; prior therapy included surgery (97%), radiotherapy (58%), and systemic therapies (30%). Among laBCC patients, 94% were previously treated; prior therapies included surgery (89%), radiotherapy (27%), and systemic/topical therapies (11%).

The primary endpoint of the trial was objective response rate (ORR) as assessed by an independent review facility. Tumor response for localized disease was based on tumor size (using measurement of externally assessable tumor) and the presence or absence of ulceration in high-quality photographs and on biopsy of local disease sites. In the mBCC cohort, tumor response for metastatic lesions was based on RECIST version 1.0 criteria. The criteria for complete response in localized disease included a requirement for tumor biopsy(ies) demonstrating no pathologic evidence of BCC.

The ORR in patients with mBCC was 30.3% (95% CI 15.6, 48.2) and was 42.9% (95% CI 30.5, 56.0) in patients with laBCC. All responses in the mBCC cohort were partial responses. In the laBCC cohort there were 13 (20.6%) patients with complete responses and 14 (22.2%) patients with partial responses of the 63 efficacy evaluable patients. The median duration of response was 7.6 months (95% CI 5.62, not estimable) for 10 responding patients in the mBCC cohort and 7.6 months (95% CI 5.65, 9.66) for the 27 responding patients in the laBCC cohort.

Safety was evaluated in 138 patients who received vismodegib as monotherapy for laBCC or mBCC. The most common adverse reactions were muscle spasms (72%), alopecia (64%), dysgeusia (55%), weight loss (45%), fatigue (40%), nausea (30%), diarrhea (29%), decreased appetite (25%), constipation (21%), arthralgias (16%), vomiting (14%), and ageusia (11%). Grade 2 adverse reactions occurring in more than 1% of patients were weight loss (7%), fatigue (5%), muscle spasms (4%), and decreased appetite (2%).

The major issue considered during this application was management of the potential teratogenic risks of ERIVEDGE. Vismodegib inhibits the Hedgehog (Hh) pathway; this pathway is activated in most BCC tumors and is also an important embryonic developmental pathway. A developmental toxicology study in rats demonstrated that vismodegib exposure during organogensis results in embryo-fetal death at higher exposures (greater than those achieved during clinical studies with doses at or above the recommended dose) and severe birth defects at exposures within the range achieved with the recommended human dose. (b) (4) (b) (4) (b) (4)

Following internal discussion and teleconferences with Genentech, a revised risk management plan was submitted consisting of revised product labeling (Pregnancy Category D; (b) (4) (b) (4) revised Medication Guide, a voluntary communication plan and an enhanced pharmacovigilance plan. (b) (4)

I concur with the clinical reviewer and CDTL that a REMS is not required to ensure safe use of ERIVEDGE. This determination is based on the following considerations: 1) ERIVEDGE will be prescribed by a self-selected group of healthcare providers, resulting in *de facto* restricted use of the drug by medical oncologists and, possibly, a small group of specialized dermatologists, 2) the clinical practice standards for oncologists include routine risk communication as an integral part of healthcare practitioner-patient discussion prior to initiation of each new anti-cancer therapy, 3) the well-understood nature of the risks of treatment-induced embryolethality and birth defects by the oncology community, and 4) the

benefits of ERIVEDGE in this population with an unmet medical need. All reviewers concurred that the more appropriate designation for this product is Pregnancy Category D, based on the data in the application. I also concur with the need to gather more information with regard to these risks; for this reason, a post-marketing requirement to establish a pregnancy registry to collect pregnancy outcomes data from pregnant women who are exposed to vismodegib, particularly beyond the period of organogenesis, is appropriate.

The Division of Risk Management, Office of Surveillance and Epidemiology agreed with the Division that a REMS with ETASU was not required in order to approve this product. While the DRISK staff preferred that a risk communication program (b) (4) be conducted under a REMS in order to ensure that assessment of the communication plan be provided, the DRISK staff agreed that this was not essential to ensure safe use of ERIVEDGE.

2. Background

Basal cell carcinoma

Basal cell carcinoma (BCC) is a non-melanocytic skin cancer that arises from basal cells, small round cells found in the lower layer of the epidermis. An estimated 1.5 million new cases of BCC were diagnosed in 2010 in the US, making it the most common form of cancer. The majority of BCCs occur on the face (70%), with 25% occurring on the trunk and extremities and 5% on the genitalia. In reported series, the incidence of multiple lesions at presentation ranged from 75 to 21%. There is a modest male predominance and most cases occur in patients 50 years of age or older. BCCs are typically slow growing and, if not resected at an early stage, locally invasive. Metastatic disease to bone, brain, or lungs is estimated to occur in less than $\leq 0.5\%$ of patients. The disease-specific mortality is estimated at less than 0.1%. Recurrence following initial treatment occurs in $\leq 5\%$ of patients; reported risk factors for recurrence are tumor stage (size & depth of invasion), tumor location (head/face), positive surgical margins, and use of poor technique in non-surgical modalities of treatment.

