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APPLICATION NUMBER:

203388Orig1s000

MEDICAL REVIEW(S)

CLINICAL AND STATISTICAL REVIEW

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Reviewer Name(s)	Michael Axelson
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Established Name	Vismodegib
(Proposed) Trade Name	Erivedge
Therapeutic Class	Hedgehog Inhibitor
Applicant	Genentech, Inc
Formulation(s)	150 mg capsules
Dosing Regimen	150 mg capsule once daily
Indication(s)	Basal Cell Carcinoma
Intended Population(s)	Patients with locally advanced or metastatic Basal Cell Carcinoma who are not candidates for or for whose disease recurred after surgery and radiation

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APPEARS THIS WAY ON ORIGINAL

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 8

1.1 Recommendation on Regulatory Action 8
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 10
1.4 Recommendations for Postmarket Requirements and Commitments 10

2 INTRODUCTION AND REGULATORY BACKGROUND 11

2.1 Product Information 12
2.2 Tables of Currently Available Treatments for Proposed Indications 12
2.3 Availability of Proposed Active Ingredient in the United States 13
2.4 Important Safety Issues With Consideration to Related Drugs 13
2.5 Summary of Presubmission Regulatory Activity Related to Submission 14
2.6 Other Relevant Background Information 22

3 ETHICS AND GOOD CLINICAL PRACTICES 22

3.1 Submission Quality and Integrity 22
3.2 Compliance with Good Clinical Practices 23
3.3 Financial Disclosures 24

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 25

4.1 Chemistry Manufacturing and Controls 25
4.2 Clinical Microbiology 25
4.3 Preclinical Pharmacology/Toxicology 26
4.4 Clinical Pharmacology 26
4.4.1 Mechanism of Action 26
4.4.2 Pharmacodynamics 26
4.4.3 Pharmacokinetics 27

5 SOURCES OF CLINICAL DATA 28

5.1 Tables of Studies/Clinical Trials 28
5.2 Review Strategy 29
5.3 Discussion of Individual Studies/Clinical Trials 29
5.3.1 SHH4476g 29
5.3.2 SHH3925g 44
5.3.3 Supportive Trials 46

6 REVIEW OF EFFICACY 48

Efficacy Summary 48
6.1 Indication 49
6.1.1 Methods 49
6.1.2 Demographics 49

Reference ID: 3068456

6.1.3 Subject Disposition ... 53
6.1.4 Analysis of Primary Endpoint(s) ... 54
6.1.5 Analysis of Secondary Endpoints(s) ... 59
6.1.6 Other Endpoints ... 64
6.1.7 Subpopulations ... 64
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations ... 65
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects ... 65
6.1.10 Additional Efficacy Issues/Analyses ... 65

7 REVIEW OF SAFETY ... 65

Safety Summary ... 65
7.1 Methods ... 66
7.1.1 Studies/Clinical Trials Used to Evaluate Safety ... 66
7.1.2 Categorization of Adverse Events ... 67
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence ... 67
7.2 Adequacy of Safety Assessments ... 68
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations ... 69
7.2.2 Explorations for Dose Response ... 70
7.2.3 Special Animal and/or In Vitro Testing ... 70
7.2.4 Routine Clinical Testing ... 70
7.2.5 Metabolic, Clearance, and Interaction Workup ... 71
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ... 71
7.3 Major Safety Results ... 71
7.3.1 Deaths ... 71
7.3.2 Nonfatal Serious Adverse Events ... 84
7.3.3 Dropouts and/or Discontinuations ... 90
7.3.4 Significant Adverse Events ... 95
7.3.5 Submission Specific Primary Safety Concerns ... 96
7.4 Supportive Safety Results ... 100
7.4.1 Common Adverse Events ... 100
7.4.2 Laboratory Findings ... 106
7.4.3 Vital Signs ... 109
7.4.4 Electrocardiograms (ECGs) ... 110
7.4.5 Special Safety Studies/Clinical Trials ... 110
7.4.6 Immunogenicity ... 110
7.5 Other Safety Explorations ... 111
7.5.1 Dose Dependency for Adverse Events ... 111
7.5.2 Time Dependency for Adverse Events ... 111
7.5.3 Drug-Demographic Interactions ... 112
7.5.4 Drug-Disease Interactions ... 114
7.5.5 Drug-Drug Interactions ... 114
7.6 Additional Safety Evaluations ... 114

Reference ID: 3068456

7.6.1 Human Carcinogenicity ... 114
7.6.2 Human Reproduction and Pregnancy Data ... 115
7.6.3 Pediatrics and Assessment of Effects on Growth ... 115
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound ... 115
7.7 Additional Submissions / Safety Issues ... 115

8 POSTMARKET EXPERIENCE ... 121

9 APPENDICES ... 122

9.1 Literature Review/References ... 122
9.2 Labeling Recommendations ... 123
9.3 Advisory Committee Meeting ... 125
9.4 Other Supportive Tables and Figures ... 125

Reference ID: 3068456

Table of Tables

Table 1: Vismodegib Product Information 12
Table 2: Currently Available Treatments for BCC 13
Table 3:DSI Clinical Inspections 23
Table 4: Summary of Financial Disclosure Responses 24
Table 5: Summary of Financial Disclosures 24
Table 6: Listing of Clinical Trials Submitted to the NDA 28
Table 7: Dates of Amendments for Protocol SHH4476g 29
Table 8: SHH476g RECIST Criteria 35
Table 9: Modifications to RECSIT for SHH4476g 36
Table 10: Overall Response based on all possible response combinations 37
Table 11: Overall Clinical Responses for All Possible Combinations of Tumor Responses for Locally Advanced BCC 39
Table 12: Clinical plus RECIST Response 39
Table 13: Statistical Assumptions for Adverse Events 41
Table 14: Vismodegib Dose by Cohort SHH3925g 46
Table 15: Demographics SHH4476g 50
Table 16: Disease Characteristics and Prior Treatment for SHH4476g Subjects by Cohort 51
Table 17: Subject Disposition SHH4476g 53
Table 18: Protocol Violations 53
Table 19: Primary Endpoint SHH447g Efficacy Evaluable 55
Table 20: FDA ORR Analysis (IRF) (All Enrolled Subjects) 56
Table 21: FDA Review of IRF and INV Assessed Response of laBCC Subjects 56
Table 22: ORR Results (INV) (Efficacy-Evaluable Patients) 59
Table 23: Concordance of ORR by IRF and INV 59
Table 24: Duration of Response SHH4476g 60
Table 26: Progression Free Survival 61
Table 27: Overall Survival Analysis 62
Table 28: Histopathology Effect in Tissue Biopsy (Target Lesions Only): Efficacy-Evaluable Subjects (*copied from submission with minor modifications)* 63
Table 29: Demographic Subgroup ORR Results (IRF) 64
Table 30: Baseline Characteristic Subgroup ORR Results 65
Table 31: Exposure Summary by Trial 69
Table 32: All Deaths from Pooled Safety Population 71
Table 33: FDA Review of Deaths from Pooled Safety Population 72
Table 34: Non-Fatal Serious AEs by Trial 85
Table 35: Non-Fatal SAEs by Preferred Term by Trial 85
Table 36: Subject Narrative for Cardiac SAEs 87
Table 37: Subject Narratives for Neoplastic SAEs 88
Table 38: Reason for Discontinuation 90
Table 39: Adverse Events Leading to Discontinuation By Trial By Grade 91
Table 40: AEs Leading to Discontinuation in SHH4489G 91
Table 41: AEs Leading to Discontinuation in SHH4429g 92

Reference ID: 3068456

Table 42: AEs Occurring within 90 Days of Discontinuation of Vismodegib in Subjects who Discontinued Vismodegib for Reasons other than AE 93
Table 43: SHH4429g Grade 3-5 SAEs 96
Table 44: All TEAEs by PT (per subject incidence of ≥5%) 100
Table 45: Most Common (≥ 10%) AEs in SHH4489g 101
Table 46: Table 28: All TEAEs by HLT (per subject incidence of ≥5%) 102
Table 47 All TEAEs by HLGT (per subject incidence of ≥5%) 104
Table 48: All TEAE by SOC 105
Table 49: Shift Table for Serum Chemistries 107
Table 50: Grade 3 Lab Abnormalities from SHH4476g with baseline Tox Grade 108
Table 51: Subjects with Grade 3 Weight Decrease 109
Table 52: TEAE Statistics 111
Table 53: Median AE Start Date by Tox Grade 111
Table 54: Adverse Event by Gender with Differences ≥ 5% 112
Table 55: Adverse Event by Age Group with Differences ≥ 5% 113
Table 56: SHH4476g Updated Disposition 116
Table 57: Updated Common AEs SHH4476g 117
Table 58: Updated Grade 3-5 AEs SHH4476g 118
Table 59: Updated SHH4476g AEs leading to Discontinuation 120

Reference ID: 3068456

Table of Figures

Figure 1: Chemical Structure of Vismodegib 11
Figure 2: SHH4476g Flowchart 34
Figure 3: SHH3925g Flow Chart during Screening and DLT Assessment 45
Figure 4: SHH3925g Flow Chart during Continuation of Treatment Period 46
Figure 5: Baseline Size Distribution by Size 52
Figure 6: Subjects with Locally Advanced BCC Not Included in Efficacy-Evaluable Population (*copied from submission*) 55
Figure 7: FDA PFS Analysis 62
Figure 8: Pooled Safety Populations from Trials Contributing to the Summary of Clinical Safety (*copied from submission*) 68
Figure 9: Dose Range of Vismodegib SHH4476g 70
Figure 10: Dose Range of Vismodegib SHH 3925g 70
Figure 11: Dose Range of Vismodegib SHH4437g 70
Figure 12: AE Count By Relative AE Start Date 111

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends full approval of New Drug Application (NDA) 203388 for the treatment of adult patients with Basal Cell Carcinoma (BCC) for whom surgery and radiation is inappropriate (advanced BCC).

The assessment of benefit in this application is based on the endpoint of overall response rate (ORR), based on response evaluation criteria in solid tumors (RECIST) in patients with metastatic BCC (mBCC) and a composite criteria of bi-dimensional measurements of externally assessable tumor, bi-dimensional measurements of tumor ulceration, and standardized digital photography of target lesion(s) in patients with locally advanced BCC (laBCC). The recommendation is based on the review of the clinical data, which supports the conclusion that vismodegib provides clinical benefit in patients with advanced BCC for whom surgery and radiation is inappropriate. Trial SHH4476g demonstrated an ORR of 30.3% in patients with mBCC and 42.9% in patients with laBCC. The median duration of response (DOR) was 7.6 months in both the mBCC and laBCC cohorts.

The NDAs or biologic licensing application (BLA) for full approval for bexarotene, romidepsin, and denileukin diftitox each relied on single arm trials with overall response rate as the primary endpoint for the treatment of cancers that primarily affect the skin and contained safety databases with less than 240 patients. These applications provide regulatory precedent for full approval for the treatment of advanced BCC, a cancer of the skin with a similar sized efficacy and safety database.

Reference ID: 3068456

1.2 Risk Benefit Assessment

Data from four clinical trials support this NDA. SHH4476g was multicenter, single arm, two-cohort, open-label phase 2 trial with 104 patients that provided the main efficacy results for the NDA. The safety data came from four clinical trials: (1)SHH4476g; (2) SHH3925g, a phase 1 dosing finding trial with a cohort of patients (n=33) with advanced BCC; (3) SHH4437g, an extension trial for patients in SHH4476g or SHH3925g; and (4)SHH4610g, a schedule optimization trial with a single subject with BCC. The effect size of on ORR and DOR and the safety profile of vismodegib provide the basis for the assessment of risk-benefit in this application.

The results of SHH4476g provide evidence of a clinically meaningful benefit in ORR and DOR in patients with advanced BCC. SHH4476g had two cohorts of patients, patients with mBCC and patients with laBCC.

1. In the patients with mBCC there are no approved therapies for metastatic disease which is rarely curable with radiation or surgery. The ORR, based on RECIST, in patients with mBCC was 30.3% (95% CI 15.6, 48.2) with a median duration of response of 7.6 months (95%CI 5.62, Not Estimable). All ten of the subjects who had a response had a partial response.
2. In patients with laBCC there are no approved therapies for locally advanced disease that is no longer amendable to radiation or surgery. The ORR, based on a composite endpoint in patients with laBCC, was 42.9% (95% CI 30.5, 56.0) with a DOR of 7.6 months (95% CI 5.65, 9.66). Of the twenty-seven patients with laBCC who experienced a response, thirteen had a complete response with biopsies showing no residual BCC.

The response criteria differed for each cohort. The response criteria for the mBCC cohort used RECIST, which specifies that a target lesion must shrink by at least 30% and maintain the reduction for ≥ 28 days. In the laBCC cohort, tumor response evaluation utilized a composite endpoint of visual assessment and measurement of externally assessable tumor and ulceration, radiographic assessment of target lesions (if appropriate), and tumor biopsy. A subject with laBCC was considered a responder if at least one of the following criteria was met and the patient did not experience progression: (1) ≥ 30% reduction in lesion size [sum of the longest diameter (SLD)] from baseline in target lesions 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. Progression in laBCC cohort was defined as meeting any of the following criteria: (1) ≥ 20% increase in the sum of the longest dimensions (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.

Tumor shrinkage as a primary endpoint supporting full approval is similar to other prior approvals for drugs treating malignancies with primary skin involvement and can be considered

Reference ID: 3068456

direct clinical benefit. BCC primarily affects sun exposed areas such as the face, head, and extremities, meaning the tumors are readily visible. Shrinkage of these tumors provides patients with a favorable cosmetic effect. In both the laBCC and mBCC cohort, patients experienced durable, median DOR of over 7 months, and clinically meaningful shrinkage of their tumors, including complete responses in 13/63 (20.6%) of the subjects with laBCC.

The safety data comes from a pooled database of 138 subjects from SHH4467g, SHH3925g, and SHH4610g who all had advanced BCC and received vismodegib. The most common adverse reactions in subjects receiving vismodegib (≥ 10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, cough, arthralgias, vomiting, headache, ageusia, insomnia, and upper respiratory tract infection. The most common serious adverse reactions (≥ 1%) in subjects receiving vismodegib were death (2.2%), pneumonia (2.2 %), cardiac failure (1.4%), gastrointestinal hemorrhage (1.4%), pulmonary embolism (1.4%), deep vein thrombosis (1.4%), and hemorrhage (1.4%). A total of 17/138 (12.3%) subjects died in trials SHH4476g and SHH3925g; the single subject in trial SHH4610g included the pooled safety population did not die. A total of 7/138 (5.1%) subjects died within 30 days of last vismodegib use and 8/138 (5.8%) deaths were due to an adverse event. The most common cause of fatal events after receiving vismodegib were disease progression and infections.

The overall safety profile of vismodegib is acceptable for an anti-cancer agent. The most common adverse reactions are not expected to be life threatening. The causal relationship for the serious adverse events reported in these trials was unclear given the low incidence and high projected background rate of such events in this older patient population Vismodegib is a Hh pathway inhibitor and is expected to be teratogenic in developing human fetuses based on its mechanism of action and observations in preclinical toxicology studies. The use of teratogenic drugs in oncology is common and the standard of medical care in oncology provides adequate safeguards through familiarity with the risks, risk communication, and patient monitoring.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This reviewer does not recommend any Postmarket Risk Evaluation and Mitigation Strategies for vismodegib. See Section 7.3.5.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer recommends the following Postmarket Requirements (PMR) to collect safety information on vismodegib exposure to developing fetuses and pregnancy outcomes:

> Implement a Pregnancy Pharmacovigilance Program to evaluate pregnancy outcomes and infant outcomes following exposure to vismodegib. Initiate Pregnancy Pharmacovigilance data collection at the time of product launch. Finalize the Pregnancy Pharmacovigilance Program, including methods of assessment, by March 31, 2012. Interim reports of cumulative data on any vismodegib-exposed pregnancies will be submitted on an annual

Reference ID: 3068456

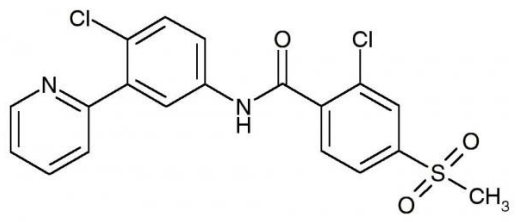
basis to the Agency until either of the following criteria is met: 10 years have elapsed (March 31, 2022) or 25 pregnancies with informative outcomes.

Negotiations were still ongoing for the final language of the PMR and the time table at the time of the completion of this review.

2 Introduction and Regulatory 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. The molecular formula for vismodegib is 2-chloro-N-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonyl-benzamide, Figure 1.

Figure 1: Chemical Structure of Vismodegib (*copied from submission)*



Vismodegib demonstrated *in vitro* inhibition of Hh signaling in mouse and human cell lines through binding and inhibiting smoothened (Yauch 2009). *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. According to the American Cancer Society (ACS), the number of total and new BCC cases is difficult to estimate because BCC reporting to cancer registries is not required and BCC is usually combined with squamous cell carcinoma into the estimates of non-melanoma skin cancers (NMSC). A recent report estimated that in 2006, 3.5 million cases of NMSC occurred and (b) (4) people received treatment based on Medicare claims (Rogers 2010). In a retrospective review in the Canadian province of British Columbia of all patients who received radiotherapy for basal cell cancer, there were no deaths among the 61 patients who underwent treatment with radiotherapy with a median follow up of 42 months (range, 1.4 – 97.1 months) and the estimate at 4 years of loco-regional control

Reference ID: 3068456

was 85% (Kwan 2004). The surgical cure rate for local disease exceeds 90%, the specific mortality due to BCC is less than 0.1%, and the incidence of metastasis in BCC ranges from 0.0028% to 0.55% with reports in the literature less than 400 cases (Chinem 2010).

Sun exposure, ionizing radiation, arsenic, and psoralen are all thought to be the primary risk factors for developing BCC (Rubin et al 2005). The observation that most cases (80%) of BCC occur on the head or neck support the role of sun exposure and UV light as a key etiologic factor. The molecular pathogenesis of BCC comes from observations of inappropriate pathway regulation and signaling in the Hg pathway and from and along with observations of along mutations in patched homologue 1 (*PTCH1*) gene in patients with nevoid basal cell carcinoma or Gorlin syndrome.

There are no FDA approved therapies for advanced or metastatic BCC. With respect to the prognosis of advanced BCC, the applicant provided case reports of locally advanced BCC causing spinal cord compression (Cohen 2000) and lethal cerebral invasion (Kovarik 2005), as well as case series of chemotherapy in metastatic BCC (Pfeffer 1990; Ganti 2011) supporting the claim that no effective therapy exists for this serious and life threatening condition. The applicant estimated that 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 (von Domarus 1984; Lo 1991; Spates 2003).

2.1 Product Information

Table 1: Vismodegib Product Information

Generic Name:	Vismodegib
Trade Name:	Erivedge
Pharmacological Category:	Hedgehog inhibitor
Drug Class:	Small-molecule inhibitor of the hedgehog signal pathway
Route of Administration:	Oral
Storage:	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15-30°C (59-86°F)
Drug Product:	The vismodegib drug product is a hard capsule. The gelatin capsule shell is (b) (4) and has a (b) (4) opaque body and a grey opaque cap. "150mg" is printed in black ink on the (b) (4) opaque body and "VISMO" is printed in black ink on the grey opaque cap.
Dose and Regimen:	150 mg capsule daily
Populations Studied:	Subjects with advanced Basal Cell Carcinoma for whom surgery and radiation is inappropriate

2.2 Tables of Currently Available Treatments for Proposed Indications

Therapy for BCC may consist of topical agents, electrodessication and curettage, surgical excision, cryosurgery, Mohs surgery, and radiation therapy. There are no FDA approved

Reference ID: 3068456

treatments currently available for the proposed indication for advanced BCC. Table 2 lists treatment options oncologists and dermatologists administer in clinical practice. Published literature and oncology guidelines (NCCN website, accessed September 2011) appear to support these therapies, although none of these agents are approved by FDA for vismodegib proposed indication. Published reports, not submitted or reviewed by FDA in support of an NDA, support some of these regimens. Inclusion of some of these regimens in Table 2 does not indicate that these agents are approved or recommended by FDA.

