CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	01/13/2012
From	Jeff Summers, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA # 203388
Applicant	Genentech
Date of Submission	September 08, 2011
PDUFA Goal Date	March 8, 2012
Proprietary Name / Established Name	Erivedge (vismodegib)
Dosage forms / Strength	150 mg capsules
Proposed Indication(s)	Treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate.
Recommended:	*Approval*

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1. Introduction

Genentech submitted New Drug Application (NDA) 201532 on September 8, 2011 for vismodegib (proposed trade name, Erivedge) for the treatment of adult patients with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate. Vismodegib is a low molecular weight, orally available inhibitor of the Hedgehog pathway that binds to and inhibits the function of the transmembrane protein smoothened (SMO).

To support this NDA, the Applicant primarily relied on the results of a single-arm, multi-center, 2 cohort study in 104 patients with either metastatic BCC (n=33) or locally advanced BCC (n=71). Study SHH4476g demonstrated a clinically meaningful overall response rate in both cohorts of patients as assessed using RECIST criteria in patients with metastatic disease and a composite scale using size, ulceration, and photography for patients with localized disease.

The following important issues were considered during the review of this application:

Clinical/Statistical: The primary issue considered during the review of this application was whether the results of a single-arm study in a limited number of patients with the primary efficacy outcome measure of response rate was sufficient to support approval. Ultimately, the primary clinical reviewer recommended approval based on the overall Objective Response Rate (ORR) and duration of response results from Study SHH447 and the lack of any approved or effective therapies for these indications (see Section 7 below). An additional issue considered during the clinical part of the review was whether a Risk Evaluation and Mitigation Strategy (REMS) was necessary to address the issue of teratogenicity. It was determined that the teratogenicity of this drug was similar to other approved oncology chemotherapeutic drugs and based on the patient population, indication, risk:benefit assessment, and treatment setting, that a REMS was not necessary.

Clinical Safety/Safe Use: Study SHH4476g demonstrated a clinically meaningful ORR and duration of response in both cohorts of patients with BCC (metastatic and locally advanced). Adverse events thought to be causally related to vismodegib, based on review of the single-arm study, pooled study data using vismodegib for other indications, and limited placebo controlled data, are muscle spasms, dysgeusia, alopecia, weight decreased, nausea, and decreased appetite. The incidence and severity of these adverse reactions are not unacceptable in light of the clinical benefit as determined by ORR and duration of response.

Additional considerations regarding safe use in special populations (i.e., patients with renal insufficiency and impaired hepatic function) were identified by clinical pharmacology review staff and are described in Section 6 of this review.

Product: Vismodegib is a small molecular weight inhibitor of smoothened protein. The chemical name is 2-chloro-N-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonylbenzamide. The solubility of vismodegib is pH dependent, 0.1 µg/mL (b) (4) at pH 7 and 0.99 mg/mL at pH 1. The (b) (4) pH dependency raised concerns about the potential differences in oral bioavailability in patients using gastric acid modifying drugs. ONDQA has not identified any CMC issues that would preclude approval to date but the final CMC review is still pending. ..

2. Background

Vismodegib is a small molecule inhibitor that binds to and inhibits smoothened (SMO), a G-protein-coupled receptor in the hedgehog (Hh) signal pathway. Vismodegib demonstrated *in vitro* inhibition of Hh signaling in mouse and human cell lines through binding and inhibiting smoothened. *In vivo* studies of vismodegib activity included growth inhibition of medulloblastoma tumors and colorectal tumors in mice, as well as suppression of *Gli1* mRNA, a transcriptional target of Hh signaling.

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. Although there are roughly 3.5 million cases of NMSC annually in the US, only an exceeding small percentage of the BCC cases become metastatic or locally advanced to the extent they are not amenable to surgical or radiation treatment. The Applicant estimates an incidence rate of approximately 2000-3000 new cases of metastatic or locally advanced disease (not amenable to surgery or radiation) per year.

There are no FDA approved therapies for advanced or metastatic BCC. There is no effective therapy for metastatic disease or locally advanced disease that is refractory to- or not amenable to- surgery or radiation. Survival is short for patients with metastases with a range of 8-14 months and a 5 year survival rate of approximately 10% in patients with locally advanced and metastatic BCC.

The following important drug development and regulatory advice was provided to the applicant over the course of the development program from 2006 to the present, as discussed extensively by Dr. Axelson in his primary Medical Officer review.

- Concerns were raised regarding the definition of locally advanced disease and specific criteria for defining unresectability were requested. The applicant agreed to provide a more detailed criteria for locally advanced disease including criteria defining subjects for whom further surgery may be medically contraindicated or who are unresectable but may not receive radiation therapy or who previously received radiation therapy.
- The evaluation for efficacy in both RECIST-measurable and non-RECIST-measurable disease in one analysis would not be acceptable due to the differences in defining the populations and the proposed endpoints.
- A primary endpoint based on assessment of cutaneous lesions may be acceptable if it was adjudicated by independent review of digital photography
- The Applicant submitted a Special Protocol Assessment (SPA) twice during 2008 and 2009, and although never approved, extensive advice regarding the composite endpoint for localized disease response assessment was provided.
- Response rates of 10% for metastatic disease and 20% for locally advanced disease did not represent clinically meaningful benefit and the adequacy of the observed response rates to support approval in both metastatic and locally advanced disease will be a review issue.
- At the May 11, 2011 pre-NDA meeting FDA stated support for NDA approval based on a single arm trial (SHH4476g) would be a review issue based on review of the data and FDA's prior concerns about the trial population and response criteria.