The etiologic role of sun exposure and sun- or UV-damaged skin in the development of BCC is supported by the location of most BCCs in sun-exposed areas, the higher incidence of BCCs in equatorial regions, and the higher incidence of BCC in light-skinned individuals. Other risk factors for BCC include prior irradiation, arsenic exposure, immunosuppression, and a variety of genetic disorders. The patched/hedgehog intracellular signaling pathway has been shown to be altered in both sporadic BCCs and nevoid BCC syndrome (Gorlin syndrome). Loss of inhibition of this pathway is correlated with an increased risk of cancer, including BCC.

Oncology practice guidelines [National Comprehensive Cancer Network (NCCN)] for the initial treatment of localized BCC are surgical excision with assessment for positive margins (Mohs micrographic surgery or surgical excision) or curettage and electrodesiccation. Radiotherapy is recommended for patients who are not candidates for surgical resection or

those with positive margins. Topical therapy is recommended for patients who are not candidates for surgery or radiotherapy. There are two FDA-approved drugs for the treatment of non-melanomatous skin cancer, as topical therapy, and two approved drugs which are used off-label as photosensitizers in conjunction with photodynamic therapy. These drugs are listed in the table below.

Currently Available Drugs for Treatment of BCC

Drug	Class	Specific Indications and Comments
Fluorouracil Cream (5%)	Antimetabolite	Indication for superficial BCC: "In the 5% strength [5-fluorouracil] is also useful for the treatment of superficial basal cell carcinoma when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. The diagnosis should be established prior to treatment, since this method has not proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%."
Imiquimod Cream	Immune response modifier	Approved July 14, 2004 for "topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types.
Porfimer	Photosensitizer	Does not have a labeled indication for BCC
Aminolevulinic acid (ALA)	Photosensitizer	Does not have a labeled indication for BCC

Given the indolent growth pattern of BCC in most individuals, the cure rate is high with definitive local therapy. Of the approximately 5% of patients who recur, treatment generally consists of additional attempts at resection or other locally ablative therapy, including radiation therapy. However, for those with multiply recurrent disease or metastatic disease, which based on estimates provided by Genentech, occurs at an incidence of 2300 new cases per year, there is no established therapy. There are no recommendations from NCCN practice guidelines and published literature is limited to case reports and case series, in which the most common approach appears to be platinum-based chemotherapy or investigational drugs/treatments.

Pre-Submission Regulatory history

Sept. 29, 2006: IND 74573 for GDC-0449 submitted.

April 28, 2008: End-of-Phase 1 meeting held, based on interim results from Phase 1 study showing evidence of anti-tumor activity in advanced BCC. Meeting requested to discuss regulatory strategy to support to receive feedback on whether the target population is appropriately defined for the proposed study in advanced BCC, to obtain feedback on whether he proposed tumor assessment endpoints represent an appropriate measure of clinical benefit for patients with advanced BCC.

Nov. 20, 2008: Protocol titled "A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma" submitted with a request for special protocol assessment (SPA).

Jan. 5, 2009: An SPA "No Agreement" letter issued. The key outstanding issue which remained unresolved was the magnitude of response rate which could support approval. The letter stated

"We agree with separate analyses for the metastatic and locally advanced cohorts. However, we do not believe that response rates of 10% for metastatic disease and 20% for locally advanced disease represent clinically meaningful benefit. The adequacy of the observed response rates to support approval in both metastatic and locally advanced disease will be a review issue. Time to event endpoints can only be considered as descriptive data in a non-randomized single arm study. You have not provided guidance on how to handle missing assessments in your primary analysis in your SAP."

April 29, 2009: Type C meeting to seeking FDA's guidance on the proposed CMC development plans for GDC-0449 to support an NDA in 2Q11. Key agreements reached were

- Acceptability of proposed starting materials provided that the level of impurity (b) (4) (b) (4) in the starting material (b) (4) was (b) (4) and provide adequate control strategies were incorporated.
- Acceptability of the proposed comparability plan for future lots of API.
- Acceptability of the strategy for supporting stability.

Areas where agreement was not reached were

- The proposed approach for process validation
- The proposed approach for setting commercial specifications

May 24, 2010: Submission of treatment protocol titled "SHH4811: A Single Arm Open Label Expanded Access Study of GDC-0449 in Patients with Locally Advanced or Metastatic Basal Cell Carcinoma".

NDA Regulatory History

September 8, 2011: NDA submitted

Data in the following applications were reviewed based on letters of cross-reference authorizing FDA to reference these INDs in support of this NDA:

- IND 74,573 Investigation of the use of GDC-0449 as an oral anti-cancer drug that can be used as a single agent or in combination with other cancer drugs, surgery and or radiotherapy for the treatment of patients with metastatic tumors.
- IND 103,846 held by the National Cancer Institute (NCI) for the Investigator Sponsored Trial for NCI Protocol 8395 entitled Evaluation of food effect on pharmacokinetics of GDC-0449, an inhibitor of Hedgehog signaling.

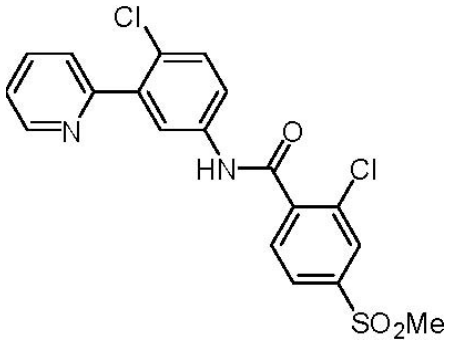
(b) (4)

[redacted]

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. The CMC reviewers state that the recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product. A final recommendation regarding the manufacturing facility for the drug substance is not available as the findings from this manufacturing site inspection are under evaluation. Aside from the final assessment of the acceptability of the drug substance manufacturing site, there are no outstanding issues.