Table 2: Currently Available Treatments for 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, NCCN recommended
Aminolevulinic acid (ALA)	Photosensitizer	Does not have a labeled indication for BCC, NCCN recommended

2.3 Availability of Proposed Active Ingredient in the United States

Vismodegib is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Vismodegib is a new molecular entity and there is no publically available information with other hedgehog inhibitors.

Reference ID: 3068456

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following section contains a list of regulatory activities including meetings held with the IND sponsor and NDA applicant, Genentech, referred to as the applicant.

On July 18, 2006 the applicant met with FDA in a pre-IND meeting to discuss submission of GDC-0449 (vismodegib). FDA and the applicant agreed upon several design aspects of the proposed phase 1 trial including dose escalation plan, monitoring plan, and once a day dosing. FDA commented that the proposed non-clinical program appeared to support the proposed clinical trial. Additional comments from Clinical Pharmacology requested the applicant address the potential of vismodegib to prolong the QT/QTc interval. Additional Chemistry, Manufacturing, and Controls (CMC) comments requested Certificates of Analysis for the drug substance and drug product batches used in the manufacture of clinical supplies. The applicant submitted the original IND for vismodegib on September 29, 2006 (received October 2, 2006). FDA issued a may proceed letter for IND 74,573 on November 3, 2006.

On April 28, 2008, the applicant met with FDA in an end of phase 1 meeting to discuss trial design aspects in future development of vismodegib in patients with BCC. (*copied from meeting minutes with minor modifications*)

- FDA agreed that the applicant had adequately defined a population with mBCC, but raised concerns with the definition of locally advanced disease and requested specific criteria for defining unresectability. 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 applicant also acknowledged that subjects with superficial multifocal BCC should be excluded.
- The applicant proposed (b) (4) FDA stated that it would not be possibl (b) (4) FDA recommended assessing and analyzing the objective response rate separately for each of the two populations. FDA further clarified that for subjects with locally advanced disease, a primary endpoint based on assessment of cutaneous lesions may be acceptable if it was adjudicated by independent review of the digital photography information and if the applicant more specifically defined the population with respect to unresectability. The applicant agreed to assess and analyze the two populations separately.

(b) (4)

Reference ID: 3068456

(b) (4)

- Progressive disease(PD): at least one of the following criteria must be met:
  - Increase in area of target lesions (product of two longest perpendicular dimensions) of ≥ 25%
  - New ulceration or bleeding of ≥ 25% of the area of target lesions
  - Appearance of any new superficial BCC (biopsy-confirmed) or new distant metastatic lesions

- FDA accepted the CR criteria if it included complete disappearance of tumor confirmed by histology and photography but expressed concerns about the subjective nature of the PR criteria and did not agree that the (b) (4) was appropriate for demonstrating clinical benefit and would support approval. FDA did not comment on whether the applicant's proposal of a (b) (4) was clinically meaningful.
- The applicant proposed (b) (4) FDA did not agree (b) (4) but did agree that additional phase 2 trials could provide additional supportive safety information.
- FDA provided additional comments to add sparse PK sampling, perform a Drug-Drug Interaction study with strong inhibitors/inducers of CYP3A4 and 2C9, and conduct *in vitro* screens to determine if vismodegib is an inducer of CYP450. FDA also recommended conducting an *in vitro* study to determine if vismodegib is a P-glycoprotein substrate or inhibitor, a formal food effect study, an absorption, distribution, metabolism and excretion (ADME study) of vismodegib in humans, an organ impairment study to characterize the effect of renal and or hepatic impairment on the PK of vismodegib, a study to assess the bioavailability (absolute or relative) of vismodegib.

On July 31, 2008 applicant submitted a special protocol assessment (SPA) for "A Pivotal Phase 2, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of vismodegib in Patients with Advanced Basal Cell Carcinoma" (see Section 5.3.1 for full overview). On September 11, 2008, FDA issued a SPA No Agreement letter based on the applicant's proposal (b) (4) On November 21, 2008 the applicant submitted proposed revisions the SPA request based on FDA comments. On January 5, 2009 FDA issued another SPA No Agreement letter

Reference ID: 3068456

based on proposed [redacted] (b) (4). The following list contains agreed upon aspects of the trial and applicant proposed revisions or items FDA did not find acceptable for an SPA agreement or to support approval: (*adapted from FDA's January 5, 2009 Special Protocol Assessment – No Agreement letter)*

- FDA agreed that the proposed definition of mBCC was acceptable.
- FDA stated that the [redacted] (b) (4) was not acceptable [redacted] (b) (4)
    - The applicant proposed deleting the proposed [redacted] (b) (4)
    - FDA accepted the proposed changes provided the protocol stated that "the externally visible component of all target lesions must be at least 10 mm in the longest dimension" to exclude cutaneous lesions < 10 mm that could be target lesions.
- FDA commented that the [redacted] (b) (4) was not acceptable:
    - The protocol should include all measurable disease in the evaluation of response, especially given the small size of the trial. FDA agreed to the applicant's proposed changes to [redacted] (b) (4) at least 10 mm.
    - The protocol deemed that if a target lesion's size remain unchanged, meeting criteria for SD, but the ulcerative component meet criteria for CR, a response would be counted, which might not be due to drug effect. The applicant should demonstrate that a subset of subjects with improvement in tumor ulceration do not solely drive the results. The applicant agreed and proposed [redacted] (b) (4)
    - The protocol did not consider all new BCC lesions as PD, depending on management and size. The protocol should consider new lesions as PD irrespective of how it is managed. The applicant made the requested changes.
    - The protocol did not consider all new lesions suspected of being BCC as PD. The protocol should consider any new lesion suspected of being BCC as PD, unless a biopsy conclusively proves otherwise. [redacted] (b) (4) (b) (4)

Reference ID: 3068456

- The protocol should not consider subjects with a PR that allows for previously inoperable target lesions rendered operable with clear margins obtained at surgery as a CR. The protocol can define the response as PR if all PR criteria were met preoperatively and can define subjects who undergo successful resection after a response in an exploratory analysis that labels these subjects as having a CR. The applicant proposed [redacted] (b) (4) FDA did not agree [redacted] (b) (4)
- The protocol should define subjects with uninterpretable baseline biopsies as initially eligible for the protocol. The protocol should not count a subject without an initial biopsy conclusively showing BCC as a responder. The applicant stated that (b) (4) [redacted] FDA did not agree [redacted] (b) (4)
- The protocol should not define subjects who have a clinical response whose biopsies show no evidence of residual BCC as having a CR. Instead the protocol should define a subject with locally advanced disease to be considered a complete responder if there is complete clinical resolution of all lesions and a negative biopsy at the time of response. The applicant agreed and revised the protocol so that in order for a subject with locally advanced disease to be considered a complete responder, the subject should have complete resolution of all lesions and a negative biopsy at the time of response.
- The protocol should clarify whether new ulceration not related to tissue biopsy or other known trauma and persisting for 2 weeks as PD is in a separate location when referring to not related to a tissue biopsy. The applicant revised to protocol to clarify that "not related to tissue biopsy" means a separate location.

- FDA stated the proposed technical procedures for tissue biopsy and case report forms (CRFs) appeared acceptable.
- FDA commented on the proposed plan for review and confirmation of response in the independent review facility (IRF) charter for centralized reading of tumor scans and the IRF charter for the standardized digital photography of skin lesions:
  - The protocol should consider any subject for whom an investigator stopped treatment because of suspected progression but whom the IRF subsequently considered stable as having progressed at the time treatment was discontinued. FDA recommend using IRF readings to guide treatment decisions in real time if possible. FDA also stated

Reference ID: 3068456

that where there are discrepancies between investigator and IRF-adjudicated progression dates, FDA will consider progression to have occurred on the earlier of the two dates. Lastly, FDA will consider progression to have occurred at either an "equivocal" assessment by investigators or when the independent adjudicator determines progression, whichever was first, irrespective of assessment of progressive disease that is equivocal or when the independent adjudicator determines progression whether the investigator believes the subject is still benefiting from treatment.

- The protocol should specify who at [redacted] (b) (4) will interpret the digital photographs of target lesions (protocol Appendix H) and their training for expertise in this task. To account for interobserver variability, FDA recommend that two reviewers interpret each photograph independently, and that a third interpreter do so in the event of discordance between the first two. Analogous to the Sequential Locked Review paradigm for reading radiographic studies, the reviewers should not communicate with one another about individual assessments. The applicant proposed that three board certified dermatologist and/or oncologist specializing in cutaneous tumors would interpret the images. FDA indicated the proposal was acceptable.
- The protocol should specify that the two pathology readings (one by the applicant and the other by an independent pathologist) are independent of each other. The applicant proposed readings by an independent pathologist only. FDA deemed the approach acceptable.

- FDA provided comments on the statistical analysis plan (SAP):
  - Separate analyses for the metastatic and locally advanced cohorts was acceptable.
  - 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 that will likely require oncology drug advisory committee discussion.
  - Time to event endpoints can only be considered as descriptive data in a non-randomized single arm study.
  - The SAP does not provide guidance on how to handle missing assessments in the primary analysis.
- The applicant expressed understanding that the adequacy of the observed rates to support approval in both metastatic and locally advanced disease would be a review issue and incorporated guidance on how to handle missing assessments in the primary analysis. FDA advised against imputing missing or uninterpretable data and that the primary efficacy results be based on all treated subjects and all enrolled subjects.
- FDA stated the sparse PK sampling in the proposed trial appeared acceptable.

Reference ID: 3068456

- FDA stated the protocol instructions for vismodegib interruption should define "intolerable" *a priori* and should reduce treatment restarted after a dose interruption. The applicant agreed to define "intolerable" toxicity *a priori.* The applicant stated that the phase 1 trial did not evaluate doses lower than 150 mg because dose-related toxicities were not observed and evidence of clinical efficacy was observed at the 150-mg dose. The applicant also stated that animal studies were not predictive of human PK, and the dose dependence of the observed nonlinear absorption and/or clearance was not understood, precluding the prediction of an appropriate lower dose in humans. FDA commented that subjects who have two dose interruptions should either have a dose reduction or go off trial.
- FDA stated the protocol did not prohibit any specific concomitant medications, but rather recommended that concomitant medications be used with care and provides a table of medications that may potentially interact with vismodegib and recommended listing substrates, inducers and inhibitors of substrates of CYP2C8, CYB2C19 and inhibitors of CYP3A4. The applicant agreed to make appropriate changes.
- FDA recommended the protocol contain a third category, besides a "yes or no" response for instructions for investigators to assign causality to adverse events. The applicant clarified that the "yes" response included the category of possibly drug related. FDA stated the causality criteria were acceptable.
- FDA stated that the applicant's November 20, 2008 responses did not fully address the Agency's concerns, but did state that the applicant and FDA were "close to an agreement."

On April 29, 2009 the applicant met with FDA in a Type C meeting to discuss, FDA's guidance on the proposed CMC development plans for vismodegib to support an NDA. FDA agreed that the applicant's proposed primary stability strategy of the drug substance, the proposed plans for the analytical assessment of future lots of the drug substance, the drug product primary stability strategy, and the proposed overall strategy and approach to setting the commercial specification of the drug product appeared to be acceptable. FDA provided comments on starting materials, proposed strategy for API process validation, and commercial specification of the drug substance.

On April 4, 2010 the applicant submitted a meeting request (meeting package June 8, 2010) to discuss the acceptability of the toxicology and clinical pharmacology programs supporting the registration of vismodegib. FDA provided answers on July 6, 2011 and the applicant canceled the meeting. (*adapted from meeting minutes*)

- FDA provided comments on the proposed toxicology plan:
    - The applicant would need to justify why carcinogenicity studies were not needed based on the life expectancy of patients with locally advanced basal cell carcinoma.
    - The applicant did not need to conduct fertility and peri/post-natal developmental studies and a pivotal developmental study (based on the limited information provided for the pilot embryofetal developmental study in rats showing embryofetal mortality or malformations), but the final decision would be made following review of data submitted in the NDA.

Reference ID: 3068456

  - The applicant would need to provide the animal exposure data for Embryofetal Developmental Study in Rats (Study 3036R09), and compare those to the human exposure at the recommended therapeutic dose. The pharmacokinetic data in rats could be based on other studies conducted at the same dose levels and schedule.

- FDA provided comments on the clinical pharmacology program:
  - FDA agreed with the applicant's proposed gated approach for Drug-Drug Interaction (DDI) assessment as a perpetrator via CYP inhibition and recommended additional PK blood samples on Days 1 and 8 and modification of the renal function inclusion criteria to include subjects with serum creatinine ≤ 1.5 x ULN.
  - FDA recommended assessment of vismodegib dose proportionality below the proposed clinical dose of 150 mg daily.
  - FDA stated that the not conducting clinical studies of CYP inhibition/induction (i.e., vismodegib as victim) would be a review issue as the submitted data did not demonstrate that the contribution of the CYP enzymes to the overall elimination of vismodegib was not substantial. FDA requested data of the extent of vismodegib metabolism and evaluation of the importance of vismodegib metabolism based on the results of *in vitro* and *in vivo* studies.
  - FDA agreed with the statistical design of the applicant's proposed dedicated QT-interval study in healthy volunteers, but commented that if the true mean difference between vismodegib and placebo after baseline correction is 5 ms or smaller, the proposed sample size would be enough to rule out 20 ms, otherwise the applicant should consider increasing sample size. In addition FDA provided comments on the dose selection, replacement of subjects violating the randomization principle, a linear mixed effects modeling approach to quantify the relationship between plasma concentrations and ΔΔQTc, a central ECG laboratory, blinding of ECG readers to date and time identifiers, review of ECGs from a particular subject be preformed by a single reviewer, prespefication of the lead for interval measurements, using the same lead for baseline and on-treatment ECGs, and technical aspects of the submission.
  - FDA agreed that the applicant's plans to address the mass balance and absolute bioavailability of vismodegib appeared acceptable, but that both renal and hepatic impairment studies would be necessary.
  - FDA agreed with the applicant's current PK model and the analysis plan for modeling and simulation, but recommended sparse PK sampling from all subjects.

In May 2010, the applicant opened an Expanded Access Protocol (SHH4437g) for an intermediate-size population titled, "A Single Arm Open Label Expanded Access Study of vismodegib in Patients with Locally Advanced or Metastatic Basal Cell Carcinoma."

On January 25, 2011 FDA and the applicant held a teleconference to discuss the toxicology and clinical development plans for vismodegib for patients with nevoid basal cell carcinoma (Gorlin) syndrome. The applicant requested Orphan Drug Designation for vismodegib in Gorlin

Reference ID: 3068456

syndrome but since the mechanism of action of vismodegib is not specific to BCC and BCC is not a rare disease or condition, FDA did not grant Orphan Drug Designation. *Reviewer's comment: The discussion in the January 25, 2011 teleconference involved Protocol SHH4949g, which is not part of NDA 203388 submission, and thus not reviewed here.*

On May 10, 2011 the applicant met with FDA to discuss Pharmacology/Toxicology and CMC aspects of the data to be submitted for an NDA. FDA stated that the dissolution method and proposed specification for an immediate–release capsule appeared acceptable. FDA also stated that because the API is a BCS class 2 drug and poorly soluble in water, acceptance criterion for particle size distribution is needed to control the manufacturing and performance of the drug product. Discussion items included assessment of genotoxic impurities and analytical comparability data between registration lots and proposed commercial scale lots. FDA did not agree with the applicant's approach for genotoxic studies (b) (4) (b) (4) (b) (4) and recommended conducting the AMES assay or assess the carcinogenicity potential of the impurities in carcinogenicity studies using the clinical lot containing the impurities at the proposed specifications. FDA commented that there was insufficient information to comment on the applicant plan regarding the analytical comparability data for the drug product registration lots and the proposed commercial-scale lots.

On May 11, 2011 the applicant met with FDA in a pre-NDA meeting to discuss the applicant's plan to submit an NDA for vismodegib. FDA raised clinical, clinical pharmacology, and toxicology concerns with the proposed submission. (*copied from meeting minutes with minor modifications*)

- 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. FDA, however, stated there did not appear to be any significant filing issues.
- FDA stated the efficacy analysis would consist of the all-treated population as well as the efficacy-evaluable population based on the baseline biopsy read by the independent pathologist. FDA also stated that any sensitivity analyses of the efficacy results would be exploratory.
- FDA stated the Integrated Safety Summary (ISS) (n=138) was acceptable with pooled safety analysis from trials SHH4476g, SHH3925g, SHH4437g, and SHH4610g with advanced BCC subjects with other supporting safety data coming from trials SHH4429g, SHH4489g, SHH 3925g, SHH4318g, SHH4610g, SHH4683g, SHH4433g, SHH4871g, SHH4811g. See Table 6 for overview.
- (b) (4)

Reference ID: 3068456

- FDA stated the applicant should submit final clinical study reports and results for the DDI Study SHH4593g, food effect Study CTEP#8395 and the renal and hepatic studies in the NDA submission at the time of filing. The applicant stated the NDA would contain a synoptic report of the DDI study and the food effect study, but that completion of these studies was to occur after the NDA filing date.
- FDA stated the applicant would need to complete carcinogenicity studies for the locally advanced BCC, but agreed with the applicant's plan to initiate a SPA with CDER's executive carcinogenicity assessment committee prior to approval and complete the assessment post-approval.

On August 2, 2011 the applicant requested a proprietary name review for vismodegib. The applicant proposed Erivedge as the proprietary name.

On September 8, 2011 the applicant submitted NDA 203388.

2.6 Other Relevant Background Information

Response Criteria in Malignant Skin Cancer:
Malignancies of the skin consist of several different subtypes including melanoma, squamous cell carcinoma (SQCC), merkel cell, and lymphomas. The prognosis, severity, and natural history of melanoma are worse than basal cell carcinoma and this reviewer does not consider treatments for melanoma as applicable to this application. Merkel cell and SQCC do not have approved therapies for advanced disease. SQCC of the skin is most analogous to BCC but the lack of approved therapies for advanced SQCC does not allow for comparisons to advanced BCC for regulatory purposes. Most local treatments for BCC can also treat SQCC, see Table 2 above. Cutaneous T Cell Lymphoma (CTCL) has several approved therapies for local and advanced disease based on single arm trials that had response rate as the primary efficacy endpoint. Even though the biology, incidence, and natural history are not exactly similar to that of BCC, this reviewer considers treatments for CTCL as applicable to this application for regulatory purposes. Even though the cancers of the skin differ significantly, the divisions in the Office of Hematology and Oncology Products have frequently accepted response rates, or the reduction in the size of a tumor in cancers with significant skin involvement, and considered tumor shrinkage as direct clinical benefit.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and integrity to allow for review of the clinical trials pertaining to the proposed indication. Electronic datasets were submitted in CDISC format as requested by the Division. This reviewer did not compare the adverse events from a subset of

Reference ID: 3068456

case report forms (CRFs) and case narratives for SHH4476g as the CRFs were electronically transferred to populate the datasets. This reviewer compared verbatim terms all adverse events (AEs) in the ISS ADAE dataset to the corresponding MedDRA lower level term to confirm the overall adequacy of AE coding; where the terms differed this reviewer considered the difference to be minor and not expected to affect the safety findings for this application.