3. CMC

Facility inspection reports have not been completed and the primary ONDQA CMC review is not finalized. Although there are no anticipated CMC issues regarding manufacturing processes, until the facility inspection reports are completed and the ONDQA CMC review finalized, no determination can be made on the CMC aspects of NDA 203388.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review team did not identify any pharmacology/toxicology issues that precluded the approval of vismodegib for the requested indication. Postmarketing requirement carcinogenicity studies were recommended because of concerns of chronic exposure to vismodegib in this patient population with a median time of exposure of approximately 10 months.

4.1 General nonclinical pharmacology/toxicology considerations

Safety Pharmacology Assessments
The pharmacology/toxicology review contained the following conclusions based on safety pharmacology studies:

- Vismodegib demonstrated no significant off-target binding 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.

Repeat-dose Toxicology Studies
Toxicities in bone and teeth were observed in rats administered oral vismodegib. The effects on bone consisted of closure of the epiphyseal growth plate and there were abnormalities in growing incisor teeth. It was noted that these toxicities should be considered if vismodegib is administered to pediatric patients.

Other toxicities observed in rats and dogs included elevations in total cholesterol (including both HDL and LDL). In rats, a reversible decrease in the number of taste buds on the tongue was observed which is consistent with the common adverse events of dysguesia and aguesia identified from the human clinical trial safety data. Other common adverse events that were observed in clinical trials with vismodegib that were also observed were alopecia (rats and dogs) and muscle spasms (tremors and leg twitches in rats)

Genetic-toxicology studies
Vismodegib was not mutagenic or clastogenic as analyzed using an acceptable standard battery of tests

4.2 Carcinogenicity

Carcinogenicity studies have not been conducted and based on the proposed indicated patient population, carcinogenicity studies are required and were recommended as PMRs by the Pharmacology toxicology review team.

4.3 Reproductive toxicology

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. There was a decrease in motile sperm in rats, and young dogs displayed increased numbers of degenerating germ cells and hypospermia. There was a decrease in the number of corpora lutea observed in female rats.

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 with 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).

4.4 Other notable issues

There were no other notable Pharmacology/Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

Overall, the review staff from the Office of Clinical Pharmacology found that the clinical pharmacology data in NDA 203388 were acceptable for approval. The review team recommended hepatic and renal impairment studies, a drug interaction trial with a sensitive CYP2C8 substrate and oral contraceptive components, as well as a study designed to assess the effects of gastric pH elevating agents on the oral bioavailability of vismodegib.

5.1 General clinical pharmacology/biopharmaceutics considerations

As described in the clinical pharmacology review, vismodegib exhibits nonlinear with saturable absorption, saturable binding to AAG, minor metabolism and major hepatic elimination. Exposure-response relationships were not identified for efficacy or safety based on the limited data. In a thorough QTc study in 60 healthy subjects, no QTc interval prolongation was observed with the therapeutic dose regimen of vismodegib.
The single dose absolute bioavailability of vismodegib at 150 mg is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg or 540 mg vismodegib. Systemic exposure of vismodegib at steady state is not affected by food.

Vismodegib plasma protein binding is greater than 99%, binding to both human serum albumin and alpha-1-acid glycoprotein (AAG). The parent drug is the predominant component (> 98%) in the circulation. Metabolic pathways of vismodegib include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant metabolites recovered in feces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5. The estimated elimination half-life (t1/2) of vismodegib is 4 days after continuous once-daily dosing and 12 days after a single dose.

5.2 Drug-drug interactions

Vismodegib is an inhibitor of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19 and transporter BCRP. Preliminary *In vivo* studies indicate that there was no clinically meaningful difference in the pharmacokinetics of rosiglitazone, a CYP2C8 substrate, ethinyl estradiol, or norethindrone when co-administered with vismodegib. The final report will be submitted as part of a PMR.

Vismodegib is minimally metabolized by CYP enzymes and primarily excreted as unchanged drug, therefore CYP inhibition would not alter vismodegib concentrations to any significant extent. *In vitro* studies results also indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (Pgp)

5.3 Pathway of elimination

Vismodegib and its metabolites are eliminated primarily by the hepatic route with 82% of the administered dose recovered in the feces and 4.4% recovered in the urine within 56 days.

5.4 Evaluation of intrinsic factors potentially affecting elimination

The effect of hepatic and renal impairment on the systemic exposure of vismodegib has not been studied. The drug is primarily excreted in the feces with only 4.4% of the drug recovered in the urine; however, only 32% is bioavailable, therefore this translates into more than 10% of the absorbed drug being eliminated through the kidney. The Applicant has agreed to conduct both hepatic and renal impairment studies. The renal impairment study will only evaluate severe renal impairment. These impairment studies are being recommended by the Clinical Pharmacology review team as PMRs.