ERIVEDGE™(vismodegib) is a synthetically-derived new molecular molecule. The proposed mechanism of action is as an inhibitor of the hedgehog (Hh) signaling pathway. Vismodegib is described chemically as 2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. The molecular formula is $C_{19}H_{14}Cl_2N_2O_3S$. The molecular weight is 421.30 g/mol and the structural formula is:



The commercial vismodegib drug product is a hard gelatin capsule formulation containing vismodegib 150 mg. The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. The drug product will be packaged in 50 mL (b) (4) HDPE bottles with child-resistant caps and (b) (4) (28 capsules/bottle). Stability testing supports an expiry of 24 months for ERIVEDGE when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). ERIVEDGE is stable and requires no special handling procedures.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

Pharmacology, pharmacokinetic and toxicology studies were conducted as a part of the nonclinical evaluation of vismodegib. Pharmacology studies included *in vitro* assessment of the binding and activity of vismodegib in murine tumor allograft (Ptch1+/- murine medulloblastoma) and xenograft (human colorectal and human pancreatic adenocarcinoma) models, which demonstrated pharmacologic activity (inhibition of tumor growth). Based on these data, the non-clinical pharmacology/toxicology review staff determined that the appropriate Established Pharmacologic Class for this new molecular entity was "hedgehog pathway inhibitor".

Toxicology studies were limited to evaluation of the active ingredient as no novel excipients were used in the manufacturing of vismodegib capsules and the safety of impurities and degradants at the proposed specifications limits have been adequately justified.

Single dose toxicology studies were conducted in mice, rats, and dogs. Repeat-dose toxicology studies were conducted in rats (4-week, 13-week, and 26-week oral gavage) and dogs (4-week, 13-week, and 26-week) with appropriate recovery periods. In rats receiving multiple doses, treatment-related effects in bone (premature closure of the epiphyseal growth plate) at doses ≥ 50 mg/kg/day for 26 weeks, teeth (e.g., 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) at doses ≥ 15 mg/kg/day for 4 weeks, and taste buds (decreased number of taste buds on the tongue) at doses of ≥ 50 mg/kg/day after 26 weeks were observed. The effects on taste buds showed a trend of reversibility following an eight week recovery period.

Findings observed in repeat-dose toxicology studies that were also in human subjects are alopecia (observed in both rats and dogs) and muscle spasms, manifesting as tremors and leg twitches, which occurred in rats administered vismodegib at doses of ≥ 50 mg/kg/day for 4 weeks. In contrast, elevations in total cholesterol, up to 3 and 5 fold, respectively, and increases in both HDL and LDL were observed in both rats and dogs but have not been observed human subjects. The effects on cholesterol levels were reversible in animals and were not correlated with histopathologic findings.

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 postimplantation 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). Findings of dilated renal pelvis and ureter were observed only in 70 vismodegib-exposed fetus, as were the cases of open perineum (n=1) and craniofacial abnormalities (n=1). The incidence of missing/fused digits, incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws were observed in both the treated- and control-fetuses, although the incidence of these events were higher in the vismodegib-exposed fetuses

> Note: *Vismodegib exhibits non-linear pharmacokinetics and saturable absorption. The concentrations of vismodegib achieved in non-clinical studies are substantially higher than was observed in human subjects.*

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.

Two rats administered vismodegib at doses of 100 mg/kg/day for 26 weeks developed pilomatricoma, a benign tumor arising from the hair follicle. The toxicology reviewer's interpretation of this finding is that it is drug-related and represents the progression of follicular cysts that were observed at this dose and duration of exposure at the end of the dosing and recovery phases. However, the clinical relevance of this finding is not known. Carcinogenicity studies have not been conducted with vismodegib; such studies will be conducted under a post-marketing requirement.

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

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

Vismodegib is a highly permeable compound with low aqueous solubility (Biopharmaceutics Classification System [BCS] Class 2). The solubility of vismodegib is pH dependent; the solubility in (b) (4) is 0.1 µg/mL at pH 7 and is 0.99 mg/mL at pH 1. The effect of gastric pH on vismodegib absorption has not been studied in humans.

Dose Selection

Dose selection is based on studies assessing the exposure in clinical trials of patients with cancer following vismodegib at doses of 150 mg, 270 mg, or 450 mg daily and comparisons of daily dosing of vismodegib 150 mg for 11 days followed by random allocation to continue 150 mg daily, 150 mg three times per week, and 150 mg weekly. There was no evidence of increased exposure at daily doses above 150 mg however there was a decrease in exposure following less frequent dosing schedules (e.g., 150 mg three times per week or weekly).