3.2 Compliance with Good Clinical Practices

The submission contained statements in the clinical study reports that the applicant conducted the clinical trials under Good Clinical Practices, as described in International Conference on Harmonization (ICH) E6 (ICH, 1996), under the principles of the Declaration of Helsinki.

Based upon analyses of site-specific efficacy data, numbers and types of protocol deviations, patient enrollment per site, and investigator financial conflict of interest disclosures, this reviewer requested a DSI consult for the clinical inspection of 2 trial sites, Table 3.

Table 3:DSI Clinical Inspections

Site Number	PI / Site	Trial	Number of Patients
S23735	Anthony E. Oro, M.D., PhD	SHH4476g	8
S25955	Michael R. Migden, M.D	SHH4476g	11

On September 28, 2011 FDA requested the applicant provide the data listings for all subjects regarding all components of the overall response rate endpoint, serious adverse events, all deviations from protocols, and subject disposition, and if there was a difference between how major and minor protocol deviations were defined. FDA requested that the data be organized by clinical sites so that verification against source records would be possible by the Agency during inspection. The applicant submitted the requested information on October 7, 2011.

The clinical inspection sites included the two above clinical sites, Table 3, two Clinical Research Organizations (CRO), and the applicant. The results of the inspections of the two clinical sites and the sponsor were Voluntary Action Indicated (VAI) and results of the CROs were No Action Indicated. For both clinical sites, the inspectors judged the data reliable based on available information. The VAI decisions were due to time reporting serious adverse events later than 24 hours, use of incorrect informed consent documents, failure to complete end of study patient reported outcome measure, failure to properly initial and date changes to CRFs, and other minor record keeping errors. The CROs were responsible for reviewing the radiographic data (b) (4) (b) (4) and the photographic data (b) (4) and the investigators found the data reliable. Lastly the review of the applicant found that the independent pathologist reviewed cases at the applicant's facility, but persons other than the independent pathologist had access to the source records. The inspector found that the data at the applicant's facility, however, was reliable.

Reviewer's comment: The DSI inspection results are unlikely to significantly affect the primary safety and efficacy analyses for this NDA and the data generated appears to be reliable.

Reference ID: 3068456

3.3 Financial Disclosures

The applicant submitted lists of investigators having disclosable financial arrangements and of investigators who did not provide financial disclosure information. The applicant was able to collect initial financial disclosure forms for 1234 out of 1236 investigators and sub-investigators and able to collect a second financial disclosure from 855 of 1059 investigators and sub-investigators after the applicant (Genentech) merged with Roche. The applicant provided the response results for each individual trial, Table 4.

Table 4: Summary of Financial Disclosure Responses
(*copied from submission with minor modifications*)

Study Protocol Number	First collection or Updated collection	Total Investigators in Study	Total Returned Financial Disclosure Forms	%
SHH3925	Updated	29	19	66
SHH4318	First	3	3	100
SHH4429	Updated	414	362	87
SHH4433	Updated	5	4	80
SHH4437	First	71	71	100
SHH4476	Updated	293	240	82
SHH4489	Updated	315	227	72
SHH4610	First	50	50	100
SHH4683	First	17	15	88
SHH4811	First	33	33	100
SHH4871	Updated	6	6	100
TOTAL	1236		1030	83

The applicant provided disclosable financial interests for 3 out of the 240 investigators who responded in Study SHH4476g and stated in the remaining 10 trials there were no disclosable financial interests, Table 5.

Table 5: Summary of Financial Disclosures
(*copied from submission with minor modifications*)

Study Protocol Number	Clinical Site Number	Number of Subjects Enrolled at Site	Investigator Name	Disclosure
SHH4476	[redacted]	(b) (4	(b) (6)	$30,000 grant for translational research
SHH4476				$25,000 honoraria for lecturing and advisory boards
SHH4476				$500,000 grant for translational research

Reference ID: 3068456

				unrelated to vismodegib.

Reviewer's comment: These disclosures would not be expected to have a sizable bias on the primary endpoint, which was an independent review of tumor response.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Vismodegib is a small molecule inhibitor that binds to and inhibits smoothened (SMO), a G-protein-coupled receptor in the hedgehog (Hh) signal pathway. The Office of New Drugs Quality Assessment (ONDQA) reviewed the data regarding the manufacture of drug substance (DS) and drug product (DP). The applicant submitted no major manufacturing changes regarding the DS to this NDA. Additionally, the applicant made no significant changes to manufacturing process development or to the DS characterization or control.

The applicant submitted data to support vismodegib as a 150 mg capsule. The ONDQA review team identified no major review issues of the DS. For the DP, ONDQA had several review issues:

1. The proposed commercial manufacturing process involves [redacted] (b) (4)
2. Need uniformity data of the [redacted] (b) (4) [redacted] the registration batches.
3. Specification on total impurity needs to be [redacted] (b) (4) Post-approval stability protocol should include additional [redacted] (b) (4)
4. EES status: two testing sites pending [redacted] (b) (4)

The biopharmaceutics review noted two review issues:

1. Need stability dissolution profiles and the actual data for individual test results for the registration batches under both long term and accelerated storage conditions.
2. Need the dissolution profiles for the lots of vismodegib drug product [redacted] (b) (4) [redacted] (b) (4) used in the clinical and PK studies.

Reviewer's comment: See CMC review for further discussion.

4.2 Clinical Microbiology

Vismodegib is an oral medication and the microbiology reviewer noted no significant efficacy or safety issues.

Reference ID: 3068456

4.3 Preclinical Pharmacology/Toxicology

The applicant found teratogenic findings at 10 mg/kg/day (corresponding to approximately 16% the human exposure at the recommended dose of 150 mg /day based on AUC) in rats. These findings included absent and/or fused digits in 21/70 (30%) fetuses examined and identified in 4 of the 5 litters, open perineum (1 fetus) and multiple craniofacial anomalies (1 fetus), and retardations or variations (dilated renal pelvis, dilated ureter, incompletely or unossified sternal elements, centra of vertebrae or proximal phalanges and claws). These findings indicate fetal toxicity and are likely related to the vismodegib mechanism of action, hedgehog pathway inhibition.

The applicant did not conduct carcinogenesis studies, but will do so for population of patients with laBCC.

Repeat-dose toxicology studies in rats and dogs revealed toxic effects in the nervous system, laboratory abnormalities, bones and teeth, skin and taste buds. Rats exhibited reversible tremors, jerking, and ataxia. Laboratory abnormalities included reversible platelet decreases in dogs, decreased hematocrit in one dog, reversible increases in cholesterol in rats and dogs. Rats exhibited irreversible alteration and loss of incisors and closure of the femoral epiphysis. Dogs and rats both exhibited alopecia and dogs exhibited reversible histopathologic correlates of follicular hyperkeratosis and granulomatous inflammation. Rats had a reduced number of taste buds.

Reviewer's comment: There are published reports of the role of Hh pathway signaling in coronary vasculature maintenance (Lavine 2008) and development (Lavine 2008) but these findings were not observed in the preclinical toxicology studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of vismodegib is inhibition of the Hh pathway, which is key to both the efficacy findings and teratogenicity findings. Vismodegib demonstrated concentration dependent inhibition of Hh signaling in human embryonic palatal mesenchymal Hh responsive cell lines through binding and inhibiting SMO. Vismodegib also demonstrated *in vivo* inhibition of tumor growth through inhibition of Gli1, a transcription factor in the Hh pathway.

4.4.2 Pharmacodynamics

SHH3925g, a phase 1 dosing finding trial, contained three different daily doses of vismodegib, 150 mg, 270 mg, and 540 mg. Increasing dose levels of vismodegib did not result in higher steady state plasma concentrations. SHH4610g, a schedule optimization trial, contained different

Reference ID: 3068456

dosing frequencies of 150 mg of vismodegib, three times a week (TIW), once a week (QW), and daily (QD). Decreasing dosage frequency resulted in a decline in total vismodegib concentrations.

The applicant measured *GLI1* expression by quantitative real-time polymerase chain reaction in hair follicle cells from pulled hair and skin punch biopsies prior to and during vismodegib administration in SHH3925g. Inhibition of SMO signaling results in the transcription factor CLI remaining inactive and prevents expression of genes that mediate the role of Hh in tumor growth. The applicant provided results of this exploratory outcome by referencing a published article which stated that "the extent of *GLI1* down-modulation did not correlate with pharmacokinetic levels of [vismodegib] in individual [subjects]" (Von Hoff 2009). From xenograph models, however, vismodegib plasma concentration-response relationship revealed a "steep interaction that operat[ed] like an on-off switch" (Wong et al. 2011). The applicant stated that small reductions in exposure may result in decreased activity of vismodegib.

4.4.3 Pharmacokinetics

Adsorption: After a single dose of 150 mg of vismodegib, the absolute bioavailability is 31.8%. Single higher dose (270 mg or 540 gm) do not result in a proportional increases. Food intake did not affect steady state concentrations, Study SHH4893s (NCI-CTEP 8395).

Distribution: The estimated steady state volume of distribution of vismodegib is 16.4L after a single dose of 150 mg. *In vitro* binding of vismodegib in human plasma is 97% and is independent of concentration up to 100 μM. Vismodegib binds humans serum albumin and alpha-1-acid glycoprotein (AAG). *In vitro* binding to AAG saturates at concentrations > 25 μM and vismodegib concentrations strongly correlate with AAG levels. Ex vivo plasma protein binding in humans is > 99%.

Metabolism: Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. *In vitro* studies demonstrated that CYP3A4 and CYP3A5 produced the greatest quantity of the oxidative metabolites M1 and M3, and CYP2C9 produced the greatest quantity of M3. Several other CYP enzymes also produced M1 and M3, but to a lesser extent. M3 is recovered in feces. In plasma, vismodegib concentration is greater than 98% of the total circulating drug-related components.

Elimination: Following single doses of 150 mg of vismodegib in healthy subjects, the apparent plasma terminal half-life of vismodegib was 11.9 days. Following the administration of a single 150 mg radiolabeled vismodegib to healthy subjects, 83% of the parent drug was recovered in feces and 4.4% in urine. Following continuous daily dosing in healthy subjects, the apparent plasma terminal half-life of vismodegib was 4 days.

Nonlinear Pharmacokinetics: Vismodegib dose increases resulted in less than dose-proportional increases in plasma concentration and lower than expected accumulation after continuous daily dosing which suggest nonlinear pharmacokinetics. According to the applicant,

Reference ID: 3068456

saturable absorption and high-affinity, saturable protein binding are two separate, non-linear processes that result in nonlinear pharmacokinetics. Nonlinear absorption is likely due to poor solubility at physiologic pH. Saturable AAG binding results in concentration changes in the pharmacokinetics of vismodegib.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6 lists all trials submitted in support of the NDA. The applicant submitted final study reports for trials SHH4476g, SHH3925g, SHH4610g, SHH4489, SHH4429g, SHH4871g, SHH4433g, SHH4683g, and SHH4318g. Trial SHH4476g is the primary trial supporting the efficacy claims and trials SHH4476g, SHH3925g, and SHH4610g are the primary trials supporting the safety findings.

Table 6: Listing of Clinical Trials Submitted to the NDA

Trial Number	Phase	Design	Disease	N[a]	Comparator	Status	Dose (mg)[b]
Primary Trials							
SHH4476	2	SA, TC, OL	LA or M BCC	104	None	Ongoing	150
SHH3925	1	SA, DE, OL	Solid Tumors	33	None	Completed	150, 270, and 540
Safety/Supportive							
SHH4437	-	E, OL	BCC	15	None	Ongoing	150 or 300
SHH4610	-	SO, TP	Solid Tumors	1	None	Completed	150; daily, TIW, or QW dosing
SHH4489	2	PC, DB	Ovarian	52	Placebo	Completed	150
SHH4429[c]	2	R, PC	mCRC	98	Placebo	Completed	150
SHH4871	-	QT,MD,R, PC	Healthy women	21	Moxifloxacin	Completed	150
SHH4433	-	,PK, SD	Healthy women	3	None	Completed	150
SHH4683	-	PK, MB	Healthy women	24	None	Completed	150
SHH4318	1	OL	Pediatric medulloblastoma	1	None	Completed	150
NCI-CTEP 8395	-	FE, R	Solid Tumors	29	None	Ongoing	150
SHH4811	-	EA	aBCC	38	None	Ongoing	150

[a] Number of subjects who received vismodegib
[b] Dosing of vismodegib is once daily unless otherwise noted
[c] Vismodegib in combination with FOLFOX plus bevacizumab or FOLFIRI plus bevacizumab
Abbreviations: aBCC = advanced basal cell carcinoma; BCC = basal cell carcinoma; DB = double blind; DE = dose escalation; E = extension; EA = expanded access; FE = food effect; LA = locally advanced; M = metastatic; MB = mass balance; mCRC = metastatic colorectal cancer; MD = multidose; OL = open label; PC = placebo controlled;

Reference ID: 3068456

PK = pharmacokinetic; QW = once weekly; R= randomized; SA = single arm; SD = single dose; SO = Schedule Optimization; TC = two cohort; TIW= three times weekly; TP = two period;

5.2 Review Strategy

This reviewer reviewed safety and efficacy data, including clinical study reports, CRFs, and datasets, for trials SHH4476g, SHH3925g, SHH4610g, and SHH4489g. In addition this reviewer also reviewed the applicant's orientation materials and performed a literature search. Trial SHH4476g was the only trial that solely examined the safety and efficacy of vismodegib in subjects with BCC. SHH3925g was a phase 1 trial examining the dose and safety of vismodegib in subjects with solid tumors, 33 of which had advanced or metastatic BCC. This reviewer reviewed all other studies for serious adverse events and deaths. These other trials contained different patient populations, combination therapies, or different dose schedules of vismodegib. Section 5.3 contains a detailed description of the design of trial SHH4476g and a review of trial SHH3925g. Section 5.3.3 contains brief descriptions of the other supportive trials.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 SHH4476g

The results from trial SHH4476g form the primary support for this NDA:

> Pivotal Phase 2, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of vismodegib in Patients with Advanced Basal Cell Carcinoma

The applicant conducted an international trial at 31 sites in Australia, Belgium, France, German, the United Kingdom, and the United States (69% of 104 subjects). The SHH4476g clinical study report contains data from the first subject visit (visit date February 10, 2009) until the date of primary data cut-off (November 26, 2010). Table 7 shows the finalization dates of the initial protocol and each amendment. The following section of this review describes the SHH4476g trial design including important details of protocol amendments.

Table 7: Dates of Amendments for Protocol SHH4476g

Amendment Number	Date of Amendment
Original Protocol:	28 July 2008
Protocol Amendment 1:	17 November 2008
Protocol Amendment 2:	15 January 2010
Protocol Amendment 3:	14 April 2011

5.3.1.1 Objectives

The primary objective of SHH4476g was "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)." *Reviewer's Comment: The applicant measured the efficacy of vismodegib using*

Reference ID: 3068456

the endpoint objective response rate (ORR) which is the basis for several other approved drugs and biologics for the treatment of other skin cancers, see Section 2.6.

Secondary objectives in SHH4476 included estimation of the duration of objective response, progression free survival (PFS), and overall survival (OS), and assessing safety, tolerability, pharmacokinetics, patient-reported outcomes, histopathologic effect, and the effect on the Hh signaling pathway of vismodegib. *Reviewer's Comment: SHH4476g is a single-arm study without an internal control. This lack of an internal control complicates the ability to determine whether vismodegib caused adverse reactions. This lack of an internal control is especially problematic in describing any additional risk that vismodegib confers.*

5.3.1.2 Inclusion and Exclusion Criteria *(modified from the protocol for brevity)*

Important Inclusion Criteria

- Locally advanced or metastatic BCC:
  - For subjects with mBCC, histologic confirmation of distant BCC metastasis (e.g., lung, liver, lymph nodes, or bone), with metastatic disease that is RECIST measurable using CT or MRI.
  - If a subject with laBCC also has a tumor that is not contiguous with cutaneous BCC, e.g., regional lymph nodes (if confirmed on biopsy as BCC and RECIST measurable), the subject should be considered as having mBCC and should be enrolled in the mBCC cohort.
  - For subjects with laBCC, histologically confirmed disease that is 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 is not considered in and of itself a criterion for inoperability. A copy of the surgeon's consultation note must be submitted.
  - Acceptable medical contraindications to surgery include:
    - BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely.
    - Anticipated substantial morbidity and/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). *Reviewer's comment: FDA did not agree with this criteria, but no subject in SHH4476g met this criteria.*
    - Other conditions considered to be medically contraindicating must be discussed with the Medical Monitor before enrolling the subject.

Reference ID: 3068456

Comment: These criteria allowed for the enrollment of two separate and distinct populations of subjects with BCC, which FDA agreed with in the SPA request, even though SPA agreement was not reached. (See Section 2.5).

- For subjects with laBCC, radiotherapy must have been previously administered for their locally advanced BCC, unless radiotherapy is contraindicated or inappropriate (e.g., hypersensitivity to radiation due to genetic syndrome such as Gorlin syndrome, limitations because of location of tumor, or cumulative prior radiotherapy dose). For subjects whose laBCC has been irradiated, disease must have progressed after radiation.
- Subjects with nevoid BCC (Gorlin) syndrome could enroll in the trial but must meet the criteria for locally advanced or metastatic disease listed above. *Comment: The applicant's proposed label includes information on subjects in SH4476g with Gorlin syndrome but the proposed indication statement does not.*
- For subjects with laBCC, willingness to consent to biopsy of tumor(s) at baseline and during the study, as mandated by the protocol.
- For all subjects, representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry of study.
    - For subjects with mBCC, the archival tissue submitted must be from a metastatic tumor site.
    - If fewer than 15 unstained slides are available, the investigator should consult with the Medical Monitor before enrolling the subject in the study.
- ECOG performance status 0, 1, or 2.
- For women of childbearing potential, agreement to the use of two acceptable methods of contraception, including one barrier method, during the study and for 12 months after discontinuation of vismodegib. *Reviewer's Comment: The applicant included the need for contraception in the proposed vismodegib label, but only for 7 months as contained in the April 14, 2010 Amendment (see below).*
- For men with female partners of childbearing potential, agreement to use a latex condom, and to advise their female partner to use an additional method of contraception during the study and for (b)(4) months after discontinuation of vismodegib.
- Agreement not to donate blood or blood products during the study and for at least 12 months after discontinuation of vismodegib; for male subjects, agreement not to donate sperm during the study and for at least (b)(4) months after discontinuation of vismodegib. *Reviewer's Comment: The applicant included blood donation in the proposed vismodegib label, but only for 7 months as contained in the April 14, 2010 Amendment (see below).*

Important Exclusion Criteria

- Prior treatment with vismodegib or other antagonists of the Hh pathway.
- Pregnancy or lactation.