5.5 Demographic interactions/special populations

Limited population pharmacokinetic (PK) analyses suggest that weight, age, creatinine clearance (range: 30 to 80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.

5.6 Thorough QT study or other QT assessment

The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the results of the thorough QTc (TQT) study and concluded that no significant QTc prolongation effect of Vismodegib was detected. The largest upper bound of the 2-sided 90% CI for the mean difference (ΔΔQTcF) between vismodegib 150 mg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance document. The largest lower bound of the two sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated indicating that assay sensitivity was established.

6. Clinical Microbiology

This section is not relevant for this chemotherapy drug. Quality microbiology issues are described in Section 3 above.

7. Clinical/Statistical- Efficacy

The clinical and statistical reviewers recommended approval of vismodegib based upon the efficacy and safety results of Study SHH4476g. The study demonstrated in patients with metastatic BCC with no other effective treatment options, an objective tumor response rate by RECIST criteria of 30% with a clinically meaningful duration of response of 7.6 months. In patients with locally advanced disease who were not candidates for surgical resection and who recurred after radiation therapy (unless radiation therapy was contraindicated) the ORR as measured using a composite lesion size and ulceration scale and evaluated by an independent

assessment committee using high resolution digital photography was 43%. Tumor shrinkage of malignancies that have primary symptomatic skin involvement is considered clinical benefit.

7.1 Background of clinical program

Refer to Section 2 above that describes the background of the clinical program.

7.2 Design of efficacy studies

The efficacy data supporting this NDA was based on the results of one single-arm, multi-center, 2 cohort study in 104 patients with either metastatic BCC (n=33) or locally advanced BCC (n=71). Study SHH4476g entitled "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"

Control Arm

This was a single arm study with no concurrent control group. The eligibility criteria requiring recurrence of tumor despite prior radiation therapy (or contraindications to radiotherapy) and lesions not amenable to surgical resection as documented by a surgeon—defined a group of patients with locally advanced BCC that did not have effective therapeutic options besides local wound care. There is also a paucity of data, other than anecdotal reports, to support chemotherapeutic approaches to metastatic BCC. The lack of effective therapy, the small size of the indicated patient population, and the encouraging results from the phase 1 study in BCC patients allowed FDA to agree to the single arm study design with the caveat of using defined response assessment scales and the understanding that the response rate and duration of response would need to be clinically meaningful.

Eligibility Criteria

The most important eligibility criteria were those intended to define a patient population for which there was no effective therapy. Patients with locally advanced disease were to have histologically confirmed BCC that was considered to be inoperable, or surgery was medically contraindicated. Locally advanced disease must have received previous radiotherapy unless radiotherapy was contraindicated or inappropriate. Patients with previously irradiated locally advanced BCC must have progressed after radiation therapy. Patients with nevoid BCC (Gorlin) syndrome could enroll in the trial but had to meet the criteria for locally advanced or metastatic disease. Patients with metastatic BCC were required to have measurable disease by RECIST criteria.

General Study Design/Treatment Plan

Patients were enrolled into either the metastatic BCC cohort or the locally advance BCC cohort based on screening evaluations. Patients received 150 mg of vismodegib daily until evidence of progression or intolerable drug related toxicity. Tumor assessments occurred every 8 weeks and at study discontinuation. Follow up for survival for was every 3 months until death or loss to follow-up.

Statistical Design

This was a single arm study that generated descriptive data, no inferential statistical analyses were conducted.

The major efficacy outcome measure of the trial was objective response rate (ORR) as assessed by an Independent Radiology Charter using RECIST criteria for patients with

measurable metastatic disease and an Independent Panel Review for patients with locally advanced disease. Tumor response evaluation for locally advanced disease included measurement of externally assessable tumor and assessment for ulceration in photographs, radiographic assessment of target lesions (if appropriate), and tumor biopsy. An objective response in locally advanced BCC required at least one of the following criteria and absence of any criterion for disease progression: (1) ≥ 30% reduction in the sum of longest diameter of the target lesions (SLD) from baseline by radiographic assessment; (2) ≥ 30% reduction in SLD from baseline in externally visible dimension of target lesions; (3) complete resolution of ulceration in all target lesions. Disease progression was defined as any of the following: (1) ≥ 20% increase in the SLD from nadir in target lesions (either by radiography or by externally visible dimension); (2) new ulceration of target lesions persisting without evidence of healing for at least 2 weeks; (3) new lesions by radiographic assessment or physical examination; (4) progression of non-target lesions by RECIST.

7.3 Study results

Summary

The efficacy of vismodegib was primarily based on the results of Study SHH4476g, a study that showed a clinically meaningful ORR and duration of response in both patients with metastatic BCC and patients with locally advanced BCC. Although the efficacy data in this NDA comes from one single-arm non-controlled study, relying on this data to support approval of vismodegib is possible because of the unequivocal clinical benefit in a sizable fraction of the patients treated, and the lack of any effective therapy for the indicated patient populations. The FDA guidance document "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*" describes the situations in which FDA can rely on a single study plus additional supportive data.