ADME

Detailed pharmacokinetic data were obtained in eight trials enrolling healthy subjects or patients with advanced cancers and the results of a population PK analysis that included pharmacokinetic sampling in the efficacy trial (SHH 4476g) were provided in the NDA. Based on these data, the absolute bioavailability of a single dose of vismodegib 150 mg is 31.8% and its absorption is saturable. Systemic exposure of vismodegib at steady state is not affected by food. Vismodegib plasma protein binding is greater than 99%. Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG), and binding to AAG is saturable. With daily dosing, the average unbound steady-state vismodegib concentrations were <1% of total vismodegib concentrations, regardless of dose (ranging from 150 mg-540 mg). The parent drug is the predominant component (> 98%) in the circulation. Vismodegib and its metabolites are eliminated primarily by the hepatic route. The estimated elimination half-life ($t_{1/2}$) of vismodegib is 4 days after multiple daily doses.

Pharmacokinetics in Specific Populations

The effect of hepatic and renal impairment on the systemic exposure of vismodegib has not been studied. Similarly, the effects of drug interactions have not been adequately studied. However limited *in vivo* data do not suggest that there are significant interactions.

Population pharmacokinetic (PK) analyses suggest that weight (range: 41-140 kg), age (range: 26-89 years), creatinine clearance (range: 30 - 80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.

Exposure-Response Relationship

Exposure-response relationships could not be identified for efficacy or safety given the limited sample size. In exploratory analyses, there was no evidence of a relationship between total or free vismodegib concentrations and either efficacy (as measured by ORR) or safety (based on NCI CTC ≥ Grade 3 toxicity).

Drug Interactions

The NDA contained an interim report for an *in vivo* drug interaction trial (SHH4593g) being conducted in patients with cancer. This DDI trial is assessing the interactions between vismodegib and rosiglitazone (vismodegib as a perpetrator of CYP2C8 inhibition) and between vismodegib and oral contraceptives (vismodegib as a perpetrator of CYP3A induction). The preliminary results indicate that vismodegib does not alter the AUC or Cmax of roxiglitazone or ethinyl estradiol. Modest effects on the Cmax (12% increase) and AUC (23% increase) were observed with norethindrone and vismodegib compared with norethindrone alone. These preliminary data suggest that the efficacy of oral contraceptives will not be compromised by concomitant administration of vismodegib.

Effects on QTc

In a thorough QTc study in 60 healthy subjects, no QTc interval prolongation was observed at vismodegib concentrations achieved in therapeutic trials.

6. Clinical Microbiology

No clinical microbiology review was required for this product.

7. Clinical/Statistical-Efficacy

Clinical efficacy was evaluated in 96 patients with locally-advanced BCC, recurring after surgery or radiotherapy and in whom salvage with additional surgery or radiation was not medically appropriate, due to medical contraindications or the likelihood of unacceptable morbidity or with distant metastatic disease. These patients were enrolled in the single single-arm, two-cohort (locally advanced and metastatic BCC cohorts), activity estimating trial, Protocol SHH 4476g.

The objectives of the primary efficacy trial were:

- To estimate the clinical benefit of vismodegib given as therapy for patients with locally advanced or metastatic BCC, as measured by objective response rate (ORR).
- To estimate of the duration of objective response
- To estimate progression free survival (PFS) and overall survival (OS)
- To assess safety and tolerability
- To characterize the pharmacokinetics
- To assess patient-reported outcomes

Key eligibility criteria were:

- For patients with metastatic BCC, histologic confirmation of distant metastatic disease was required.
- For patients with locally advanced BCC, histologically confirmed disease considered to be inoperable or medical contraindication to surgery in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon. [Note: For this protocol, the presence of multifocal superficial subtype BCC was not sufficient to meet the criterion for inoperability]. Acceptable medical contraindications to surgery included:
  - BCC that has recurred in the same location after two or more surgical procedures where curative resection is deemed unlikely.
  - Anticipated substantial morbidity or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation).
  - Medical conditions predisposing to poor surgical outcome (e.g., diabetes with history of poor wound healing).
  - Other conditions considered to be medically contraindicating as discussed with and approved by the Medical Monitor before enrolling the subject.
- For patients with locally advanced BCC, radiotherapy must have been previously administered for locally advanced BCC with documented disease progression following radiotherapy or radiotherapy was contraindicated or medically inappropriate (e.g., hypersensitivity to radiation due to genetic syndrome such as Gorlin syndrome, effective treatment dose limited because of location of tumor, or cumulative prior radiotherapy dose).
- Patients with nevoid BCC syndrome (Gorlin syndrome) were eligible provided they met eligibility criteria for locally advanced or metastatic disease as listed above.

All patients received a single dose of 150 mg vismodegib daily until disease progression. Patients were monitored for tumor activity (growth or regression) with serial photographs of lesions as well as physical examination and radiographic assessment of known disease. Standard tumor response criteria (RECIST) were utilized to classify tumor response status both by investigators and by independent review facility (IRF) in which assesors were masked to the investigator's classification of tumor response status. Supplemental criteria for classification of lesion response were also employed, which considered both lesion size and ulceration.

The planned sample size of 100 patients was selected based on ability to detect safety signals and an approximately 80% probability of rejecting the null hypothesis given a true overall response rate (ORR) of 37% in the metastatic BCC cohort (with 20 treated patients) and 34% in the locally advanced BCC cohort (with 80 treated patients), based on investigator assessment. With regard to the IRF-determined response rate, the goal was exclusion of an ORR of <20% in the locally advanced cohort and <10% in the metastatic cohort.