Reference ID: 3068456

- Life expectancy of < 12 weeks
- Concurrent non–protocol-specified anti-tumor therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy).
    - For subjects with multiple cutaneous BCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target BCCs with surgery may be permitted but must be discussed with the Medical Monitor prior to any surgical procedure.
    - For subjects with locally advanced BCC whose target lesion(s) is/are inoperable at baseline but is/are later deemed potentially operable because of tumor response to vismodegib, surgery with curative intent may be permitted but must be discussed with the Medical Monitor prior to any surgical procedure.
- History of other malignancies within 3 years of Day 1, except for tumors with a negligible risk for metastasis or death, such as adequately treated squamous-cell carcinoma of the skin, ductal carcinoma in situ of the breast, or carcinoma in situ of the cervix
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or renders the subject at high risk from treatment complications

5.3.1.3 Protocol Specified Trial Discontinuation Criteria

Subject Discontinuation:

- Investigator's judgment due to medical reasons
- Subject non-compliance
- Pregnancy

Trial Discontinuation:

- The incidence or severity of adverse events in this or other trials indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

5.3.1.4 Definitions of Prohibited Therapies

The protocol did not define specific, prohibited concomitant medications outside of the exclusion criteria, but warned that vismodegib may potentially affect the pharmacokinetics of other drugs by altering their metabolism. In addition, the protocol cautioned that metabolic inducers could possibly modify the pharmacokinetics of vismodegib.

Reference ID: 3068456

5.3.1.5 Trial Design and Treatment Plan

- SHH4476g was a single arm, open-label, two-cohort, multicenter, international phase 2 trial to evaluate the efficacy and safety of vismodegib in subjects with advanced BCC.
- The screening evaluation included blood samples, physical examination, tumor assessment (CT scan for subjects with metastatic disease and tumor assessments per the composite tumor response criteria for subjects with locally advanced disease).
- All subjects received 150 mg of vismodegib daily until evidence of progression, intolerable toxicities most probably attributable to vismodegib, or withdrawal from the trial.
- The protocol enrolled subjects into either the mBCC or laBCC cohort.
- Day 1 of the trial was the first day a subject received vismodegib (for the list of trial assessments, see the Trial Flowchart in Figure 2). Tumor assessments occurred every 8 weeks and at the end of the trial or at early termination.
- The protocol determined follow up for survival for subjects who discontinued trial drug was approximately every 3 months until death, loss to follow-up, or trial termination by the applicant.

Reference ID: 3068456

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Figure 2: SHH4476g Flowchart (*copied from submission*)

APPENDIX A
Study Flowchart

Assessment or Procedure	Screening		Treatment							
	Days –14 to –1	Day 1	Every 4 Weeks (±3 Days)	Every 8 Weeks (±3 Days)	Week 8 (±3 Days)	Week 12 (±3 Days)	Clinical Response if before Wk 24	Week 24 (±3 Days)	Early Term./ End of Study	Follow-Up
Informed consents [a]	x									
Assignment of patient identification number through the IVRS [b]	x									
Medical, surgical, and cancer history, and demographics	x									
Complete physical examination [c]	x									
Limited physical examination			x						x	
Height (at screening only) and weight	x	x	x						x	
Vital signs [d]	x	x	x						x	
ECOG performance status	x	x	x						x	
12-Lead electrocardiogram	x									
Tumor assessment [e]	x			x					x	
Standardized digital photographs [f]	x			x					x	
Tumor biopsy [g]	x						x [g]	x [g]	x [g]	
SF-36 Health Survey		x				x		x	x	
Hematology [h]	x		x							
Serum chemistry [i]	x		x							
Urinalysis [j]	x									

Assessment or Procedure	Screening		Treatment							
	Days –14 to –1	Day 1	Every 4 Weeks (±3 Days)	Every 8 Weeks (±3 Days)	Week 8 (±3 Days)	Week 12 (±3 Days)	Clinical Response if before Wk 24	Week 24 (±3 Days)	Early Term./ End of Study	Follow-Up
Plasma PK sample for GDC-0449 concentration (for patients enrolled at selected sites)					x					
Archival tissue [k]	x									
Serum or urine pregnancy test [l]	x	x	x						x	x
GDC-0449 accountability [m]			x						x	
Dispense GDC-0449 [m]		x	x							
Concomitant medications [n]	x	x	x						x	
Adverse events	x [o]	x	x						x	x [o]
Cancer-related medical or surgical procedures [p]		x	x						x	
Survival [q]										x

Note: Results of tests or examinations performed as standard of care prior to obtaining informed consent prior to trial entry may be used rather than
repeating required tests.

[a] All subjects must provide written informed consent prior to any trial-specific procedure being performed and any exclusionary medications are discontinued for the purposes of establishing eligibility. Subjects will sign two informed consent forms: one for trial participation, and a separate consent detailing teratogenic risk.

[b] Contact the IVRS within 5 days of Day 1 for assignment of a subject's identification number.

[c] A complete physical exam includes evaluation of the head, eyes, ears, nose and throat; cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

[d] Vital signs include pulse, systolic and diastolic blood pressure while the subject is in a seated position, respiratory rate, and temperature.

[e] Tumor assessments must be performed at screening and every 8 weeks thereafter. Assessments should include an evaluation of all sites of disease. Subjects in the metastatic BCC cohort will undergo tumor assessments per the Response Evaluation Criteria in Solid Tumors (see Appendix B). Subjects in the locally advanced BCC cohort will undergo tumor assessments per the composite tumor response criteria (see Appendix C). f Instructions for obtaining digital photographs are given in Appendix H.

[g] For subjects with locally advanced BCC, a baseline tumor biopsy must be performed in accordance with guidelines (see Appendix G). Perform biopsy again either at best clinical response if achieved prior to Week 24 or at Week 24. A tumor biopsy is recommended at the time of progression.
[h] Hematology consists of hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent or absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells).
[i] Serum chemistry includes glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT.
[j] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood.
[k] Archival metastatic tissue (i.e., representative tumor specimens in paraffin blocks [preferred] or at least 15 unstained slides, with an associated pathology report) must be available and requested any time prior to trial entry. For metastatic BCC subjects, the archival tissue must be from a metastatic site.
[l] For women of childbearing potential, including those who have had a tubal ligation, a serum pregnancy test is required at screening and urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During the follow-up period, monthly pregnancy tests should be performed for 12 months after discontinuation of vismodegib.
[m] Dispense, administer, and maintain drug accountability of vismodegib. For women of childbearing potential, the investigator must confirm the subject's negative pregnancy test, the subject's understanding of the teratogenic potential of vismodegib, and the use of two acceptable methods of contraception prior to dispensing vismodegib.
[n] The recording of concomitant medications will begin at the time of informed consent and continues through the end of the trial period. Record all concomitant medications administered to the subject within the 14 days preceding Day 1
[o] The reporting period for adverse events (AEs) and serious adverse events (SAEs) will begin at the time of enrollment through the IVRS and continues until 45 days after the last dose of vismodegib. During screening, only SAEs related to protocol-mandated procedures should be reported. At the end of the trial period, any subject with an ongoing AE or SAE leading to vismodegib discontinuation will be followed until the event resolves, the investigator assesses the event as stable, or the subject is lost to follow-up.
[p] The recording of cancer-related medical and surgical procedures begins on Day 1 and continues through the end of the trial period.
[q] All subjects with documented disease progression will be followed for survival unless the subject requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. Survival follow-up information will be collected via telephone calls and/or at clinic visits every 3 months until death, loss to follow-up, or trial termination by Genentech.
Abbreviations: BCC = basal cell carcinoma; IVRS = interactive voice response system; PK = pharmacokinetic; SF-36 = Short Form 36

5.3.1.6 Definition of Response (*copied from submission with minor modifications*)

5.3.1.6.1 Metastatic Disease

The protocol used modified RECIST criteria. Table 8 provides the definitions of the criteria used to determine objective tumor response for target lesions.

Table 8: SHH476g RECIST Criteria

Response Category	Description
Complete Response	Disappearance of all target lesions
Partial Response	At least a 30% decrease in the sum of the longest diameter of target lesions,

Reference ID: 3068456

Response Category	Description
	taking as reference the baseline sum longest diameter
Progressive Disease	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started

Table 9 contains relevant modifications to RECIST. *Reviewer's Comment: The modifications to RECIST are minor and do not significantly affect the overall findings.*

Table 9: Modifications to RECSIT for SHH4476g
(*copied from submission with minor modifications*)

RECIST Criteria Item	RECIST Modifications for SHH4476
Section 2.1 List of non-measureable lesions	Addition of types of non-measurable lesions: bone lesions, ascites, pleural and/or pericardial effusions, lymphangitis cutis/pulmonis, cystic lesions, non-measurable skin lesions, irradiated lesions, and groups of lesions that are small and numerous.
Section 2.1 Lesions in prior sites of radiation	If radiation has been administered to a lesion, there must be radiographic evidence of progression of that lesion in order for that lesion to constitute measurable disease or to be included in the measured target lesions. Prior radiation therapy documentation must be provided by the site to (b) (4)
Section 2.2.6 Cytology and Histology	Unequivocal new or significant increase in pleural effusions, ascites or other fluid collections is sufficient evidence of progression and will not require cytological confirmation of malignancy.
Section 3.2.1 Evaluation of target lesions	Addition of the following evaluation terms: **Unable to Evaluate** (UE): Any target lesion present at baseline which was not assessed or which was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point; **Not Applicable** (NA): No target lesions identified at baseline; **Too Small to Measure** (TSTM): Target lesions which are being followed and decrease to less than 5 mm in LD will be considered TSTM.
Section 3.2.3 Evaluation of best overall response	For the purposes of the independent review, the subject response at each time point will be assessed based on the time point response of the target lesions, the response of the non-target lesions and the presence or absence of new lesions. Once the time point response (TPR) has been determined for all time points, the best overall response the subject has at each time point will be determined by comparing two (2) subsequent assessments.
Section 3.2.4: Frequency of tumor	Subjects will be evaluated every eight (8) weeks until disease progression is documented. Responding disease will be confirmed no less than 4 weeks after

Reference ID: 3068456

RECIST Criteria Item	RECIST Modifications for SHH4476
re-evaluations.	the criteria for response (CR/PR) are first met. Subjects with symptoms suggestive of disease progression should be evaluated for tumor response at the time symptoms occur.
Section 3.3.1: Confirmation	For clarification purposes, the best overall response would be determined by applying the TPR from two (2) subsequent time points to determine if a response is confirmed. Assessment of stable disease requires being on study for a period of 8 weeks (56 days).
Section 4: Response review	Independent review will consist of a complete radiographic review of selected information from the subjects' records, not a complete review of the subjects' medical record. All reasonable attempts are made to obtain images that do not have annotations on them from the sites. Occasionally, some images will be read with site-initiated annotations
Section 5: Reporting of results	Subjects will be assigned one of the following categories: • Complete Response (CR), • Partial Response (PR), • Stable Disease (SD), • Progressive Disease (PD), and • Unevaluable (UE). (b) (4) (b) (4) assessments will not include information about death. Genentech, not will report response rate.

The protocol defined best overall response as the best response recorded from the start of treatment until disease progression/recurrence. Table 10 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 10: Overall Response based on all possible response combinations
(*copied from submission with minor modifications*)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the subject is still deriving benefit from treatment, treatment with vismodegib should be continued, and the subject should be re-evaluated at the next tumor assessment time point. If progressive disease is confirmed at the next tumor assessment

Reference ID: 3068456

timepoint, the date of progressive disease should be recorded as the original date at which equivocal progression was assessed.
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

The investigator recorded the partial or complete response on the eCRF at the time when criteria for partial or complete response were first met, regardless of whether the response was confirmed at a later assessment. The applicant accounted for PR and CR in the final analysis. In the case of SD, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

5.3.1.6.2 Locally Advanced Disease

The protocol used a composite tumor response criteria to define response for subjects with locally advanced BCC.

Externally Visible Tumor Dimension: The externally visible component of target lesion(s) was measured in the longest dimension at each tumor assessment and was documented using standardized digital photography. If the border of the tumor is no longer visible but a scar is present, the dimensions of the scar should be measured.

Response criteria for tumor dimension were as follows:

- CR: target lesion(s) no longer visible, maintained for at least 4 weeks
- PR: decrease of 30% or greater in the longest dimension of target lesion(s), maintained for at least 4 weeks
- SD: not meeting criteria for CR, PR, or progressive disease (PD)
- PD: increase of ≥ 20% in the longest dimension of target lesion(s)

Tumor Ulceration: For subjects whose target lesion(s) are ulcerated at baseline the protocol included response criteria categories:

- CR: re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained for at least 4 weeks
- PR: there are no criteria for PR
- SD: not meeting criteria for CR or PD
- PD: new ulceration of target lesion(s), not related to tissue biopsy or other known trauma, persisting without evidence of healing for at least 2 weeks

New Lesions: A new BCC will be considered as PD if the lesion is > 5 mm, can be clearly documented as not being previously present, is confirmed on biopsy to be BCC, and cannot be managed with standard therapy (such as surgical excision or topical palliation). A new distant metastatic lesion must be confirmed on biopsy to be BCC to be considered as PD. *Reviewer's comment: The applicant changed the definition of PD in response to FDA comments to no*

Reference ID: 3068456

longer exclude new BCC lesions that can be managed with standard therapy, see July 15, 2010 amendment below or Section 2.5 under July 31, 2008 SPA discussion.

Overall Clinical Response: Table 11 contains the visible and ulceration tumor response combinations for assessment of Clinical Response. *Reviewer's Comment: FDA did not agree with the assessment of CR under clinical response unless there was complete clinical resolution of all lesions and a negative biopsy at the time of response.*

Table 11: Overall Clinical Responses for All Possible Combinations of Tumor Responses for Locally Advanced BCC
(copied from submission with minor modifications)

Externally Visible Tumor Dimension	Tumor Ulceration (If Applicable)	New Lesions [a]	Clinical Response
CR or PR	Non-PD	No	Response [b]
SD	CR	No	Response [b]
SD	SD	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

[a] See above for definitions.
[b] In subjects achieving clinical response, histologic analysis of biopsies will be used for final determination of CR versus PR
Abbreviations: CR = complete response; PD = partial disease; SD = stable disease.

Clinical plus RECIST: Table 12 contains the clinical plus RECIST response combinations for final response assessment for subjects with locally advanced BCC whose target lesion(s) have both externally visible and RECIST-measurable components.

Table 12: Clinical plus RECIST Response
(copied from submission with minor modifications)

Clinical Response	RECIST Response	Clinical + RECIST Response
Response	Non-PD	Response [a]
SD	CR or PR	Response [a]
SD	SD	SD
PD	Any	PD
Any	PD	PD

[a] In subjects achieving clinical response, histologic analysis of biopsies will be used for final determination of CR vs. PR
Abbreviations: CR =complete response; PD =progressive disease; PR =partial response; RECIST =Response Evaluation Criteria in Solid Tumors; SD =stable disease.

Reference ID: 3068456

In subjects with a clinical response, histologic analysis of biopsies determined the final choice of CR (absence of residual BCC) versus PR (residual BCC present). In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, the protocol considered this response to be a CR. *Reviewer's Comment: FDA did not agree with this assessment of CR, see Section 2.5.* If the investigator deemed a previously inoperable lesion to be potentially operable, the Medical Monitor should be consulted prior to any surgical procedure.

Guidelines for Tissue Biopsy in Subjects with laBCC: The protocol required representative tumor biopsies for subjects in the laBCC cohort several time points:

- At Screen, and
- At the investigator's assessment of best clinical response or best clinical/RECIST response, if occurring prior to 24 weeks

  OR

  At 24 weeks, if subject is still in study and is without evidence of progression

The protocol defined subjects experiencing a clinical response whose biopsies show no evidence of residual BCC on biopsy as having a CR; subjects experiencing a clinical response, but whose biopsies show evidence of residual BCC, the protocol defined response was PR.

At any time during a subject's participation in the trial, an optional tumor biopsy may be requested to clarify the response status of a subject. In addition, biopsy of any accessible target lesion(s) is highly recommended at the time of progression. The sites, number, and technique of representative biopsies will be determined by the investigator on the basis of the size and location of the accessible lesions. It is recommended that any areas suspicious for residual disease be biopsied, as well as areas which appear to be free of disease. These biopsies will be reviewed by an independent dermatopathologist.

At least one and up to five punch biopsies of at least 3 mm in size, or 14-gauge or larger core needle biopsies, as determined by the investigator, should be obtained. For large, accessible lesions in the skin and/or soft tissues, punch biopsies of 3 to 4 mm are strongly recommended to allow for optimal assessment of residual disease. Biopsies should be fixed and paraffin embedded according to site standards. The entire block must be submitted to the vendor as per the Central Laboratory Manual. If a biopsy obtained after administration of vismodegib cannot be interpreted because of technical issues (e.g., crush artifact), the investigator will be contacted and additional biopsies will be requested, if available.

Digital Photographic Procedures for Serial Photographic Documentation of BCC: The protocol stated that in these clinical photographs for the duration of the trial, the only variable allowed to change was the skin condition itself and anything extraneous to the condition (furniture, etc.) should be eliminated from the photographic field, starting at the entry visit through the final visit. The images were to read like a time-lapse movie.

Reference ID: 3068456

5.3.1.7 Statistical Design / Sample Size

Sample Size: ORR calculations were the basis of the sample size assumptions for the protocol. The protocol defined a population of 100 subjects in order to have adequate sensitivity to detect safety signals with a relatively low incidence. Table 13, lists the probabilities of a particular adverse event occurring in a study of size 100, with a "signal" being expressed as one or more or two or more particular adverse events.

Table 13: Statistical Assumptions for Adverse Events

Incidence of Adverse Event	Probability of One or More Adverse Events Occurring	Probability of Two or More Adverse Events Occurring
2%	87%	60%
3%	95%	81%
4%	98%	91%
5%	99%	96%

For efficacy, the trial was to have at least 80% probability of detecting an response rate of 37% or higher in the metastatic BCC cohort (with 20 treated subjects) and 34% or higher in the laBCC cohort (with 80 treated subjects).

Primary Endpoint: The protocol defined primary endpoint was ORR as a function of a radiographic IRF, photographic IRF, and pathological IRF. The protocol defined objective response as a complete or partial response determined on two consecutive assessments ≥ 4 weeks apart and labeled such subjects as responders. ORR was the proportion of responding subjects within each cohort. The protocol considered subjects without a post-baseline tumor assessment as non-responders. The formal testing method of the magnitude of ORR occurred in two parallel analyses using one-sided exact binomial tests in the metastatic and locally advanced BCC cohorts. *Reviewer's comment: FDA stated that the applicant could exclude subjects whose baseline biopsy was unevaluable or did not show BCC, confirmed by an independent pathologist, but the applicant should also exclude those subjects from the primary analysis.*

Secondary Efficacy Endpoints: Secondary endpoints included duration of objective response, PFS, OS, change from Day 1 in subject-reported symptoms, and absence of residual BCC in subjects with locally advanced BCC. The IRF and investigators assessed duration of objective response and PFS. Investigators also assessed ORR. The IRF-assessed duration of objective response was the major secondary endpoint. The protocol defined duration of objective response only for subjects who achieved an objective response as the time from the initial confirmed compete response or partial response to the earlier of documented disease progression or death within 30 days of last exposure to study treatment. The protocol defined duration of PFS as the time from the initial dose of vismodegib until the earlier of documented disease progression or death within 30 days of last exposure to trial treatment. The protocol defined duration of OS as the time from the initial dose of vismodegib until death from any cause.

Reference ID: 3068456

Interim Analysis: The protocol defined the interim analysis plan as subject monitoring based on the safety plan.

Safety Reporting: The safety reporting plan consisted summaries of laboratory test results, all adverse events, including serious adverse events, trial drug related adverse events, and adverse events leading to discontinuation of vismodegib using the all treated subject population. The protocol used NCI CTCAE version 3 for reporting of all treatment-emergent adverse events.

5.3.1.8 Amendments

The following section describes important amendments to the protocol or changes that occurred after discussion with the FDA. This section does not discuss minor or editorial changes to the protocol.

November 17, 2008: The applicant amended the protocol to correct the EURDRACT number and added ECOG Performance scale.