The ORR in patients with metastatic BCC was 30.3% (95% CI 15.6, 48.2) and 42.9% (95% CI 30.5, 56.0) in patients with locally advanced BCC. All ten responses in the metastatic BCC cohort were partial responses. In the locally advanced BCC cohort there were 13 (20.6%) complete responses and 14 (22.2%) partial responses of the 63 efficacy evaluable patients (patients were excluded who did not have BCC diagnosed by pathology at baseline). The median duration of response was 7.6 months (95% CI 5.62, Not Estimable) for subjects with metastatic BCC and 7.6 months (95% CI 5.65, 9.66) for subjects with locally advanced BCC.

Demographics of Study 305

The median age at enrollment was 62, 60% were male, 100% were Caucasian, and over 60% of the patients were from the United States. The vast majority of patients (94%) received prior cancer treatment. The most common prior treatment for patients with locally advanced BCC and metastatic BCC were surgery and radiation, followed by non-anthracycline chemotherapy, biologic therapy, and anthracycline chemotherapy. Although 74% of patients did not receive prior radiotherapy, this was secondary to having a diagnosis of Gorlin's syndrome or large tumor size with involvement of structures that did not allow for radiation therapy without undesirable complications.

Analysis of the Primary Endpoint

As previously stated, the primary endpoint was ORR using RECIST criteria for metastatic disease or a composite endpoint of lesion size and extent of ulceration by digital photography for locally advanced disease.

Objective response was defined as a CR or PR determined on two consecutive assessments ≥ 4 weeks apart, using RECIST for metastatic BCC patients and a composite endpoint for locally advanced BCC patients. The protocol definition of ORR was the proportion of responding patients within each cohort.

A total of 10/33 (30.3%) patients with metastatic BCC met criteria for objective response (all partial responses). A total of 27/63 (42.9%) of patients with locally advanced BCC met criteria for objective response; thirteen had CR and fourteen had PR. Table 1 and 2 are excerpted from the medical officer clinical review.

Table 1 : Primary Endpoint SHH447g Efficacy Evaluable

Primary Endpoint	mBCC (n=33)	laBCC (n=63)
Subjects with objective response	10 (30.3%)	27 (42.9%)
95% CI for objective response	(15.6%, 48.2%)	(30.5%, 56.0%)
p-value (2-sided)	0.0021	< 0.0001
Complete response	0	13 (20.6%)
Partial response	10 (30.3%)	14 (22.2%)
Stable disease	21 (63.6%)	24 (38.1%)
Progressive disease	1 (3%)	8 (12.7%)
Missing (no post-baseline tumor assessment)	1 (3%)	4 (6%)

Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma;

An FDA analysis of all enrolled patients, including patients without protocol specified pathology evaluations, demonstrated similar findings.

The median duration of response for both subjects with metastatic BCC and locally advanced BCC was 7.6 months.

Table 2: Duration of Response SHH4476g

DOR	mBCC (n=33)	laBCC (n=63)
Subjects with objective response	10	27
Number censored	7 (70.0%)	14 (51.9%)
Number of events	3 (30.0%)	13 (48.1%)
Earliest contributing event:		
Disease progression	3	12
Death	0	1
Duration of objective response (mo)		
Median (95% CI)	7.6 (5.62, NA)	7.6 (5.65, 9.66)
25th-75th Percentile	5.7-NE	5.7-9.5

Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; DORS = duration of response; NE = not estimable

8. Safety

8.1 Adequacy of database, major safety findings

Overall, safety was demonstrated in the primary study and by careful analysis of pooled data across the vismodegib development program. FDA previously agreed to pool data across studies of patients with advanced basal cell carcinoma. The only study that evaluated vismodegib at the does and schedule for which the applicant is seeking approval was the single-arm study SHH476g used to support efficacy. The small size of the pooled safety database limits the evaluation of adverse events that only occurred once or at a low frequency.

In addition, only two studies with placebo controlled data conducted in 104 patients with ovarian cancer and approximately 200 patients with mCRC randomized 1:1 to vismodegib or placebo was provided that could be used to help determine attribution of adverse reactions to vismodegib.

The adverse reactions thought to have a causal association to vismodegib, based on their frequency in the pooled safety data base and correlation to differences in incidence rates observed in the placebo controlled studies are: muscle spasms, dysgeusia, alopecia, weight decreased, nausea, decreased appetite, constipation, and vomiting. The AE findings of dysgeusia and muscle spasms were corroborated by findings in the preclinical toxicology studies.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

As described in the clinical review, a total of 17 patients died in the pooled studies. The Applicant stated that none of the deaths were thought to be attributable to vismodegib. Most of the deaths were due to progressive disease or secondary sequelae from progressive disease. The cases of death from "unknown cause" or for cardiac related reasons could not be definitively ruled out as vismodegib related by the medical officer; however, there was no preclinical data to suggest this toxicity and no QTc prolongation was seen in a TQTc study. These cardiac events would not be unexpected in this patient population. The lack of a concurrent placebo control arm greatly reduces the ability to determine a causal association to study drug of an adverse reaction that spontaneously occurs in specific patient population.