> Note: As stated in FDA's Jan. 5, 2009: An SPA "No Agreement" letter, FDA informed Genentech that *"We agree with separate analyses for the metastatic and locally advanced cohorts. However, we do not believe that response rates of 10% for metastatic disease and 20% for locally advanced disease represent clinically meaningful benefit. The adequacy of the observed response rates to support approval in both metastatic and locally advanced disease will be a review issue.*
>
> *Time to event endpoints can only be considered as descriptive data in a non-randomized single arm study. You have not provided guidance on how to handle missing assessments in your primary analysis in your SAP."*

Results: One hundred four patients were enrolled in Protocol SHH 4476g; of these, 96 were eligible for objective response, 63 patients with locally advanced disease and 33 with metastatic disease. The following tables, abstracted from the NDA, provide an overview of the patient population demographics and prognostic information.

SHH4476g Demographic and Baseline Prognostic Variables by Disease Cohort

Baseline Variable	Metastatic BCC (n=33)	Locally advanced BCC (n=63)
Age (yrs)		
Median	62	62
≥ 65 yrs	14 (42%)	30 (48%)
Gender		
Male	24 (73%)	35 (56%)
Ethnicity		
White (non-Hispanic)	100%	97%
Hispanic/Latino	0	1.6%
Unknown	0	1.6%
ECOG PS		
0	13 (39%)	48 (76%)
1	19 (57%)	13 (21%)
2	1 (3%)	2 (3%)
Prior Treatment		
Surgery	32 (97%)	56 (89%)
Radiotherapy	19 (58%)	17 (27%)
Systemic or Topical Therapy	10 (30%)	7 (11%)
Number of Target Lesions		
1	9 (27%)	40 (64%)
2	4 (12%)	12 (19%)
3	9 (27%)	6 (9%)
4+	11 (33%)	5 (8%)

The baseline tumor burden was determined by the sum of the maximum externally visible tumor diameters for all lesions at screening. The median tumor burden at baseline was 56.6 cm (range 6.6 cm to 305 cm). Twenty-one percent of patients carried a diagnosis of Gorlin's syndrome.

All patients enrolled in the trial received one or more doses of vismodegib. The median duration of treatment was 9.8 months and was similar in patients with metastatic and locally advanced disease. The median dose intensity was > 95%. The most common reason for discontinuation of treatment in the metastatic disease cohort was disease progression, whereas the most common reason for discontinuation in the locally advanced disease cohort was patient choice. Fifty-one patients remained on active treatment at the time of the NDA submission.

The primary and key secondary efficacy endpoints are summarized in the following table.

SHH4476g Efficacy Results

Efficacy Endpoints	Metastatic BCC	Locally Advanced BCC
	(n = 33)	(n = 63)
Primary Endpoint		
Objective response rate by IRF (%) (95% CI)	30.3% (15.6%, 48.2%)	42.9% (30.5%, 56.0%)
Complete response	0	13
Partial response	10	14
Secondary endpoints		
Objective response rate by investigator (%) (95% CI)	45.5% (28, 62)	60.3% (47.2%, 71.7%)
Complete response	0	20
Partial response	15	18
Duration of response (IRF) Median (95% CI)	 7.6 mos (5.6, NE)	 7.6 mos (5.6, 9.7)
Duration of response (investigator) Median (95% CI)	 12.9 mos (5.6, 12.9)	 7.6 mos (7.4, NE)

8. Safety

Clinical safety and efficacy were established in 138 patients with BCC enrolled in one of two trials, a single-arm, activity estimating trial (SHH 4476g, the primary efficacy trial) and a single-arm, dose-escalation trial (SHH 3925g, a supportive dose-finding trial). The size of the safety database is insufficient to identify all adverse events occurring at an incidence of less than 2.2%. In addition, due to the lack of an internal control in both of these trials, attribution of toxicity has been made primarily on a higher than expected for non-severe or serious events or unexpected severity (e.g., fatigue). The causal relationship for the serious adverse events (e.g., pneumonia, cardiac events) reported in these trials could not be determined given the low incidence of the adverse event and high projected background rate of such events in this older patient population. Despite these limitations, the database is sufficient to make a risk:benefit determination for vismodegib, considering the magnitude of the benefit and unmet medical need as well as the orphan nature of this indication, where acquisition of additional safety data would significantly delay approval.

Adverse Reactions Occurring in ≥ 10% of Advanced BCC Patients

MedDRA Preferred Term[2]	All aBCC[1] Patients (N= 138)		
	All Grades[3] (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorder			
Nausea	42 (30.4%)	1 (0.7%)	-
Diarrhea	40 (29.0%)	1 (0.7%)	-
Constipation	29 (21.0%)	-	-
Vomiting	19 (13.8%)	-	-
General Disorders and administration site conditions			
Fatigue	55 (39.9%)	7 (5.1%)	1 (0.7%)
Investigations			
Weight decreased	62 (44.9%)	10 (7.2%)	-
Metabolism and nutrition disorders			
Decreased appetite	35 (25.4%)	3 (2.2%)	-
Musculoskeletal and connective tissue disorders			
Muscle spasms	99 (71.7%)	5 (3.6%)	-
Nervous system disorder			
Dysgeusia	76 (55.1%)	-	-
Ageusia	15 (10.9%)	-	-
Skin and subcutaneous tissue disorders			
Alopecia	88 (63.8%)	-	-

[1]aBCC = Advanced Basal Cell Carcinoma

[2]MedDRA = Medical Dictionary for Regulatory Activities.