January 15, 2010: The applicant amended the protocol in response to comments from FDA:

- Requirement to consult the Medical Monitor before restarting vismodegib if a subject experienced two treatment interruptions.
- Clarification that the minimum target lesion size (≥10 mm) for subjects in the eligibility criteria, which had previously only appeared in the appendix.
- Clarification for providing archival and on-study tissue samples for subjects with locally advanced disease and multiple target lesions.
- Clarification that subjects with metastatic disease confined to bone are not eligible because of a lack of RECIST-measurable disease.
- Elimination of serum creatinine or creatinine clearance parameters for eligibility based on data from another study that showed that vismodegib is minimally renally excreted.
- Addition of inability or unwillingness to swallow capsules to the exclusion criterion.
- Clarification that if the investigator believed the subject had equivocal progressive disease, continues on treatment, and the experienced progressive disease at the following time point, the date of progressive disease would be the original date when the investigator noted equivocal progression.
- Clarification of the timing and nature of assessments for subjects who discontinue treatment with vismodegib but do not request withdrawal from the trial.
- The timing for confirmatory tumor assessments for subjects exhibiting a response to therapy (using either Response Evaluation Criteria in Solid Tumors [RECIST] or composite endpoint criteria) has been re-emphasized in the text and in Appendix A.

Reference ID: 3068456

- Addition of a requirement for a baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis for subjects in the locally advanced cohort, to rule out occult metastatic disease or other preexisting radiographic abnormalities.
- Clarification of the criteria for progressive disease, with respect to use of the smallest sum of longest diameters recorded as a reference, and with respect to new cutaneous or metastatic lesions.
- Clarification of the timing of screening biopsies for subjects with locally advanced disease.
- Clarification that for both mBCC and laBCC cohorts, a new BCC would be considered as PD if the lesion is > 5 mm, and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with BCC. If the new lesion is not biopsied the histology is inconclusive, it should be considered to be BCC and indicative of PD. The applicant removed the phrase [redacted] (b) (4) as a descriptor of new lesions.

April 14, 2011: The applicant amended the protocol to update safety information for defining female subjects of childbearing and non-childbearing potential and reduced the time period after which female subjects can become pregnant or plan to become pregnant following vismodegib from [redacted] (b) (4) to 7 months.

5.3.1.9 Independent Radiology Charter (IRF) (*copied from submission with minor modifications)*

The IRF [redacted] (b) (4) consisted of a two-reader, Sequential Locked Review paradigm in a batch read mode, that is the radiologist read the film with no knowledge of future time points. The radiologists were blinded to the following: subject demographics per GCP and HIPAA requirements, treatment arm, site assessment of response, site choice of target and non-target lesions and the identification of new lesions (with the exception of subjects with locally-advanced disease for whom [redacted] (b) (4) received target and non-target lesion location information), the number of time points for a subject during the read, clinical history, and read number 1 (or read number 2) results. The radiologist did not communicate with trial sites. The radiologists provided the applicant with the Best Overall Response, the Date of Progression (if applicable) and the Date of First Response.

5.3.10 Independent Panel Review of Photographs (*copied from submission with minor modifications)*

The Independent Panel Review consisted of three board certified physicians qualified and experienced in the diagnosis and treatment of BCC. The reviewers were not Investigators participating in the trial. The reviewers were blind to subject identifiers and investigator information. The applicant chose two primary reviewers to assess the images and record their assessments of tumor dimension and ulceration for each lesion, at each time point, and record their response assessment for tumor dimension and ulceration across all investigator-identified target lesions. The third reviewer was an adjudicator that reviewed the images that were not in agreement with the two primary reviewers. The adjudicator chose one of the two primary

Reference ID: 3068456

reviewer's response assessments (tumor dimension and ulceration across all investigator-identified target lesions) as the final reading to be recorded in the database, or if the adjudicator disagreed with both primary reviewers response assessments, the adjudicator performed his/her own measurements and response assessments, which were considered the final reading to be recorded in the database.

5.3.2 SHH3925g

Protocol SHH3925g was an open-label, two part, phase 1 dose escalation trial in which the applicant administered vismodegib to subjects with advanced solid tumors. The first part of the protocol used a standard 3 + 3 dose escalation to assess the safety and tolerability of vismodegib. The second part enrolled additional subjects with BCC or other advanced tumors or to a different formulation of vismodegib to characterize the safety and the PK and PD properties of vismodegib.

The protocol enrolled subjects from three study sites. The dose levels were 150 mg, 270 mg, and 540 mg. The protocol measured tumor response via RECIST for those with measurable disease. Figure 3 and Figure 4 show that the AE reporting period began at the first dose. The AE collection occurred every week during the screen and every two weeks during continuation period and ended 45 days after last dose. The protocol used graded AEs using CTCAE version 3.0. *Reviewer's comment: The applicant coded the AEs using MedDRA version 12.1 for the SHH3925 ADAE dataset and version 13.1 for the ISS ADAE, which incorporated SHH3925g AEs.*

Reference ID: 3068456

Figure 3: SHH3925g Flow Chart during Screening and DLT Assessment

Visit No.	1	2	3 [a]	4 [b]	5 [b]	6	7	8	9	10
Study Week	Screening [c]	1	1	1	1	2	3	4	5	6
Study Day	−14 to −1	1	2	3	4	8	15	22	29	36
Visit Window (Day)						±1	±1	±1	±1	±1
Informed consent(s)	x									
Medical history, including demographics	x									
Complete physical examination	x					x				x
Limited physical examination		x					x	x	x	
Weight and height	x	x [d]				x [d]	x [d]	x [d]	x [d]	x [d]
Vital signs (pulse, BP, RR, and temp.)	x	x				x	x	x	x	x
ECOG performance status	x					x				x
12-Lead ECG [e]	x	x				x	x	x	x	x
Tumor assessment [f]	x									
DLT assessment										x
CBC with platelet and differential	x					x	x	x	x	x
Fasting lipid profile [g,h]	x					x	x	x	x	x
Serum chemistries [i]	x					x	x	x	x	x
INR and aPTT	x									
PSA or CA-125 [j]	x									
Urinalysis (laboratory UA)	x									
Pregnancy test [k]	x	x						x		
Archival tissue		x								
Hair sample from scalp [g]		x [l]				x [m]	x [b]	x [m]	x [b]	
Skin punch biopsy [g]		x [l]				x [m]	x [b]	x [m]	x [b]	
Tumor biopsy (optional)		x [l]				x [m]	x [b]	x [m]	x [b]	
PK samples [n]		x	x	x [g]	x [g]	x	x	x	x	x
GDC-0449 drug accountability [o]		x				x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x

Figure 4: SHH3925g Flow Chart during Continuation of Treatment Period

Visit Nos.	11, 13, 15, 17, 19 [a]	12, 16, 20, 22, 24	14, 18, 21, 23, 25	Treatment Extension	EOT [b]	EOS1/ Term [b]	EOS2, EOS3, and EOS4
Study Week(s)	8, 12, 16, 20, 24	10, 18, 26, 34, 42	14, 22, 30, 38, 46	49+ Every 4 weeks *(± 1 week)*		7 days after last dose	14, 21, 28 days after last dose
Study Day(s)	50, 78, 106, 134, 162	64, 120, 176, 232, 288	92, 148, 204, 260, 316	345+			
Visit Window (Day)	±3	±3	±3	±3	±3	±1	±1
Complete physical examination		x	x	x	x	x	
Weight		x	x	x	x	x	
Vital signs (pulse, BP, RR, and temp.)		x	x	x	x	x	
ECOG performance status		x	x	x	x	x	
12-Lead ECG [c]		x	x		x		
Tumor assessment [d]		x		x [d]	x		
CBC with platelet and differential		x	x	x	x	x	
Fasting lipid profile [e,f]		x	x				
Serum chemistries [g]		x	x	x	x	x	
Hair sample from scalp [e]							
Skin punch biopsy [e]							
Tumor biopsy (optional)						x	
PK samples [h]		x	x	x	x	x	x
GDC-0449 drug accountability [i]	x	x	x	x	x		
Adverse events	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x
Pregnancy test [j]	*x*			*x*	*x*	*x*	

The applicant included 33 subjects from SHH3925g in the pooled safety analysis, but not all of these subjects received the same dose or formulation of vismodegib. Table 14 contains the different doses and formulations for the subjects with advanced BCC.

Table 14: Vismodegib Dose by Cohort SHH3925g

Cohort	Dose of Vismodegib			
	150MG	270MG	540MG	Total Subjects
BCC	6 (18.2%)	14 (42.4%)	0 (0%)	20 (60.6%)
Dose Escalation	1 (3%)	1 (3%)	1 (3%)	3 (9%)
New Formulation	10 (30%)	0 (0%)	0 (0%)	10 (30.3%)
Total Subjects	17 (51.5%)	15 (45.4%)	1 (3%)	33 (100%)

Source: SHH3925g ADEX dataset with BCCFL = Y. Cohort variable COHORTG1 and dose variable TRT01A. % Total is based on 33 subjects with BCCFL = Y and not the total trial population of 68 subjects.

5.3.3 Supportive Trials

The following supportive studies evaluated vismodegib in different populations or used different dosing schedules than that proposed for this NDA. In general, doses were the same. The usefulness of these studies in the safety analysis is primarily limited to additional data regarding deaths and SAEs. The incidence of more common adverse reactions may differ in these studies

due to differences in indication, concomitant chemotherapy, and doses or duration of vismodegib administered.

5.3.3.1 SHH4437g

SHH4437g is an ongoing open label extension trial for SHH3925g and SHH4610g. The applicant submitted safety narratives of subjects with BCC who received vismodegib.

5.3.3.2 SHH4610g

SHH4610g was a two-stage, phase 1b trial that examined the pharmacokinetics of QD, TIW, and QW dosing of 150 mg vismodegib in 9 subjects with advanced solid tumors. Stage 1 was a two-part (loading and maintenance), randomized, open-label, multicenter design in which all subjects received a daily loading dose for 11 days (loading phase), followed by a maintenance dose administered QD, TIW, or QW. Stage 2 was an open-label, sequential (Group 1 followed by Group 2), multicenter design, in which additional subjects received vismodegib TIW (Group 1) or QW (Group 2) without a loading phase. The AE reporting in SHH4610g was weekly for the first nine weeks then every 4 weeks for subjects who continued vismodegib after week 9 during the 'treatment continuation' phase of the protocol, at discontinuation, and at follow up visits.

5.3.3.3 SHH4489g

SHH4489g was a phase 2, randomized, placebo-controlled, double-blind, multicenter clinical trial of vismodegib in subjects with ovarian cancer in a second or third complete remission. The protocol randomized (1:1) subjects to either 150 mg vismodegib or placebo with stratification based on whether their cancer is in a second or third complete remission. Administration of vismodegib or placebo continued until evidence of radiographic progression, until the subject experienced intolerable toxicities most probably attributable to vismodegib, or until the subject withdrew from the trial. The AE reporting in SHH4489g was every 4 weeks, at discontinuation of vismodegib, and at follow up visits. *Reviewer's comment: SHH4489g has similar AE reporting guidelines as SHH4476g and the inclusion of a placebo arm allows for an assessment of the treatment emergent adverse events likely due to vismodegib. This reviewer considers SHH4489g as a key supportive trial in the safety analysis of vismodegib as the comparison of AEs in this trial may identify AEs in SHH4476g that are likely due to vismodegib.*

5.3.3.4 SHH4429g

SHH4429g was a phase 2, randomized, placebo-controlled, double-blind, multicenter clinical trial of vismodegib or placebo in combination with FOLFOX plus bevacizumab or FOLFIRI plus bevacizumab in subjects with metastatic colorectal cancer (mCRC). The protocol randomized (1:1) subjects to either 150 mg vismodegib or placebo with stratification based on chemotherapy regimen and whether the subject had RECIST measurable disease at baseline. Administration of vismodegib continued until disease progression or intolerable toxicities attributed to placebo or vismodegib. The AE reporting in SHH4429g was every three weeks, at discontinuation of vismodegib and at follow up visits. *Reviewer's comment: SHH4429g has similar AE reporting*

Reference ID: 3068456

guidelines as SHH4476g and the inclusion of a placebo arm allows for an assessment of the treatment emergent adverse events likely due to vismodegib, but the co-administration of chemotherapy and bevacizumab may confound attribution of some adverse reactions. This reviewer considers SHH4429g as a key supportive trial in the safety analysis of vismodegib as the comparison of AEs in this trial may identify AEs in SHH4476g that are likely due to vismodegib.

6 Review of Efficacy

Efficacy Summary

The results of a single, international, single-arm, multi-center, open-label, two-cohort trial in 104 subjects with either metastatic BCC (n=33) or locally advanced BCC (n=71) support the primary efficacy results. Subjects had to have measurable metastatic disease for the mBCC cohort. For subjects with laBCC, the subjects had to have lesions that had recurred after radiotherapy, unless radiotherapy was contraindicated (e.g. Gorlin Syndrome), and where the lesions were either unresectable or surgical resection would result in substantial deformity. The primary endpoint was best overall response, based on RECIST in subjects with mBCC and a composite of clinical, histopathologic, and photographic criteria in subjects with laBCC. Subjects in both cohorts received 150 mg vismodegib per day orally until disease progression or unacceptable toxicity.

The major efficacy outcome measure of the trial was objective response rate (ORR) as assessed by an independent review facility (IRF). In the mBCC cohort, tumor response was assessed according to RECIST version 1.0. In the laBCC cohort, tumor response evaluation 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 laBCC required at least one of the following criteria and absence of any criterion for disease progression: (1) ≥ 30% reduction in lesion size [sum of the longest diameter (SLD)] from baseline in target lesions 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. The protocol specified that only subjects with confirmation of BCC by histopathology would be assessed for response, the efficacy population and 63 of the 71 subjects with laBCC met this criteria.

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

Reference ID: 3068456

Tumor shrinkage as a primary endpoint supporting full approval is similar to other prior approvals for drugs treating malignancies with primary skin involvement and can be considered direct clinical benefit. In both the laBCC and mBCC cohort, patients experienced durable and clinically meaningful shrinkage of their tumors.

Efficacy analyses and demographics presented in the following Section were performed by the Biometrics Division, Biologics and Therapeutics Statistical Staff, Dr Jiang. Refer to the statistical review for the statistical reviewer's conclusions.

6.1 Indication

The proposed indication for this application is (b) (4) There is regulatory precedent establishing that the endpoint overall response rate (ORR) represents an adequate efficacy measure.

Reviewer's comment: The indication statement initially did not contain information about prior radiation which was a key eligibility criteria and does not sufficiently describe the eligibility criteria with respect to prior surgical or radiation treatment. This reviewer suggests revising the indication statement to more closely reflect the eligibility criteria of SHH4476g,

ERIVEDGE is indicated for the treatment of adult patients with basal cell carcinoma *that has recurred following* surgery *and radiation or who are not candidates for surgery and radiation.*

Tumor shrinkage is an established regulatory endpoint. For subjects with advanced metastatic disease with no approved therapy, FDA has accepted response rate, i.e. a shrinkage of tumor size as measured by radiographs, most commonly using RECIST criteria. For subjects with laBCC, a cancer with predominately skin manifestations, the reduction in size or ulceration of tumors of the skin represents similar benefit.

6.1.1 Methods

This efficacy review contains the results from a single trial, SHH4476g. SHH4476g was the only trial to evaluate 150 mg of vismodegib in subjects with locally advanced BCC (laBCC) or metastatic BCC (mBCC).

6.1.2 Demographics

Table 15 contains subject characteristics for SHH4476g. The median age at enrollment was 62 years for both the mBCC and laBCC cohorts. In both cohorts, over 40% of the subjects were ≥ 65 years of age. The majority of subjects were male in both cohorts. All the subjects were White. In both cohorts, over 60% of the subjects were from the United States. A total of 6/104 (5.8%) of subjects were of childbearing potential.

Reference ID: 3068456

Table 15: Demographics SHH4476g

Demographics	mBCC (n=33)	laBCC (n=71)	Total (n=104)
Age (yr)			
Mean (SD)	61.6 (11.4)	61.2 (16.8)	61.4 (15.2)
Median	62	62	62
Range	38 - 92	21 - 101	21 - 101
Age group (yr)			
18-40	1 (3%)	8 (11.3%)	9 (8.7%)
41-64	18 (54.5%)	30 (42.3%)	48 (46.2%)
≥ 65	14 (42.4%)	33 (46.5%)	47 (45.2%)
Sex			
n	33	71	104
Male	24 (72.7%)	39 (54.9%)	63 (60.6%)
Female	9 (27.3%)	32 (45.1%)	41 (39.4%)
Childbearing Potential			
N	24 (72.7%)	39 (54.9%)	63 (60.6%)
Y	2 (6.1%)	4 (5.6%)	6 (5.8%)
Ethnicity			
Hispanic or Latino	0 (0%)	1	1 (1.0%)
Not Hispanic or Latino	33 (100%)	69 (97.2%)	102 (98.1%)
Not Available	0 (0%)	1	1 (1.0%)
Race			
White	33 (100%)	71 (100%)	104 (100%)
Weight (kg)			
Mean (SD)	76.50 (15.30)	84.94(21.13)	82.23 (19.78)
Median	74.8	82.2	79.0
Range	54.2-122.0	42.0-170.0	42.0-170.0
Country			
USA	26 (78.8%)	46 (64.8%)	72 (69.2%)
Germany	1 (3%)	13 (18.3%)	14 (13.5%)
France	1 (3%)	6 (8.5%)	7 (6.7%)
Belgium	3 (9.1%)	4 (5.6%)	7 (6.7%)
United Kingdom	2 (6.1%)	0 (0%)	2 (1.9%)
Australia	0 (0%)	2 (2.8%)	2 (1.9%)

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

Table 16 contains the prior treatments and disease characteristics for SHH4476g. A total of 66/71 (93%) subjects with laBCC and a total of 32/33 (97%) subjects with mBCC received prior cancer treatment. The most common prior treatment for subjects with laBCC and mBCC were surgery and radiation, followed by non-anthracycline chemotherapy, biologic therapy, and anthracycline chemotherapy.

Reference ID: 3068456

Table 16: Disease Characteristics and Prior Treatment for SHH4476g Subjects by Cohort

Disease Characteristics	mBCC (n=33)	laBCC (n=71)	Total (n=104)
ECOG			
0	13 (39.4%)	51 (71.8%)	64 (61.5%)
1	19 (57.6%)	15 (21.1%)	34 (32.7%)
2	1 (3.0%)	5 (7.0%)	6 (5.8%)
Number of Target Lesions			
1	9 (27.3%)	48 (67.6%)	57 (54.8%)
2	4 (12.1%)	12 (16.9%)	16 (15.4%)
3	9 (27.3%)	6 (8.5%)	15 (14.4%)
3+	11 (33.3%)	5 (7.0%)	16 (15.4%)
Prior Cancer Treatment			
N	1 (3.0%)	5 (7.0%)	6 (5.8%)
Y	32 (97.0%)	66 (93.0%)	98 (94.2%)
Prior Surgery			
Y	32 (97.0%)	62 (87.3%)	94 (90.4%)
N	1 (3.0%)	9 (12.7%)	10 (9.6%)
Prior Radiation			
Y	19 (57.6%)	22 (31.0%)	41 (39.4%)
N	14 (42.4%)	49 (69.0%)	63 (60.6%)
Systemic Treatment			
Y	10 (30.3%)	8 (11.3%)	18 (17.3%)
N	23 (69.7%)	63 (88.7%)	86 (82.7%)

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

No subject with mBCC received prior radiation to a target lesion. Of the twenty two subjects with laBCC who received prior radiation, eighteen (18/22, 81.8%) received prior radiation to a target lesions. A total of 53 (53/71, 74.6%) subjects with laBCC did not receive prior radiation to a target lesion, Table 17.