SAEs

Determination of a causal association of the SAEs captured in the pooled safety data base to vismodegib was not possible because the studies did not include a control arm. None of the SAEs were of such an unusual nature i.e., a "designated medical event" that attribution could be assigned tentatively based on that finding alone. Five patients experienced cardiac related SAEs and 7 patients experienced infectious related SAEs. There was no preclinical evidence of cardiac toxicity and a TQTc study did not demonstrate QTc prolongation. Clinical trial laboratory data did not reveal myelosuppression as a drug toxicity that might predispose a patient to infectious agents.

In a placebo controlled study conducted in patients with metastatic CRC there was an imbalance in deep vein thrombosis and pulmonary embolism as shown in the following table:

SHH4429g Grade 3-5 SAEs

	Placebo n = 98 (%)	**Vismodegib n = 98 (%)**
Pulmonary Embolism	4 (4.1%)	7 (7.1%)
Deep Vein Thrombosis	1 (1.0%)	4 (4.1%)

As noted in the clinical review, although there were numerically more thrombotic events in the vismodegib arms in Study SHH4429g, the small size of this placebo controlled study make interpretation of causality difficult.

Drop-outs and Discontinuations due to Adverse Events

According to the clinical reviewer's analysis of the safety data, the major reason for discontinuing study treatment in the pooled study data was "missing" (45%) followed by progressive disease (21%) and adverse reaction (9%). The clinical review notes that muscle spasms, fatigue, and dysgeusia were the only AEs in the single-arm study used to support efficacy for which some causality could be inferred based on the limited placebo controlled data available from the vismodegib development program.

Common Adverse Events

The clinical reviewer conducted a review of all adverse events and severe adverse events using the structure of the MedDRA hierarchy. Common adverse events, across the pooled study data, occurring in at least 10% of patients who received vismodegid were muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, nausea, diarrhea, decreased appetite, constipation, couth, arthralgias, vomiting, headache, ageusia, insomnia, and upper respiratory tract infection. The most common Grade 3 or greater AEs were weight decreased, fatigue, muscle spasms, and dysgeusia.

These observations in the pooled data were supported by the two placebo controlled studies in different patient populations with different indications as show below in the tables excerpted from the clinical review and the Applicant's mCRC clinical study report. The metastatic colorectal cancer study employed a background chemotherapy regimen of either FOLFIRI of FOLFOX (irinotecan or oxalilatin and leucovorin plus bolus or infusional 5-fluorouracil).

Table 3: Most Common (≥ 10%) AEs in SHH4489g (Ovarian Cancer) with higher incidence in the vismodegib arm compared to placebo

Adverse Events 4489	Placebo	Vismodegib		Vismodegib	
	N= 52	N = 52	All AEs%	AEs G3-4	AEs G3-4 %
DYSGEUSIA	9	35	67%	11	21%
MUSCLE SPASMS	1	35	67%	9	17%
ALOPECIA	4	28	54%	-	0%
NAUSEA	9	17	33%	5	10%
CONSTIPATION	5	12	23%	-	0%
ABDOMINAL PAIN	7	10	19%	5	10%
DECREASED APPETITE	1	10	19%	5	10%
ABDOMINAL PAIN UPPER	3	9	17%	4	8%
VOMITING	5	8	15%	4	8%
WEIGHT DECREASED	1	6	12%	2	4%
RASH	2	6	12%	2	4%
BACK PAIN	4	6	12%	2	4%
ASTHENIA	3	5	10%	1	2%
DRY MOUTH	1	5	10%	1	2%
MUSCULOSKELETAL PAIN	3	5	10%	2	4%

Table 4: Most Common (≥ 10%) AEs in SHH4429 (metastatic colorectal cancer) with higher incidence in the vismodegib arm compared to placebo

Adverse Events	Placebo (n%) + (FOLFIRI or FOLFOX)	Vismodegib (n%) + (FOLFIRI or FOLFOX)
VOMITING	31 (31.6)	42 (42.9)
ASTHENAI	9 (9.2)	19 (19.4)
WEIGHT DECREASED	13 (13.3)	35 (35.7)
DECREASED APPETITE	24 (24.5)	49 (50.0)
DEHYDRATION	9 (9.2)	24 (24.5)
MUSCLE SPASMS	2 (2.0)	16 (16.3)
DYSGEUSIA	9 (9.2)	41 (41.8)

Laboratory Tests

There were no Grade 4 laboratory toxicities observed. Treatment-emergent Grade 3 laboratory abnormalities observed in clinical trials were hyponatremia in 6 patients (4%), hypokalemia in 2 patients (2%), and azotemia in 3 patients (2%). Only one patient experienced a grade 3 lymphopenia that was not a pre-existing toxicity.

8.3 Immunogenicity

Issues regarding immunogenicity are not applicable to this small molecule drug.