[3]Grading according to NCI-CTCAE v3.0.

Based on the 120-day safety update, the adverse reactions most frequently resulting in drug discontinuation were muscle spasms (2.9%) and decreased weight (1.9%). The most common severe adverse reactions (NCI CTC ≥ Grade 3) were muscle spasms (5.8%), decreased weight (5.8%), fatigue (4.8%), asthenia (2.9%), decreased appetite (2.9%), and syncope (2.9%). The most common serious adverse events identified in uncontrolled clinical trials (incidence 2% or less) were dyspnea, pneumonia, urinary tract infections, pulmonary embolism, cardiac failure, deep vein thrombosis, gastrointestinal hemorrhage, and hypokalemia. While high incidence and unusual nature of many of the common, non-serious adverse events make attribution to the drug likely, the causal relationship of the serious adverse events to vismodegib treatment is uncertain.

Teratogenicity Risk

There are no human data on the effects of vismodegib on fetal development, however, the extent of the nonclinical data, consistency of findings across the class (e.g., cyclopamine), the well-established mechanism for vismodegib, and the established role of this pathway in embryofetal development are sufficient to establish this risk.

In a pilot embryo-fetal developmental toxicity study, 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 (approximately ≥ 2 times the systemic exposure (AUC) in patients at the recommended human dose), which included early resorption of 100% of the fetuses. Malformations were observed in pregnant rats at a dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended dose) administered during organogenesis. This included an increased incidence above the background rate in control animals within the same pilot study of missing and/or fused digits, incompletely or unossified sternal elements, centra of vertebrae or proximal phalanges and claws (30% of the 70 vismodegib-exposed fetuses). Additional findings included multiple fetuses with retardations or variations (including dilated renal pelvis, dilated ureter) occurring only in the vismodegib-exposed fetuses, one fetus with an open perineum and an additional fetus with craniofacial anomalies among the 70 vismodegib-exposed fetuses in rats receiving doses of 10 mg/kg/day.

(b) (4)

(b) (4)

[redacted] (b) (4)

Following internal discussion and teleconferences with Genentech, [redacted] (b) (4) (Pregnancy Category D; [redacted] (b) (4) revised Medication Guide, a voluntary communication plan, and an enhanced pharmacovigilance plan. [redacted] (b) (4)

The DOP2, DRISK, and MHT reviewers agreed that the revised plan was sufficient to mitigate risks through risk communication to patients and healthcare providers while minimizing burden and limitations on access to ERIVEDGE. Genentech's proposed pregnancy pharmacovigilance plan is designed to collect prospective and retrospective reports of pregnancy exposures to vismodegib. While not a formal pregnancy registry, it contains key elements described in the current Guidance for Industry Establishing Pregnancy Exposure Registries. Under this post-marketing requirement, Genentech will analyze the information submitted and provide descriptive statistics in a stand-alone annual report (separate from the PSUR).

9. Advisory Committee Meeting

ERIVEDGE was not referred for review to the Oncologics Drugs Advisory Committee because outside expertise was not necessary. The Division's recommendation is consistent with actions on prior approvals granting regular approval for cutaneous malignancies for which there is no effective alternative treatment based on durable objective tumor responses or 30-45%. There were no controversial issues that would benefit from advisory committee discussion; following an internal regulatory briefing, additional advice from the ODAC was not considered necessary to determine whether a REMS was needed to ensure safe use of ERIVEDGE.

10. Pediatrics

The Pediatric Review Committee (PeRC) recommended that a full waiver be granted for vismodegib for studies required under PREA (Pediatric Research Equity Act) because the disease (BCC) does not exist in children. [redacted] (b) (4)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. Specifically, no issues were identified as a result of clinical study site inspections or financial disclosures that would preclude approval.

12. Labeling

- Proprietary name
  Conditional approval of the proposed proprietary name of ERIVEDGE was granted on November 28, 2011. The Division of Oncology Products 2 and the Division of Prescription Drug Promotion also concurred with this recommendation.

- Physician labeling: Agreement was reached between FDA and Genentech on physician labeling. The following requested revisions by FDA were incorporated into the final label
  - Indications and Usage
    - Modifications to more accurately reflect the population studied
  - Dosage and Administration
    - Edited for brevity
  - Dosage Forms and Strengths
    - Description of printed information on capsules (e.g., "150 mg" and "VISMO") added. The term "pink" substituted for (b) (4) describing capsule color.
  - Contraindications
    - (b) (4) As stated in FDA Guidance, "A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible benefits." (b) (4)
  - Warnings and Precautions
    - The proposed subsections titled (b) (4) was retitled for clarity as "Embryo-Fetal Death and Severe Birth Defects". This section was expanded to include a summary of the results of the reproductive toxicology study in rats and to provide specific advice for use of effective contraception in females, barrier contraception in males, pre-treatment pregnancy testing, and advises counseling of patients prior to treatment and in the event of pregnancy while receiving ERIVEDGE. Although this risk has been observed only in animals, it was included in Warnings and Precautions given the known mechanism of action of vismodegib and available data on the necessary role of the Hh signaling pathway in embryofetal development.
    - The subsection titled (b) (4) These data