Table 17: Target Lesion Prior Radiation

Prior Radiation	mBCC (n=33)	laBCC (n=71)	Total (n=104)
Yes	(0.0%)	18 (25.4%)	18 (17.3%)
No	(0.0%)	53 (74.6%)	53 (51.0%)
Radiation Contraindicated	(0.0%)	38 (53.5%)	38 (36.5%)
Radiation Inappropriate	(0.0%)	15 (21.1%)	15 (14.4%)

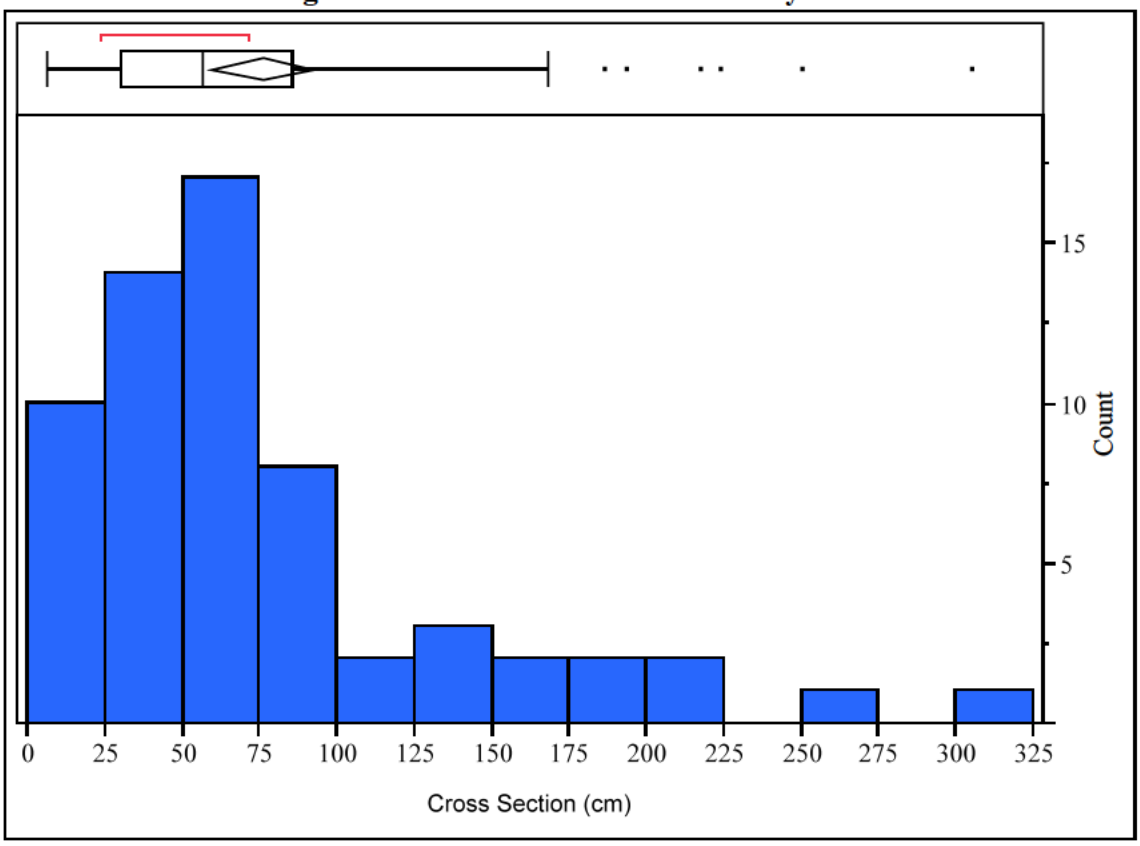
The most common reason for not receiving radiation was Gorlin syndrome (20/53, 37.7%) with another three subjects who had a history of radiation causing more lesions, genetic condition not specified, and xeroderma pigmentosum. The other reasons listed in the CRFs included concern for damage to local structures including vascular and nervous structures including the eye, extent of disease, and concern for morbidity. *Reviewer's comment: A total of 23/53 subjects had Gorlin syndrome or similar condition as a reason for not receiving radiation to their target lesions. Review of the rest of the cases indicate radiation oncology consultation for several*

Reference ID: 3068456

cases. As discussed below, the median size for these lesions was large (Figure 5) and the reasons for not radiating target lesions due to concerns over toxicity to local structures or inability to treat the entire lesions seemed appropriate to this reviewer.

Figure 5 show the distribution of baseline subject lesions for subjects the efficacy population in SHH4476g with laBCC. The baseline lesion size is the sum of the maximum externally visible tumor diameters for all lesions at screening where the maximum diameter is the sum of the maximum of the longest tumor diameters and the maximum of the perpendicular diameters as determined by digital photography.

Figure 5: Baseline Size Distribution by Size



The median lesion size was 56.6 cm (range 6.6 cm to 305 cm) and the mean was 75.8 cm. For the subjects with locally advanced BCC, a total of 28 subjects had inoperable disease and 43 had medically contraindications for surgery, 17 for recurrent BCC "unlikely to be curatively resected" and 36 for "anticipated substantial morbidity and/or deformity from surgery."

Reviewer's comment: Even though a total of 74.6% of subjects with laBCC did not receive radiation prior to enrollment in SHH4476g, the large size of the laBCC lesions indicates, in this reviewer's opinion, that the SHH4476 protocol adequately defined subjects for radiation was inappropriate.

Reference ID: 3068456

6.1.3 Subject Disposition

Table 18 contains subject disposition for SHH4476g. The majority of subjects in both cohorts were still in the study period at the time of data cut off. The most common reason for study discontinuation was subject decision to withdraw, followed by disease progression and adverse event, see Section 7.3.3.

Table 18: Subject Disposition SHH4476g

Disposition	mBCC (n=33)	laBCC (n=71)	Total (n=104)
Subjects still in study period	19 (57.6%)	36 (50.7%)	55 (52.9%)
Subjects discontinued the study period	14 (42.4%)	35 (49.3%)	49 (47.1%)
Study discontinuation reason	14 (42.4%)	35 (49.3%)	49 (47.1%)
Adverse event	1 (3.0%)	9 (12.7%)	10(9.6%)
Death	1 (3.0%)	2 (2.8%)	3 (2.9%)
Lost to follow-up	2 (6.1%)	1 (1.4%)	3 (2.9%)
Physician decision to withdraw subject from study	2 (6.1%)	1 (1.4%)	3 (2.9%)
Subject decision to withdraw	2 (6.1%)	13 (18.3%)	15 (14.4%)
Disease progression	6 (18.2%)	8 (11.3%)	14 (13.5%)
Other	0 (0.0%)	1 (1.4%)	1 (1.1%)
Subjects entered survival follow-up	11 (33.3%)	22 (31.0%)	33 (31.7%)

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

A total of 15/104 (14%) subjects in SHH4476g had protocol violations. All subject had IRF baseline tumor assessments, a total of 15 subjects missed at least one post-baseline IRF time point response assessment, Table 19.

Table 19: Protocol Violations

Violation	Subject*	Cohort
More than 3 months between two IRF time-point responses	20505	LA
	20507	LA
	20522	LA
	20762	LA
	20920	LA
	20960	LA
Last IRF time-point response more than 3 months prior to study completion date for patients who discontinued the study	20540	LA
	20560	LA
	20562[a]	LA
	20506	LA
	20901	LA
Missing IRF time-point response	20561	LA
	20682	LA
	20845	M
First IRF time-point response more than 3 months after first dose More than 3 months between two IRF time-point responses	20603	LA

[a] Subject not included in efficacy-evaluable population.

Reference ID: 3068456

Abbreviations: LA = locally advanced; M = metastatic

Reviewer's comment: These protocol violations would not be expected to affect the primary endpoint of response rate, and have a small effect on the median duration of response for subjects with laBCC, see Section 6.1.5.2.

6.1.4 Analysis of Primary Endpoint(s)

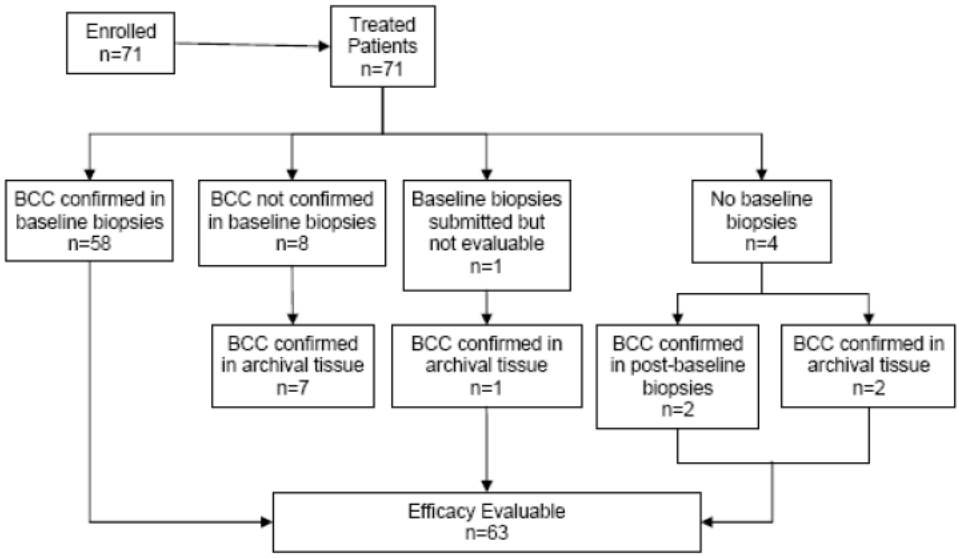
Efficacy analyses presented in the following Section were performed by the Biometrics Division, Biologics and Therapeutics Statistical Staff, Dr Jiang. Refer to the statistical review for the statistical reviewer's conclusions.

The primary endpoint for SHH4476g was IRF ORR in two pre-specified cohorts, subjects with laBCC and subjects with mBCC. The protocol specified that modified RECIST was the basis for ORR in subjects with mBCC, see Section 5.3.1.6.1, and a composite of tumor size, ulceration, and photographs made up ORR for subjects with laBCC, see Section 5.3.1.6.2.

All subjects had to have central pathologic review of archival or baseline tissue to confirm their diagnosis of BCC. All thirty three subject with metastatic BCC met this criteria. Not all subjects with locally advanced BCC had tissue available for central pathology review, Figure 6, and the efficacy population consisted of 61 subjects out of the 73 subjects who received vismodegib. *Reviewer's comment: FDA agreed to a primary analysis of ORR based on the efficacy population with central pathologic review confirming BCC, see Section 2.5 discussion of SPA.*

Reference ID: 3068456

Figure 6: Subjects with Locally Advanced BCC Not Included in Efficacy-Evaluable Population (*copied from submission*)



BCC=basal cell carcinoma.
Note: For Patient 20600, screening tissue was submitted, but there was insufficient accompanying information to identify the tissue. After the tissue sample was returned to the site, the patient's tissue sample was lost. This patient's baseline biopsy is therefore shown as "submitted but not evaluable" in the diagram above.
Source: Table 10.1/5.

The protocol defined an objective response as a CR or PR determined on two consecutive assessments ≥ 4 weeks apart, using RECIST for mBCC subjects and a composite endpoint for laBCC subjects. The protocol definition of ORR was the proportion of responding subjects within each cohort.

Table 20 contains the primary endpoint efficacy analysis for SHH4476g. A total of 10/33 (30.3%) subjects with mBCC met criteria for objective response, all partial responses (PR). A total of 27/63 (42.9%) subject with laBCC met criteria for objective response; thirteen had CR and fourteen had PR.

Table 20: 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;

Table 21 contains the FDA analysis of all enrolled subjects for the primary endpoint for SHH4476g.

Table 21: FDA ORR Analysis (IRF) (All Enrolled Subjects)

FDA ORR	mBCC (n=33)	laBCC (n=71)
Confirmed ORR, n (%) [95%CI]	10(30.3) [15.6, 48.7]	27 (38.0) [26.8, 50.3]
Complete response	0 (0.0)	13 (18.3%)
Partial response	10 (30.3%)	14 (19.7%)
Median Response Duration (mon) [95%CI]	7.62 [5.62, NE [a]]	7.62 [5.65, 9.65]

[a] Cannot be estimated due to small number of events
Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; mon = months; NE = not estimable

An analysis of IRF ORR, by the statistic reviewer confirmed the above results, Table 21, (analysis performed by the statistical reviewer for this application, Xiaoping Jiang, PhD)

Reviewer's comment: This reviewer agrees with the applicant's assessment of ORR based on IRF assessment and reviewed the individual responses for the 10 subjects with mBCC and the 27 subjects with laBCC who had responses. The FDA analysis of the primary endpoint is the same as the IRF analysis, but this reviewer did not individually review all 104 subject responses due to accepting the IRF response assessment for the 10 subjects with mBCC and 27 subjects with confirmed IRF response after reviewing datasets, photographs, CRFs, and vignettes. See Sections 6.1.5 through 6.1.10 for discussion of supportive analyses of the primary endpoint.

Table 22 contains this reviewer's evaluation and comments on the IRF and INV assessment of response for subjects with laBCC, sorted by agreement between IRF and INV. *Reviewer's comment: This reviewer did not review response assessment where the IRF and INV agreed the response was SD, PD, or UE or subjects whose baseline biopsy did not confirm BCC (20562, 20523, 20500, 21080, 20923, 20781, 20564, 20844).*

Table 22: FDA Review of IRF and INV Assessed Response of laBCC Subjects

Subject	IRF	INV	Notes
Agreement between IRF and INV			
20521	CR	CR	The investigator selected a lesion on the scalp. The Week 24 biopsy did not show BCC.
20544	CR	CR	The investigator selected three baseline target lesions on the central vertex, scalp; distal lateral, back; and distal paramedian, right back. The sampling biopsies at Week 20 did not show evidence of residual basal cell carcinoma.
20581	CR	CR	The investigator selected a single baseline target lesion on the right frontal scalp. The sampling biopsy at Week 16 did not show evidence of residual basal cell carcinoma.
20604	CR	CR	The investigator selected two baseline target lesions on the left ear, postauricular, and the mid scalp, center. The sampling biopsies performed at Week 16 did not show evidence of residual basal cell carcinoma.

Reference ID: 3068456

Subject	IRF	INV	Notes
20842	CR	CR	The investigator selected a single baseline target lesion on the right lower eyelid medial canthus. The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma.
20848	CR	CR	The investigator selected a baseline target lesion on the cheek (left malar). The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma.
20920	CR	CR	The investigator selected a single baseline target lesion on the forehead. The sampling biopsies at Week 16 and Week 24 did not show evidence of residual basal cell carcinoma.
20961	CR	CR	The investigator selected a single baseline target lesion on the nose. The sampling biopsy performed at Week 16, did not show evidence of residual basal cell carcinoma.
21140	CR	CR	The investigator selected a single baseline target lesion on the right upper parietal area of the scalp. The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma.
20502	PR	PR	The investigator selected a lesions on the right medial canthus of the nose: The sampling biopsy at Week 24 did not show evidence of basal cell carcinoma.
20522	PR	PR	The investigator selected a lesion on the scalp. The biopsy at Week 24 did not show BCC. The subject had progressive disease at EOT with new lesion on neck.
20546	PR	PR	The investigator selected three baseline target lesions on the forehead, preauricular area and the back, The biopsies at Week 8 did not indicate presence of basal cell carcinoma in the preauricular lesion; biopsies of the forehead and back lesions did show evidence for basal cell carcinoma. The sampling biopsies at Week 24 showed evidence of residual basal cell carcinoma in all target lesions.
20641	PR	PR	The investigator selected two baseline target lesions on the posterior neck and anterior nose (tip). The sampling biopsy of the scalp/crown lesion at Week 24 showed evidence of residual basal cell carcinoma; however, sampling biopsies of the preauricular area, nose, temple and neck lesions did not show evidence of basal cell carcinoma.
20840	PR	PR	The investigator selected five baseline target lesions in the following locations: arm (left brachium erythematous plaque), left medial canthus, left forehead (left temple extending to root of helix on left ear), right lateral neck, and right forehead (lateral eyebrow extending to orbital rim to temple). The sampling biopsies at Week 24 did not show evidence of residual basal cell carcinoma in four of the five target lesions; histology of the arm lesion was consistent with basal cell carcinoma.
20901	PR	PR	The investigator selected a single baseline target lesion described as "capillitium frontal" on the forehead. The sampling biopsy at Week 24 showed evidence of residual basal cell carcinoma.
20960	PR	PR	The investigator selected a single baseline target lesion, "ulcerated plaque on mid-upper back." The sampling biopsy at Week 24 showed evidence of residual basal cell carcinoma.
Disagreement but counted as Responders			
20841	CR	PD	The investigator selected a single baseline target lesion "scalp wound extending from the left auricle past midline and forward to the left eyebrow." The sampling

Reference ID: 3068456

Subject	IRF	INV	Notes
			biopsy at Week 24 did not show evidence of residual basal cell carcinoma. The investigator response at Week 16 was PD but at Week 24 was CR.
20847	CR	PR	The investigator selected two baseline target lesions on the left ear antihelix and the right nasal tip,. The sampling biopsies at Week 24 did not show evidence of residual basal cell carcinoma. The investigator's response at Week 32 was CR and PD at EOT.
20849	CR	SD	The investigator selected a baseline target lesion on the left external ear "involving parotid [and] contiguous with left mastoid tip and stylomastoid foramen." The sampling biopsies at Week 24 did not show evidence of basal cell carcinoma. The investigator's response at Week 16 was PD, Week 24 CR, Week 32 PD.
20940	CR	SD	The investigator selected a single baseline target lesion, "head." The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma. The investigator's response through the study was SD.
20507	PR	SD	The investigator selected a single baseline target lesion "left cheek, tumor with ulceration." The sampling biopsy at Week 24 did not show evidence of basal cell carcinoma. The investigator's response at Week 8 was PR, Week 16 PD, Week 24 PD, Week 32 UE, and Week 40 PD.
20520	PR	CR	The investigator selected a single baseline target lesion on the "lateral aspect of the left groin just lateral to scrotal sac." The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma. The investigator's response at week 8 was PR, Week 16 PR, Week 24 CR, Week 32, Week 40 CR, Week 48 PD, Week 56 PD, and End of Treatment PD.
20541	PR	SD	The investigator selected five baseline target lesions on the left arm, left anterior and posterior shoulder, mid back and right shoulder. The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma in four lesions; one lesion did show evidence of basal cell carcinoma. At Week 24 assessments the IVF assessment was PD whereas the IRF assessment was PR.
20584	PR	CR	The investigator selected a single baseline target lesion, the left naris. The biopsy at Day 69 was consistent with basal cell carcinoma, and the sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma. Subject had large defect on left naris at end of treatment.
20721	PR	UE	The investigator selected a single baseline target lesion in the right masticator space (neck). The sampling biopsies at Week 24 did not show evidence of residual basal cell carcinoma. The investigator was unable to evaluate response.
20821	PR	SD	The investigator selected two baseline target lesions, "scalp" and "forehead." The sampling biopsy of the forehead lesion at Week 24 did not show evidence of residual basal cell carcinoma; the scalp target lesion was not biopsied. The investigator response at Week 8 was SD, Week 16 - PR, and Week 24 – PD, Week 32 - PD, and Week 40 - PR.
21120	PR	CR	The investigator selected a single baseline target lesion on the scalp (erythematous ulcerated plaque). The sampling biopsy at Week 24 did not show evidence of residual basal cell carcinoma. The IRF and INV assessments at Week 24 were CR, but at Week 32 the INV assessment was CR and the IRF assessment was PD.