8.4 Special safety concerns

The pharmacology/toxicology and clinical review teams, as well as the Applicant, identified teratogenicity as a safety concern. (b) (4) (b) (6) As previously discussed in section 4, vismodegib was teratogenic, embryotoxic, and fetotoxic in an embryo-fetal toxicology study at doses that reflect the expected human exposure for the indicated use of the drug. Review of prior oncology drug approvals revealed multiple approved drugs with a similar incidence and severity of teratogenic effects as documented in animal studies that were conducted using dosing regimens that would be relevant to the anticipated human exposures in clinical practice.

A detailed review of the various risk minimization strategies currently employed for teratogenic drugs across the agency, and specifically for oncology drugs was conducted by DRISK. A CDER regulatory briefing to discuss the risks of oncology drugs with respect to teratogenicity, risk management, and pregnancy labeling was held. Highlights of those discussions included the following:

- The risk of teratogenicity for the vast majority of oncology drugs is managed through professional labeling only (except for drugs approved for non-oncology indications and had risk management programs developed prior to subsequent approvals for oncology indications).
- There already exits a de facto restricted distribution program in the practice oncology for cancer drugs.
- Concerns regarding the burden to the healthcare system imposed by a REMS where adequate safeguards are already employed.

- The premise, based on over 40 years of using highly cytotoxic and teratogenic drugs, that the standard of medical care in oncology provides adequate safeguards for risk communication and patient monitoring.

The panel acknowledged that a regulatory decision for vismodegib requiring a REMS could set a precedent for future approvals of other antineoplastic drugs and raise the question if drugs approved prior to vismodegib should be re-evaluated for a REMS program.

These discussions supported the determination that the teratogenicity risk of vismodegib did not warrant a REMS and that labeling including a Medication Guide would be sufficient to communicate the risk of teratogenicity for the majority of drugs used in the practice of oncology where the drug was shown to have a meaningful clinical impact on an endpoint likely to predict effects on irreversible morbidity or mortality.

8.5 Discussion of primary reviewer's comments and conclusions

In light of the mild to moderate toxicities associated with the drug, the primary reviewer considered the safety profile of vismodegib to be acceptable for the indicated population based on the finding of a clinically meaning ORR and duration of response in patients with both metastatic BCC and locally advanced BCC.

8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

The only major difference between the CDTL and discipline specific review teams regarding this section of the review is the recommendation by DRISK that the risk of teratogenicity associated with vismodegib be communicated to prescribers and patients through a communication plan and prescriber education program under a REMS. The clinical review team, pharmacology/toxicology review team, and general non-binding advice from a CDER regulatory briefing were of the opinion that prescribing information and patient prescribing information would effectively communicate the risk of teratogenicity associated with vismodegib.

8.7 Discussion of notable safety issues (resolved or outstanding)

There are no safety issues that would preclude approval of this application; however, there are ongoing discussions with the Applicant regarding a PMR to develop and implement a pregnancy registry to capture data on pregnancy and infant outcomes in women exposed to vismodegib.

9. Advisory Committee Meeting

An advisory committee meeting was not held for vismodegib. This decision was agreed upon by the clinical and statistical review team and division/office management. The primary justification for this decision relates to the magnitude and duration of the ORR observed in this study that reflects unequivocal clinical benefit in this patient population with no other effective therapeutic options.

10. Pediatrics

Genentech requested a disease-specific waiver for pediatric patients (0-18 years) based on the intended indication of metastatic- or locally advanced- BCC because BCC rarely occurs in the pediatric population. Thus, studies in children would be impossible or highly impractical to conduct because the patient population is too small. PeRC held a meeting on November 16,

2011 to discuss the PREA waiver requirement for vismodegib. PeRC notified the Division by email regarding the decision to grant the waiver on November 22, 2011.

(b) (6)

Based on this and additional pediatric development data expected to be provided to the FDA, the division can issue an informed Pediatric Written Request in the future under the Best Pharmaceuticals for Children Act.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

Based on the review of the CRFs by the clinical reviewer and DSI audits, the primary data submitted to this application were found to be reliable for the primary analyses of safety and efficacy. The applicant certified that no investigators or persons debarred under section 306 of the Federal Food, Drug and Cosmetic Act were involved with the conduct of the studies supporting NDA 210532.

11.2 Financial disclosures

As described in the clinical review, Genentech reported 3 financial conflicts as defined in 21 CFR 54.2(a) (b) and (f) for the primary efficacy study SHH4476g. One of these conflicts, although not related to vismodegib, was for 500,000 dollars. This investigator enrolled only 2 patients into the study. The conflicts that were reported were unlikely to have any substantive impact on the reliability of the clinical trial results.

11.3 GCP issues

The SHH447g study report contained a statement that the study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice for Trials on Medicinal Products. Genentech audited one investigator each at two study sites.

11.4 DSI audits

The review division and DSI chose two clinical sites for inspection based on site-specific efficacy data, number and types of protocol deviations, and patient number enrolled at each site. The two IRFs responsible for assessment of the radiographic images and photographic images were also inspected.