have been moved to the subsection on Pediatrics under Use in Specific Populations.
    - Editorial changes to subsection entitled "Blood Donation" – use of command language.
- Adverse Reactions
    - No listing of serious adverse reactions was included in the labeling given lack of control group and inability to conclude that these events occurred at rates above expected background rates.
    - Information regarding exposure at doses above 150 mg per day moved to Clinical Pharmacology section and data regarding actual drug exposure and demographic characteristics of the safety database (n=138) added.
    - Listing of most common adverse reactions provided in text as well as table.
    - Removal of a (b) (4)
    - Revision of information on metabolic/electrolyte findings temporally-related to treatment and occurring above expected background levels.
- Drug Interactions
    - Subsections created for ease of identification of specific risks.
    - Edited for brevity and limited to expected interactions (b) (4)
    - Addition of potential risk of altered bioavailability (reduced exposure) in patients taking pH lowering agents, based on exploratory PK analyses and predicted interactions between gastric pH and absorption.
- Use in Specific Populations
    - Pregnancy Category (b) (4) changed to Pregnancy Category D (b) (4). Pregnancy Category D was assigned, despite lack of human data, in accordance with the standard practice of the Division of Hematology and Oncology Toxicology to label drugs as Category D based on mechanism of action and predicted effects on a developing fetus. Summary of non-clinical reproductive toxicology data added to this subsection. Directions for patient counseling and information on the pregnancy surveillance program added to this subsection.
    - Pediatric Use subsection revised to include a summary of relevant non-clinical toxicology data on effects on bone development.
    - Addition of new subsection titled "Females of Reproductive Potential and Males" which provides direction for patient counseling on contraception (for females of reproductive potential) and barrier methods to prevent/reduce exposure of females to vismodegib through semen (for males).
    - Addition of sections on Hepatic Impairment and Renal Impairment, informing prescribers on the lack of data regarding use of ERIVEDGE in patients with renal or hepatic organ dysfunction.
    - Subsections on Nursing Mothers and Geriatric Use revised for consistency with FDA guidance documents and regulations.
- Overdosage
    - Editorial changes

- Description
  - Minor editorial changes
  - Vague or potentially promotional qualifiers deleted.
- Clinical Pharmacology
  - Mechanism of Action subsection edited for brevity and essential information; (b) (4)
  - Moved data regarding effects on electrocardiography (QTc) to specific subsection (12.6) in accordance with labeling policy of the Office of Clinical Pharmacology. (b) (4)
  - Subsection on Pharmacokinetics edited for brevity and essential information. Information on pharmacokinetics in Specific Populations revised (b) (4)
- Nonclinical Pharmacology/Toxicology
  - Subsection on Carcinogenesis, Mutagenesis, and Fertility edited for brevity and essential information
  - Subsection on Animal Toxicology revised (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) Edited information on muscle tremors and twitching to essential information.
- Clinical Experience
  - Description of Trial HHS 4476g edited for brevity.
  - Results describing (b) (4) removed from table (b) (4) (b) (4)
  - (b) (4) removed (b) (4) (b) (4) (b) (4)
  - (b) (4) removed (b) (4)
  - Removed (b) (4)
  - In accordance with FDA's Jan 5, 2009 letter, (b) (4) were removed (b) (4)
- Storage and Handling
  - Edited for brevity and to limit redundancy.
- Patient counseling information
  - Bulleted for legibility; edited for brevity and command language.

- Carton and immediate container labels: Agreement was reached between FDA and Genentech on final carton/container labeling. There were no major problems identified; FDA's recommended changes were based on applicable regulations and guidances.

- Patient labeling/Medication guide
  - Edited for consistency with physician package insert and applicable guidances and regulations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that this application be approved.

- Risk Benefit Assessment

  ERIVEDGE approval is sought for the treatment of patients with locally advanced or metastatic basal cell carcinoma that has recurred following surgery and radiation [redacted] (b) (4) This is an uncommon serious medical condition, with an estimated 2300 cases per year, which carries clinically important morbidity in all patients and early mortality in patients with metastatic disease. There are no FDA-approved agents for treatment of metastatic basal cell carcinoma and the FDA-approved topical agents have been studied in small volume disease (lesions less than 2 cm) whereas median tumor burden for patients in this trial was 56 cm. The evidence of effectiveness in this trial is based on durable objective tumor responses in a sufficient fraction of patients to justify the risks of treatment in the overall population; FDA has used similar data to support the approval of drugs for the treatment of CTCL, another cutaneous malignancy. The evidence of overall response rate and durability of response were confirmed by an independent panel and are thus considered robust. Furthermore, the NDA contained photographic evidence of localized disease, which was reviewed by Dr. Axelson, who confirmed evidence the IRF's determination of response. In light of the unmet medical need, these data are sufficient to establish that the drug is effective. The toxicity profile of this product is dominated by mild to moderate muscle spasms, fatigue, and weight loss, as well as alopecia in most patients, however these toxicities led to termination of treatment in a small fraction of the patients, primarily those with localized disease. The major risk is to the fetus of a woman exposed to ERIVEDGE during pregnancy. As discussed below, this risk can be minimized through contraception (females) and barriers (males); this risk is common to other antineoplastic agents has been generally well-managed by medical oncology community through education of patients and contraceptive use. These risks do not outweigh the benefits of durable tumor shrinkage in the indicated patient population.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  In general, the Office of Hematology and Oncology Products has not required risk evaluation and mitigation strategies (REMS) for common, well-understood toxicities of a variety of products approved for the treatment of cancer; instead the requirement for a REMS have been reserved for mitigation of serious toxicities which are novel or where risk mitigation strategies are not well known or understood in the medical oncology community. Examples of such REMS include the REMS to mitigate the risks of QT prolongation for Caprelsa (vendetanib) or to mitigate risks of autoimmune disorders for