Abbreviations: CR = complete response; EOT = end of treatment; IRF = independent review facility; INV = investigator; PD = progressive disease; PR = partial response; SD = stable disease

Reference ID: 3068456

Reviewer's comment: This reviewer agrees with the above assessments for subjects with locally advanced BCC and recommends using the IRF assessment for determining response. No subject above with CR had previously inoperable target lesions rendered operable with clear margins obtained at the time of surgery, which the protocol considered to be a CR, but FDA did not agree with, see Sections 2.5 and 5.3.1.6.2.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 ORR by Investigator

Table 23 shows ORR by investigator, which had higher response rates, 45.5% and 60.3% for subjects with mBCC and laBCC, respectively, than the IRF ORR results.

Table 23: ORR Results (INV) in Efficacy-Evaluable Subjects

	mBCC (n=33)	laBCC (n=63)
Confirmed ORR, n (%) [95%CI]	15 (45.5%) [28.1 , 62.2]	38 (60.3%) [47.2 , 71.7]
Complete response	0 (0.0%)	20 (31.7%)
Partial response	15 (45.5%)	18 (28.6%)
Median Response Duration (mon) [95%CI]	12.9 [5.56, 12.9]	7.6 [7.43, NE [a]]

[a] Cannot be estimated due to small number of events
Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; NE = not estimable

An analysis of INV ORR, by the statistic reviewer confirmed the above results, Table 23, (analysis performed by the statistical reviewer for this application, Xiaoping Jiang, PhD)

Table 24 shows the concordance between IRF and INV assessment of ORR. The concordance rate between IRF and INV assessment of ORR was 79% for subjects with metastatic disease and 60% for subjects with laBCC.

Table 24: Concordance of ORR by IRF and INV
(copied from submission with minor modifications)

IRF ORR	INV ORR	
	Responder	Non-Responder
mBCC Subjects (n=33)		
Responder	9 (27.3%)	1 (3.0%)
Non-responder	6 (18.2%)	17 (51.5%)
laBCC Subjects (n=63)		
Responder	20 (31.7%)	7 (11.1%)
Non-responder	18 (28.6%)	18 (28.6%)

Reference ID: 3068456

Abbreviations: IRF = independent review facility; IRV = investigator; laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; ORR = overall response rate

The applicant claimed the main reason for discrepancy between IRF and INV assessment of ORR in subjects with laBCC was attributable to the INV assessing response and the IRF not assessing response. *Reviewer's comment: This reviewer reviewed the cases where the INV assessed a response and the INF assessed no response and agrees with the applicant's assessment for the discrepancy.*

6.1.5.2 Duration of response by IRF

Table 25 contains the duration of response by IRF. The median duration of response for both subjects with mBCC and laBCC was 7.6 months.

Table 25: 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

An analysis of DOR, by the statistic reviewer confirmed the above results, Table 25 (analysis performed by the statistical reviewer for this application, Xiaoping Jiang, PhD)

Reviewer's comment: In this reviewer's opinion, a duration of response of over 7 months combined with 14/27 responses in subjects with laBCC achieving CR demonstrate that ORR in this trial represents clinical benefit for subjects with advanced or inoperable BCC.

A total of 5 subjects, all with laBCC, who had IRF confirmed responses had protocol violations related to TPR assessment, 20507, 20522, 20901, 20920, and 20960. The only subject to have documented progression after a response assessment is Subject 20522 who had PR on July 7, 2009 and progressed on March 2, 2010, based on a new lesion. The duration of response in the CSR is 232 days, but the last confirmed response was November 3, 2009, more than three months prior to the assessment of progressive disease on March 2, 2010. The duration of response for Subject 20522 was between 112 and 232 days. Sensitivity analysis (performed by the statistical reviewer for this application, Xiaoping Jiang, PhD) using a duration of response of

Reference ID: 3068456

112 days for Subject 20522 decreased the median DOR for subjects with laBCC to 7.49 months (95%CI 5.59, 9.66).

Reviewer's comment: The sensitivity analysis including Subject 20522's shorter duration of response did not substantially alter the median duration of response for subjects with laBCC.

6.1.5.3 Progression Free Survival (PFS)

Table 26 contains the PFS analysis for SHH4476g, which was 9.5 months for subjects with mBCC and subjects with laBCC.

Table 26: Progression Free Survival

PFS	mBCC (n=33)	laBCC (n=71)
Number of events	15	33
Median PFS (mon) [95%CI]	9.5 [7.36, NE [a]]	9.5 [7.40, 11.90]

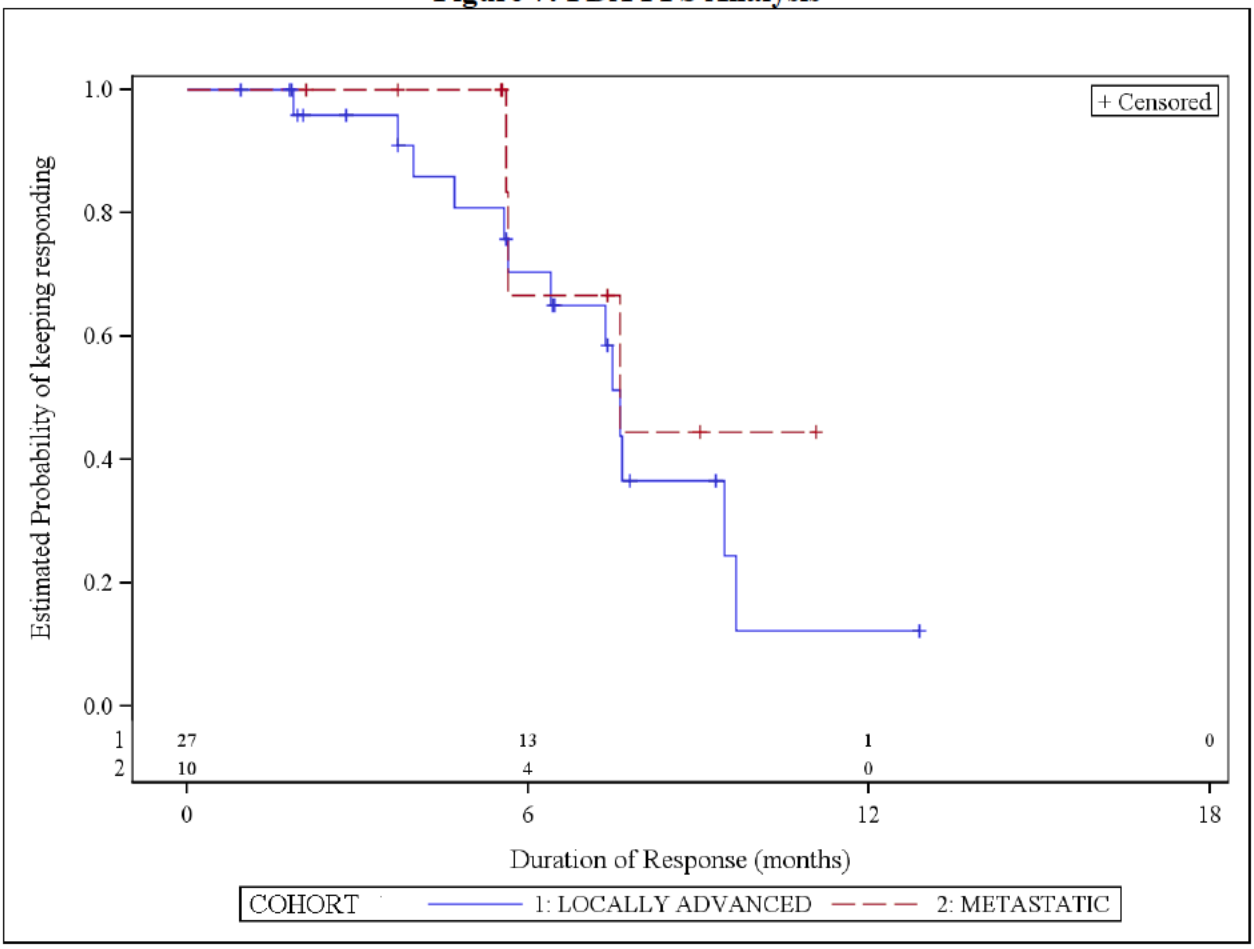
[a] Cannot be estimated due to small number of events
Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; Mon = months; NE = not estimable; PFS = progression free survival

An analysis of PFS, by the statistic reviewer confirmed results, Table 26 and Figure 7, (analysis performed by the statistical reviewer for this application, Xiaoping Jiang, PhD)

Figure 7 contains the FDA PFS analysis Kaplan Meier (KM) curve for subjects with mBCC and laBCC.

Reference ID: 3068456

Figure 7: FDA PFS Analysis



Reviewer's comment: Analysis of PFS in a two cohort trial without an internal control is difficult to interpret. The lack of internal control does not allow estimation on the magnitude of PFS effect and this reviewer considers the PFS estimate supportive or exploratory only.

6.1.5.5 Overall Survival (OS)

Table 27 contains the OS analysis for SHH4476g, which was not estimable, due to the small number of events.

Table 27: Overall Survival Analysis

OS	mBCC (n=33)	laBCC (n=71)
Number of events	7	9
Median PFS (mon) [95%CI]	NE [a] [13.86, NE [a]]	NE [a] [17.6, NE [a]]

[a] Cannot be estimated due to small number of events
Abbreviations: laBCC = locally advanced Basal Cell carcinoma; mBCC = metastatic Basal Cell Carcinoma; Mon = months; NE = not estimable; OS = overall survival;

An analysis of OS, by the statistic reviewer confirmed the above results, Table 27, (analysis performed by the statistical reviewer for this application, Xiaoping Jiang, PhD)

Reviewer's comment: Analysis of OS in a two cohort trial without an internal control is difficult to interpret. The lack of internal control does not allow estimation on the magnitude of OS effect and this reviewer considers the OS estimate supportive or exploratory only.

6.1.5.6 Patient Reported Outcomes

The applicant submitted patient reported outcome (PRO) data using the SF-36 in the efficacy-evaluable population. The SF-36 is a health survey consisting of eight subscales: Physical Functioning, Role−Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role−Emotional, and Mental Health. The applicant also derived two summary scores from the eight subscales: mental component survey (MCS) and physical component survey (PCS). The score range is 0 to 100 with higher scores relating to higher or better quality of life. Measurements occurred on Day 1, at Week 12, Week 24, and at the end of trial or early termination visit. A total of 95 of the 96 (99%) subjects completed at least one question of the SF-36 at baseline, but only 20 subjects (20.8%) completed responses at the end of study. Comparing changes from baseline to Week 24, the mean increase in MCS scores was 2.3 points (95% CI: 0.05, 4.53) and a mean decrease in PCS scores was 1.9 points (95% CI: − 3.75, − 0.05).

Reviewer's comment: The lack of internal control and amount of missing data make the SF-36 PRO data difficult to interpret. The applicant did not include this data in the USPI which is appropriate.

6.1.5.7 Histopathologic response

The applicant assessed the effect of vismodegib in tumor biopsies obtained at baseline and following vismodegib administration in subjects with laBCC. Only 59 of the 63 subjects with laBCC had a baseline biopsy available for analysis and only 51 subjects had a post baseline biopsy assessment by an independent pathologist. A total of 34 subjects had a post baseline biopsy that did not show presence of BCC, which is numerically higher than the 27 subjects who had a response, 14 of which had CRs. Table 28 contains the results for the histopathologic response analysis.

Table 28: Histopathology Effect in Tissue Biopsy (Target Lesions Only): Efficacy-Evaluable Subjects (*copied from submission with minor modifications*)

	laBCC n= 63
Baseline biopsy available	59 (93.7%)
Pathology confirmed BCC in baseline biopsy	58 (92.1%)
Post-baseline biopsy available [a]	51 (81.0%)
Post-baseline biopsy assessed by independent pathologist	51 (81.0%)
Absence of residual BCC [b]	34 (54.0%)

Reference ID: 3068456

	laBCC n= 63
Prior to Week 24	6 (9.5%)
At Week 24 [c]	27 (42.9%)
After Week 24	1 (1.6%)
Post-baseline biopsy not available	7 (11.1%)

Note: Post-baseline biopsies were taken from target lesions only.
[a] Patients with more than one post-baseline biopsy were included only once.
[b] As assessed by independent pathology review. For patients with a biopsy of a target lesion(s) obtained at more than one timepoint, those with at least one timepoint showing absence of residual BCC were included; if more than one sample at a given timepoint was free of residual BCC, the earliest timepoint was used. For patients with more than one target lesion, biopsies from all target lesions had to be free of residual BCC.
[c] At Week 24 = 24 × 7 days from first drug intake ± 7 days time window (prior to Week 24 and after Week 24 defined accordingly).
Abbreviations: laBCC = locally advanced basal cell carcinoma.

Reviewer's comment: Missing data, a lack of control for sampling errors, sampling of only target lesions, and lack of internal control limits the interpretation of the histopathologic response analysis and should not be contained in the USPI. Furthermore, the trial measured ORR in subjects with laBCC on measures of size, ulceration, and histopathology. These results should be considered exploratory only.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Table 29 shows the ORR results for subjects with mBCC and laBCC by age, gender, and region. The responses were generally comparable for gender within each cohorts. Subjects who were ≤ 65 years of age and subjects from the United States had numerically higher ORRs than subjects who were > 65 years of age or from Non-US sites.

Table 29: Demographic Subgroup ORR Results (IRF)

Demographic Subgroup ORR	mBCC n=33(%[a])	laBCC n=71(%[a])
Age (yr)		
<=65	6/19 (31.6)	19/33 (57.8)
>65	4/14 (28.6)	8/30 (26.7)
Gender		
Male	7/24 (29.2)	15/35 (42.9)
Female	3/9 (33.3)	12/28 (42.9)
Region		
Non-United States	1/7 (14.3)	7/21 (33.3)
United States	9/26 (34.6)	20/42 (47.6)

[a] Responders/total Subjects n (%)

Abbreviations: laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; ORR = overall response rate

Table 30 contains ORR by ECOG PS and number of baseline lesions. Subjects in the ECOG subgroups with mBCC had similar response rates, but the subjects with ECOG PS of 0 with laBCC had a numerically higher response rate (31.4% versus 42.6%) compared to those with ECOG PS of 1 or 2. For both subjects with mBCC the ORR was higher for those with 3 or > 3 lesions. For subjects with laBCC the ORR was highest for those with > 3 lesions.

Table 30: Baseline Characteristic Subgroup ORR Results

Baseline Characteristic Subgroup ORR	mBCC n=33(%[a])	laBCC n=71(%[a])
ECOG performance status		
0	4/13 (30.8)	26/61 (42.6)
1 or 2	6/20 (30.0)	11/35 (31.4)
Number of target lesions at Baseline		
1	0/9 (0.0)	17/40 (42.5)
2	0/4 (0.0)	5/12 (41.7)
3	5/9 (55.6)	2/6 (33.3)
>3	5/11 (45.5)	3/5 (60.0)

[a] Responders/total Subjects, n (%)

Reviewer's comment: Due to small numbers, lack of internal control, and no stratification, these subgroup analyses should be considered exploratory and interpreted with caution.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

None

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.5.2

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

SHH4476g was the only trial to evaluate vismodegib at the dose and schedule for which the applicant is seeking approval. The safety data, however, comes from a pooled database of 138 subjects from SHH4467g, SHH3925g, and SHH4610g who all had advanced BCC and received vismodegib. The clinical pharmacology studies did not reveal an exposure-response relationship for tumor response, type of clinical responder, or for the adverse events of weight loss, alopecia,

Reference ID: 3068456

dysgeusia, fatigue, muscle spasms, or nausea, which allowed for pooling of the safety information.

The most common adverse reactions in subjects receiving vismodegib (≥ 10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, cough, arthralgias, vomiting, headache, ageusia, insomnia, and upper respiratory tract infection. The most common serious adverse reactions (≥ 1%) in subjects receiving vismodegib were death (2.2%), pneumonia (2.2 %), cardiac failure (1.4%), gastrointestinal hemorrhage (1.4%), pulmonary embolism (1.4%), deep vein thrombosis (1.4%), and hemorrhage (1.4%).

A total of 17/138 (12.3%) subjects died in trials SHH4476g and SHH3925g; the single subject in trial SHH4610g included the pooled safety population did not die. A total of 7/138 (5.1%) subjects died within 30 days of last vismodegib use and 8/138 (5.8%) deaths were due to an adverse event. The most common cause of fatal events after receiving vismodegib were disease progression and infections.

Vismodegib is a Hh pathway inhibitor and is expected to be teratogenic in developing human fetuses based on its mechanism of action and observations in preclinical toxicology studies. The applicant initially proposed a (b) (4) to address this risk, but revised their proposal to consist of a Dear Health Care Provider letter and Brochure, a pharmacovigilance plan, and a medication guide, after discussions with review team.

Due to the lack of an internal control, labeling of safety information can only be done descriptively. This lack of an internal control resulted in uncertainty regarding the attribution of adverse events to vismodegib.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 6 in Section 5 of this review contains a listing of all trials the applicant submitted to the NDA containing safety data. The applicant pooled trials SHH4476, SHH3925g and SHH4610g for a pooled safety population of 138 subjects, Figure 8. All subjects received at least one dose of vismodegib. SHH4489g is a placebo controlled trial in subjects with advanced ovarian cancer that provided additional comparisons of adverse event rates. SHH4476g and SHH4610g subjects received vismodegib at the same dose and schedule for which the applicant is seeking approval. SHH3925g contained subjects with BCC who received different doses, Table 14. Data from a total of 104 safety subjects from trial SHH4476g were available for analysis at the time of the original NDA submission. Trial SHH4476g was the only study to evaluate vismodegib at the doses and schedule for which the applicant is seeking approval.