One notable observation was the work environment of the independent pathologist. The independent pathologist performed her evaluation in a Genentech controlled facility. The expectation per the charter was that "Histopathologic review would be performed by the Pathologist as an independent function and not subject to input from Genentech, its designees, or any site involved in this clinical trial." There were annotations in the Independent Pathologist's log that three cases were discussed with Genentech physicians or employees. OSI confirmed that there were no inspectional observations that suggested any inappropriate manipulation of (b) (6) source records or any evidence that someone other than (b) (6) (b) (6) had logged into the electronic data capture system in her absence. (b) (6) functioned more like that of a Genentech Inc. employee instead of an independent CRO.

The OSI reviewer Dr. Lauren Iacono-Connors and the primary medical officer, Dr. Michael Axelson, agreed that while the circumstances related to the work environment of the Independent Pathologist/CRO were not ideal, the data generated by (b) (6) may be considered reliable because there was no evidence of inappropriate manipulation of source records.

In their preliminary overall assessment, DSI stated that the deficiencies did not appear to have resulted in significant issues with conduct of the study and were unlikely to affect data reliability. Finally according to DSI, no evidence from the inspection of Genentech suggested a lack of reliability of efficacy data or significant underreporting of safety data.

11.5 Other discipline consults

Pediatric and Maternal Health had the following recommendations and conclusions:

- The product should be labeled pregnancy category D, to allow access to drug due to lack of alternative therapies.
- The Division should work closely with the sponsor on the voluntary communication plan for HCPs to ensure that the essential elements of risk for vismodegib are communicated adequately.
- A post-marketing requirement to establish a pregnancy pharmacovigilance plan to ensure collection of outcomes data regarding vismodegib pregnancy exposures should be required.
- The Maternal Health Team provided advice regarding label language for Embryo-fetal toxicity and teratogenicity information that should be conveyed in the Boxed Warning, Warnings and Precautions section, and Pregnancy subsection under Use in Specific Populations.

11.6 Other outstanding regulatory issues

Facility inspection reports have not been completed and the primary CMC review is not finalized. Although there is no anticipated CMC issue regarding manufacturing processes, until the facility inspection reports are completed and the CMC review finalized, no determination can be made on the CMC aspects of NDA 203388.

12. Labeling

12.1 Proprietary name

The proposed proprietary name for vismodegib is Erivedge. The DMEPA review dated November 28, 2011 determined that the name Erivedge was acceptable from a look-alike and sound-alike perspective. The proprietary name was found to be acceptable from both a promotional and safety perspective. Additionally, no objections to the name Erivedge were identified by DDMAC or the clinical review team during the review cycle.

12.2 Labeling issues raised by OPDP

The OPDP reviewer, Carol Broadnax, provided labeling advice regarding consistency between statements in various sections of the label, sections that could potentially be cross referenced to other sections for further information, statements that could have promotional implications, advice regarding addition of clarifying information on various sections of the label, word choice, and consistency between the PI and Medication Guide. These comments were

discussed and considered during labeling meetings and OPDP's advice was utilized when appropriate.

OPDP provided a second review from Karen Munoz regarding the Medication Guide. This provided advice on consumer friendly language, consistency between the Prescribing Information (PI) and the Medication Guide, potential promotional language, and questions regarding whether additional information from the PI should be included in the Medication Guide. These comments were discussed and considered during labeling meetings and OPDP's advice was utilized when appropriate.

There was no specific advice or review provided by OSE regarding labeling issues for the PI. DRISK was consulted regarding the Medication Guide. Their advice was discussed and considered during labeling meetings and utilized when appropriate. The finalized DRISK review on the Medication Guide has not been completed at the time of this review.

12.3 Physician labeling

In general, all sections of the label were revised for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Genentech. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

Boxed Warning
Revised to remove language indicating (b) (6).

1. Indications and Usage
The review team recommended revising the indication statement to include information regarding the requirement for recurrence after radiation therapy or that patients are not candidates for radiation therapy in order to accurately reflect the eligibility inclusion criteria of the pivotal Study SHH4476g.

4. Contraindications

(b) (4) (b) (6)

5. Adverse Reactions
This section was slightly revised to include introductory information on the most common, and most common serious adverse reactions. There are ongoing discussions between FDA and the

Applicant regarding whether some of the FDA included adverse reactions have enough evidence to suggest causal association with vismodegib. Amenorrhea and arthralgia were included as adverse reactions.

7. Drug Interactions
Review staff recommended that vismodegib be considered a substrate, based on *in-vitro* data, for the efflux transporter P-glycoprotein. Information regarding the potential effect of stomach-pH- altering drugs on solubility and bioavailability of vismodegib were included. A cautionary statement was included regarding administration of vismodegib with narrow therapeutic window drugs that are substrates of BCRP.

8. Use in Specific Population
The Pregnancy Category was revised from the Applicant proposed (b) (4) to D. This section was revised to include detailed information on the pre-clinical findings of teratogenicity and information on contacting Genentech regarding the enhanced pregnancy pharmacovigilance program for vismodegib. The Pediatric Use section was also augmented to include pre-clinical toxicology data. An additional section on "Females and Males of Reproductive Potential" was added to include language regarding pregnancy testing and prevention, contraceptive methods, and the pregnancy pharmacovigilance program.