Yervoy (ipilimumab). In contrast, the risk of severe birth defects and intrauterine death is common to many cancer treatments across multiple product classes. With the exception of products/product classes first approved for non-cancer indications (e.g., thalidomide), REMS have not be required to mitigate the risks of teratogenicity.

REMS programs are intended to provide sufficient safeguards to permit approval of a drug which, absent the REMS, would not be approved because the risks of the drug would outweigh the benefits. The Office of Hematology and Oncology Products is responsible for making marketing decisions for drugs which often carry serious toxicities but are also intended to treat serious and life-threatening diseases (various cancers) where the options are limited and alternatives treatments, when available, are generally also toxic although the profile may differ. For this reason, even when there is an approved treatment, alternatives treatments may be desirable because the toxicity profile of a new drug may be offer advantages for individual patients over the toxicity profile of the approved drug(s).

Since many therapeutic options in oncology carry substantial toxicities, the clinical practice of oncology has evolved standards of care for risk communication and risk mitigation, including the routine practice of informed consent at the initiation of a new treatment regimen, standardized risk communication tools for commonly used agents, specific training in elicitation of symptoms of potentially serious toxicity which enhance early identification and mitigation of more serious risks. Based on SEER reporting, it is estimated that 13% of cancers will occur in women of child-bearing potential and that one in 1000 pregnancies will be complicated by concurrent cancer. Thus, although relatively uncommon, the potential for identification of a pregnancy in patients with cancer and counseling on both contraceptive use and potential risks to the fetus based on animal data are well-understood by the oncology community. What is less well understood is the incidence of specific risks to the fetus throughout the duration of pregnancy (i.e., beyond organogenesis). The known risks are based on case reports or small case series, however there are no controlled trials and case-controlled series suggest that the risks may have been overestimated based on animal data.

I concur that, despite the seriousness of the teratogenic risk, a REMS should not be required for the following reasons

- There are no effective alternative therapies
- Treatment is administered for a limited duration of treatment (median 10 months)
- The number of individuals potentially affected by these risks (estimated at 230 women of child-bearing potential per year) is small
- The standard of medical care in the medical oncology community prescribing this drug provides adequate safeguards through familiarity with the risks, risk communication, and patient monitoring.

- Recommendation for other Postmarketing Requirements

    - To conduct a pregnancy surveillance program and submit annual reports on data collected. Rationale: Vismodegib resulted in embryolethality (exposures higher than that achievable in humans) and severe birth defects (at exposures expected with clinical use) in a rat reproductive toxicology study. The hedgehog signaling pathway is highly conserved across animal species, thus effects observed in rats are likely to occur in humans.

    - To conduct two rodent carcinogenicity studies, in rats and mice to assess the potential for vismodegib to cause carcinogenicity. Rationale: In the clinical trial used to support marketing (Study SHH 4476g) the median time of exposure to vismodegib was approximately10 months. It is anticipated that patients in the indicated population may be chronically exposed to vismodegib for up to three years. Since vismodegib is in a pharmacologic class with no other approved drugs, the carcinogenic potential is unknown, and therefore should be investigated in appropriately designed non-clinical studies.

    - To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function -Study Design, Data Analysis and Impact on Dosing and Labeling". Rationale: Hepatic excretion is the primary route of elimination for vismodegib, however there are insufficient data from the clinical trials to determine the effect of hepatic impairment on the pharmacokinetics of vismodegib.

    - To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling". A "reduced" renal impairment study could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The rationale for this PMR is that, while renal elimination accounts for approximately 4% of the total vismodegib dose, the Agency is aware of examples where renal impairment has had substantial impact on PK for drugs with minimal renal excretion.

    - To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone). Rationale: Vismodegib has a potential for inhibiting CYP2C8, CYP2C9 andCYP2C19, based on the *in vitro* studies with human liver microsomes. Women of child-bearing potential may be prescribed oral contraceptives and it is essential that the final report for the trial assessing the potential for drug-interactions between vismodegib and oral contraceptives be reviewed.

- Conduct a clinical trial to evaluate if gastric pH elevating agents (e.g. proton pump inhibitors, H_2 antagonists and antacids) alter the bioavailability of vismodegib. Rationale: vismodegib has limited solubility which may be pH-dependent.

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/s/

PATRICIA KEEGAN
01/24/2012