12. Clinical Pharmacology
This section was revised for clarity and brevity.

13. Nonclinical Toxicology
Toxicology data regarding specific populations was moved to the relevant respective sections under 8.0 Use in Specific Populations.

14. Clinical Studies Section
Information on the number of patients with Gorlin syndrome in the pivotal study was added. Additional information regarding complete responses was included in narrative and tabular form. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4)

17. Patient Counseling and PPI
Patient Counseling in the PPI was revised to a succinct, bulleted format and concepts were made consistent between the PPI and Medication Guide.

12.4 Major issues not resolved

Not applicable.

12.5 Carton and immediate container labels

ONDQA has not finalized their review and therefore a final carton and container assessment cannot be made at this time. The DOP2 RPM and OPDP "carton and container" reviews did not identify issues that needed to be addressed and ONDQA has not identified any carton and container issues during the regularly held team meetings. DMEPA provided comments

regarding deficiencies in the cartoon and container labeling on 12/6/11 that were addressed and agreed to by the Applicant on 12/22/11.

12.6 Patient labeling/Medication guide

A Medication Guide was provided by the Applicant for this NDA. The drug product is one for which patient labeling could help prevent serious adverse effects and therefore could have been required had it not be voluntarily submitted. The Medication Guide was revised to be consistent with the final prescribing information, to adhere to federal regulations, and to follow current FDA Medication Guide policy regarding format, content and language.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

The tentative recommendation of this Cross Discipline Team Leader is for approval of NDA 203388. ONDQA has not finalized their review and until such time a final approval recommendation cannot be made. To date, no issues have been identified or raised during regular team meetings that would preclude approval.

13.2 Risk-benefit assessment

As previously stated, the recommendation for approval is based primarily on the results of one single-arm study that showed a clinically meaningful ORR and duration of response in both patients with metastatic BCC and patients with locally advanced BCC. There was unequivocal clinical benefit in a sizable fraction of the patients treated, and there is no approved or generally effective therapy for the indicated patient populations.

As described in section 7, the ORR in patients with metastatic BCC was 30.3% (95% CI 15.6, 48.2) and 42.9% (95% CI 30.5, 56.0) in patients with locally advanced BCC. The median duration of response was 7.6 months (95% CI 5.62, Not Estimable) for subjects with metastatic BCC and 7.6 months (95% CI 5.65, 9.66) for subjects with locally advanced BCC.

The toxicities of vismodegib identified, based on the totality of the safety data available in the development program, were generally mild to moderate in severity and consisted of muscle spasms, dysgeusia, alopecia, weight decreased, nausea, decreased appetite, constipation, and vomiting. The limited size of the safety data base and placebo controlled data therein make determination of causal associations and identification of rare but severe adverse reactions difficult. However, the beneficial effects of the drug clearly outweighed the safety concerns identified to date in these highly selected patient populations. The off label use of vismodegib in patients with BCC that should be treated with surgery or radiation would entail a negative risk:benefit assessment in this reviewers opinion. The economic realities of pharmaceutical pricing and reimbursement practices make the likelihood of off label use for less advanced BCC highly unlikely.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

As discussed in section 8, (b) (4) (b) (4) The genesis for the Applicant's concern and initial approach likely rests both in the evolving use of REMS across approved drugs at FDA and the exquisite delineation of the Hedgehog gene's evolutionarily conserved effects on morphogenesis. However, most drugs in oncology, whether older cytotoxic drugs or drugs developed as more "targeted" therapies, can cause profound deleterious effects on fetal development. The practice

of oncology entails that detailed and frequent discussions occur between a patient and their oncology team regarding the highly toxic drugs used to treat the patient's disease. In addition, close monitoring of patients for drug toxicity and continued ongoing counseling regarding such issues as pregnancy are a mainstay of oncology practice. FDA requested that the Applicant re-evaluate the teratogenic toxicity of this drug in relation to oncology drugs in general and alternative mechanisms whereby the described goals of the program could be achieved. (b) (4) (b) (4) After thorough discussion including a CDER regulatory briefing, the primary review division determined that a REMS was not necessary and that Prescriber and Patient labeling would be sufficient to address the risk of teratogenicity. The Applicant also intends to provide prescribers with additional outreach materials discussing the risk of teratogenicity.

13.4 Recommendation for other postmarketing requirements and commitments

The following postmarketing requirements (PMRs) have been proposed by the review teams and have been discussed with the Applicant: A pregnancy surveillance registry, a rodent carcinogenicity study, hepatic and renal impairment trials, a drug interaction trial with a sensitive CYP2C8 substrate as well as oral contraceptive components, and a trial to evaluate gastric pH elevating agents on vismodegib bioavailability. The exact language of the PMRs is pending final sign-off at the Division, Office, and OND levels.

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/s/

JEFFERY L SUMMERS
01/13/2012