Reference ID: 3068456

7.1.2 Categorization of Adverse Events

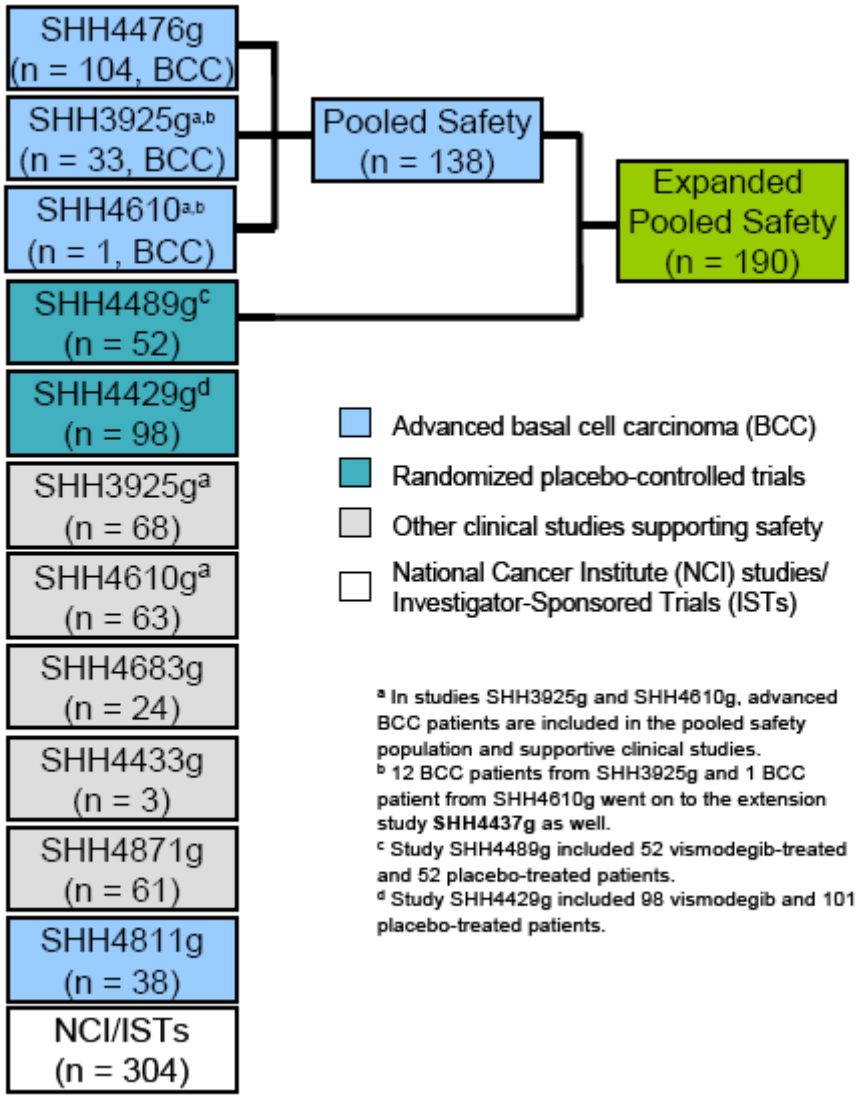
The applicant used version 13.1 of the MedDRA coding dictionary to code the adverse event data. The ISS ADAE dataset contained 2,263 individual adverse event listings. A total of 473 verbatim terms described all 2,263 of the adverse events. This reviewer reviewed the verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded. In general, coding was acceptable. The protocols used NCI CTCAE version 3.0 for toxicity grading.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This reviewer analyzed trials SHH4476g, SHH3925g, SHH4610g, SHH4437g and SHH4489g both individually and in pooled analysis. The applicant provided several trials for the safety analysis and pooled trials SHH4476g, SHH3925g, and SHH4610g for the primary safety population and added 52 subjects from trial SHH4489g who received placebo for an expanded pooled safety population, Figure 8. The ISS ADAE dataset contained safety information the 13 subjects who continued from SHH4476g or SHH3925g on to SHH4437g, an extension trial.

Reference ID: 3068456

Figure 8: Pooled Safety Populations from Trials Contributing to the Summary of Clinical Safety (*copied from submission*)



The dosing of vismodegib in trial SHH3925g was either 150 mg, 270 mg, or 540 mg. The dosing for the single subject in SHH4610g was 150 mg daily except for days 2 and 3. This reviewer did not separate out the individuals who received vismodegib at doses or schedules other than 150 mg daily because the clinical pharmacology studies did not reveal an exposure-response relationship for tumor response, type of clinical responder, or for the adverse events of weight loss, alopecia, dysgeusia, fatigue, muscle spasms, or nausea. Section 7 contains pooled safety analysis based on the "Pooled Safety" and contains safety comparison information from SHH4489g and SHH4429g.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For this NDA, the applicant submitted data from three trials that involved the target population, advanced BCC. SHH4610g, SHH4476g and SHH3925g enrolled subject 18 years of age or older with a performance status of ≤ 2 . Both trials excluded subjects with positive pregnancy tests and mandated women use two forms of contraception. Neither trial contained specific exclusion criteria for medical diseases.

Assessment of Size of Premarketing Safety Database
The size of the population with advanced BCC who still have disease after local therapy such as radiation or surgery influences the assessment of the pre-marketing safety database. Cancer registries do not require reporting BCC which makes estimations of the true number of patients difficult, see Section 2. The applicant submitted information on 138 subjects with advanced BCC who received vismodegib. The applicant also included safety information from several other completed and ongoing trials with vismodegib in subjects with different tumor types.

Reviewer's comment: FDA agreed that the applicant's pooled safety population from trials SHH4476g, SHH3925g, SHH4437g, and SHH4610g (n=138) with advanced BCC subjects with other supporting safety data coming from trials SHH4429g, SHH4489g, SHH 3925g, SHH4318g, SHH4610g, SHH4683g, SHH4433g, SHH4871g, SHH4811g was acceptable, see Section 2.5. The small size of the pooled safety database, however, limits the evaluation of adverse events that only occurred once or at a low frequency. Other therapies for cancers affecting the skin had similar sized safety populations (Bexarotene – 58 subjects; Vorinostat – 107 subjects; Romidepsin -185 subjects; Denileukin Diftitox – 234 subjects) based on review of FDA medical officer reviews.

Table 31 summarizes vismodegib exposure for SHH33925g, SHH4476g, and SHH4610g by individual cohorts. Mean duration of exposure was 316 days (SD=186.5). The median cumulative dose was 44 grams with a median of 52.7 grams (range 3-276). The single subject in trial SHH4610g had lower exposure but was within the range of doses seen in trials SHH3925g and SHH4476g.

Table 31: Exposure Summary by Trial

Exposure Summary by Trial	SHH3925	SHH4476		SHH4610	Total
	n=33	laBCC n= 71	mBCC n= 33	n=1	n=138
Doses of Vismodegib (mean)	326.9	281.3	284.5	135	316.1
Range of Vismodegib (days)	36-810[a]	33-561	31-492	137	19-1026
Median Cumulative dose (gm)	52.92	42.2	42.7	20.55	44
Range (gm)	5-204	3.8-84.6	2.9-75		3-276

[a] Subject 13104 went on to SHH4437 extension trial and had 1026 doses of vismodegib
Abbreviations: Gm = grams; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma

Reviewer's comment: The exposure in SHH3925g was higher than SHH4476, due mainly to 12 subjects from SHH3925g who went on to receive further vismodegib in SHH4437. The total

Reference ID: 3068456

number of doses, range and median cumulative dose for subjects with laBCC and mBCC were similar. This reviewer did not analyze adverse events by trial as the population demographics and exposure summary were similar across trials.

7.2.2 Explorations for Dose Response

Figure 9, Figure 10, and Figure 11 show the range of the number of doses of vismodegib received for SHH3925g and SHH4476g, as well as SHH4437 an extension trial. The median number of doses was similar between SHH4476g and SHH3925g, Table 31.

Figure 9: Dose Range of Vismodegib SHH4476g

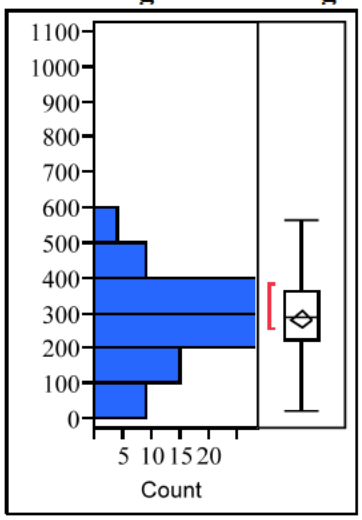


Figure 10: Dose Range of Vismodegib SHH 3925g

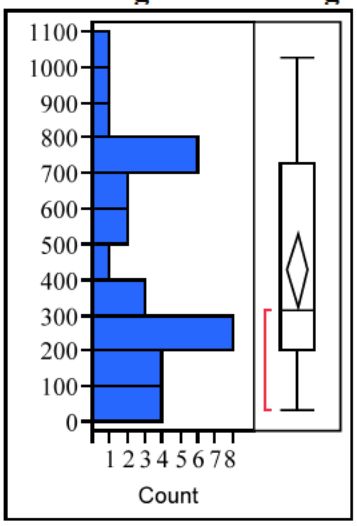
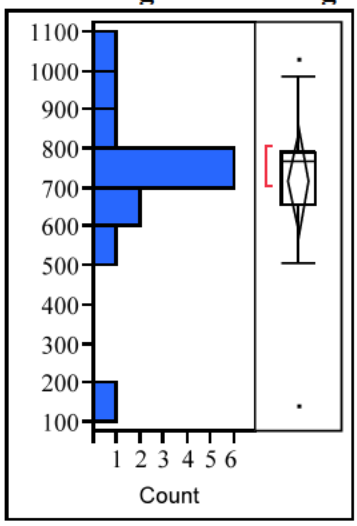


Figure 11: Dose Range of Vismodegib SHH4437g



There was no exposure-response relationship, see Section 4.4.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Overall, routine clinical and laboratory evaluations were adequate to assess the safety of vismodegib in trials SHH4476g, SHH3925g, and SHH4610g. Refer to Section 5.3 for a description of the laboratory schedule of assessments and Section 7.4.2 for details of chemistry, hematology, and other monitoring and Section 7.4.4 for ECG testing.

Reference ID: 3068456

7.2.5 Metabolic, Clearance, and Interaction Workup

None. See Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no currently marketed drugs for a similar drug class. Drugs that are currently approved that may also inhibit Hh pathways include vitamin D (Bijlsma 2006), itraconazole (Kim 2010), and HMG-CoA reductase inhibitors (i.e. statins) (Tang 2007). The common adverse event profile of these drugs are different than the observed adverse events in this application. These published reports are of preclinical data, making any comparisons between vismodegib and these drugs difficult.

7.3 Major Safety Results

7.3.1 Deaths

A total of 17/138 (12.3%) subjects died in trials SHH4476g and SHH3925g; the single subject in trial SHH4610g included the pooled safety population did not die, Table 32. This reviewer analyzed fatal adverse events by MedDRA preferred term (PT) for each trial and for the pooled safety population as well as CRFs, narratives, and the applicant provided vignettes.

Table 32: All Deaths from Pooled Safety Population

Deaths from Pooled Safety Population	SHH3925 n=33	SHH4437 n=13	SHH4476 n=104	SHH4610 n=1	Total n=138 (%)
All deaths	1	0	16	0	17 (12.3)
<=30 days from last study drug administration	1	0	6	0	7 (5.1)
> 30 days from last study drug administration	0	0	10	0	10 (7.2)
Cause of Death Adverse Event	1	0	7	0	8 (5.8)
Progressive Disease	0	0	7	0	7 (5.1)
Other	0	0	2	0	2

FDA Review of Deaths:
In SHH4476g, a total of 16 subjects died. In SHH3925g a single subject died at the time of data cut-off. For SHH4476g, the median follow up was 10.4 months (range 0.9 - 18.6), 10.6 months (1.2 - 26.6) for SHH3925g, 25.6 months (range 5.5 - 35.8) for SHH4437g, and 2.9 months for SHH4610g. Table 33 lists subjects who died in SHH4476g and SHH3925g and lists notable AEs that occurred within 90 days of death that potentially contributed. The applicant stated at no deaths were related to vismodegib. All subjects whose numbers begin with "1" were in SHH3925g and those that begin with "2" were in SHH4476g.

Reference ID: 3068456

Table 33: FDA Review of Deaths from Pooled Safety Population

Subject	Age(yr)	Sex	Cause of Death	Notable AEs within 90 Days of Death
SHH3925g Deaths within 30 Days of Last Dose in Subjects mBCC				
12003	63	M	Disease Progression	Grade 1 pneumonia (Days 32-38) Grade 3 Pneumonia (Days 37 - Day 59); (b) (4)
SHH4476 Deaths within 30 Days of Last Dose in Subjects with laBCC				
20600	51	M	Adverse event (acute myocardial infarction)	Grade 5 acute myocardial infarction (Day 536); (b) (4) (b) (4)
21080	85	M	Adverse event (hypovolemic shock)	Grade 5 hypovolemic shock (Day 188); (b) (4) (b) (4)
20821	55	F	Adverse event (death)	Grade 3 hyperkalemia (Day 309, resolved same day) (b) (4)
20844	55	M	Adverse event (meningeal disorder)	Grade 4 viral meningitis (Days 73-84); Grade 2 right ear staph infection (Day 96- ongoing); Grade 2 leptomeningeal disease (days 113-124); (b) (4)
20940	71	F	Progressive disease	Grade 3 sinus infection (Days 280 –ongoing); Grade 3 urinary tract infection (Days 280 – ongoing); UTI (Days 280-331); (b) (4)
SHH4476 Deaths within 30 Days of Last Dose in Subjects with Metastatic Disease				
20822	53	M	Progressive disease	Grade 2 convulsions (Days 218-219) (b) (4)
SHH4476 Deaths > 30 Days from Last Dose in Subjects with Locally Advanced Disease				
20540	59	F	Adverse event (ischemic stroke)	Vismodegib end date (Day 419); Grade 3 ischemic stroke (Days 445-449); Grade 3 ischemic stroke (Days 452-453); Grade 5 ischemic stroke (Day 475) ; (b) (4)
20921	89	F	Adverse event (death unknown cause)	Vismodegib end date (Day 65); Grade 3 pneumonia (Days 67-87); Grade 3 cardiac failure (Days 67-87); Grade 3 LVEF dysfunction (Days 93-101); Grade 3 kidney insufficiency (Days 93-101); Death (Day 109)
20781	67	F	Other—unknown	None
20661	84	M	Progressive disease	None
SHH4476 Deaths > 30 Days from Last Dose in Subjects with Metastatic Disease				
20720	72	M	Adverse event (death unknown cause)	Vismodegib end date (Day 309); Grade 3 decreased performance status (Days 310 – ongoing); Grade 2 urinary tract infection (Days 310-317); (b) (4)
20501	67	F	Other—unknown	None
20601	54	M	Progressive disease	None
20640	62	F	Progressive disease	None
20740	51	F	Progressive disease	None
20900	38	M	Progressive disease	None

Abbreviations: AEs = adverse events; F = female; M = male; YR = years

The applicant stated no AE related death was related to vismodegib. This reviewer reviewed narrative summaries for the subjects in SHH3925 and SHH4476g who died, as well as SAE

Reference ID: 3068456

listings, and notable AEs that occurred within 90 days of the subjects' deaths to determine whether other AEs may have contributed to the cause of death. Subjects 12003 and 20940 died of disease progression and had AEs within 30 days of death that might of contributed to their death. Subject 20822 had metastatic disease involving his left frontal and temporal lobes making disease progression a more probable cause of death than Grade 2 convulsions. Subjects 20781 and 20501 died of unknown causes greater than 30 days from the last dose of vismodegib and had no recent AEs that might of contributed to their deaths.

Death Narratives: (*copied from submission with minor modifications*)

SHH3925g Deaths within 30 Days of Last Dose in Subjects mBCC
Subject 12003 was a 63 year old male with metastatic BCC to his skin, lung and abdomen at screening died on (b) (4) after stopping vismodegib on (b) (4) He was assigned to the Dose Escalation Stage 1 cohort, 540 mg on a once daily schedule.

The subject was diagnosed with basal cell cancer in 1984. Prior surgical therapy included right post-auricular scalp surgery, right occipital region excision, left lower lobe pulmonary nodule (unspecified procedure), resection in right temporal region, and resection of preauricular region. His prior radiation sites included head and neck, scalp, and "scalp skull." Prior systemic therapy included the following agents: pemetrexed, carboplatin, gemcitabine, erlotinib, paclitaxel, and docetaxel. Sites of metastasis at the time of enrollment included skin. The subject's medical history included broken leg, arm, and wrist as a child, and chemotherapy-related low blood counts. His surgical history included an open-heart double bypass, appendectomy, and eye operation. The subject's concurrent conditions included anorexia, coronary artery disease, hypercholesterolemia, foul odor, hypertension, non-productive cough, surgical nerve damage, acid reflux, decreased right hearing, facial drooping, and Grade 2 lymphopenia. Concomitant medications at baseline included atorvastatin calcium, cetirizine hydrochloride, gabapentin, hydrochlorothiazide, lansoprazole, metoprolol tartrate, naproxen sodium, and potassium chloride.

At baseline, the subject's ECOG status was 1.

The subject received a single dose of study drug on (b) (4) and daily dosing started on (b) (4). On (b) (4) (b) (4) the subject experienced serious Grade 3 pneumonia and was hospitalized on (b) (4) for the event. That day, a CT scan showed ground glass opacity in the right upper lobe and increasing bilateral pleural effusions, and "was too large with large loculation and peripheral enhancing pleural nodularity." The scan showed an increase in some of his target lesions, with the right lower lobe lesion increasing 4.2 × 4.2 cm (increased from 3.6 × 3.18 cm) and left lower lobe mass, 1.6 × 2.4 cm (previously 1.5 × 2.2 cm). It was noted that "while these lesions were suggestive of progression, he had definitive progression with evidence of bilateral adrenal masses since his baseline study." It was reported that the subject's pleural effusions were tapped by thoracentesis. Pleural effusions "looked exudative" with a sample on the right showing 613 white blood cell count with 8% polymorphonuclear leukocytes and 90% monocytes in addition to 15,175 red cells. The LDH was 205 and pH was alkaline at 7.53. Further relevant laboratory tests that day

Reference ID: 3068456

included white blood cell count 9010/cumm, hemoglobin 15 g/dL, platelet count 307 K/mm^3, lymphocytes 4.1%, neutrophils 35.3%, lymphocyte count 370/cumm, and absolute neutrophil count 7950/cumm. The subject was evaluated with a chest X-ray after the first thoracentesis and removal of 1400 cm^3 of fluid. The next day, the subject underwent a diagnostic thoracentesis on the left which showed "46 white blood cell count," with 48% polymorphonuclear leukocytes, 52% monocytes, and 17,422 red blood cells with a bloody clear appearance. The LDH was elevated at 481. Cultures showed no acid-fast bacilli or gram stain bacteria. Treatment for the event included unspecified medications. The subject was discharged from the hospital on (b) (4) and the event was considered to be resolved on (b) (4) No action was taken with the study drug in response to the event.

On (b) (4) the subject presented with progression of basal cell carcinoma with skin metastases and died the same day; because of the death, the disease progression was reported as serious and Grade 5. It was not known whether an autopsy was performed. No treatment was provided for the event and action taken with study drug was not applicable. The last administration of the study drug was given on (b) (4). That day, the subject was discontinued early from the study because of radiographic disease progression. The investigator assessed the events of pneumonia and progression of basal cell carcinoma as unrelated to study treatment. In the investigator's opinion, other possible causes for both events included the subject's concurrent illness.

Reviewer's comment: The presence of underlying lung lesions at baseline and death due to disease progression with lung lesions that increased in size confounds assessment of pneumonia as possibly contributing to the subject's death.

SHH4476 Deaths within 30 Days of Last Dose in Subjects with laBCC

Subject 20600 was a 51 year old male with laBCC who died on (b) (4) due to Grade 5 acute myocardial infarction, the same day as last vismodegib administration. At the time of enrollment, surgery was medically contraindicated because of a recurrent lesion on his forehead that was unlikely to be curatively resected and because of anticipated substantial morbidity and/or deformity from surgery. Radiotherapy had been previously administered to at least one target lesion.

The subject was initially diagnosed with a basal cell carcinoma in 1982. Prior surgery included initial diagnostic resection (1982); large resection with skin flap on the forehead (1990); second resection of re-occurrence underneath skin flap (1992); third resection of re-occurrence (1994); Mohs surgery on the forehead (2000 and 2002); and anterior orbitotomy with exploration and excision of bilateral lesions (2007). Radiation directed to the glabellar region was administered in 2003. Prior systemic therapy included the following agents: carboplatin and paclitaxel (2007), cetuximab (2008), and methotrexate (2009).

The subject's medical history included multiple fractures of right arm and hip, ruptured pancreas and spleen. General surgical history included irrigation and debridement of right open tibial plateau fracture with placement of spanning external fixator to the right knee; open reduction internal fixation right tibial plateau fracture; resection of mass on right long finger; and

Reference ID: 3068456

appendectomy. Concurrent conditions at baseline included brain injury with secondary visual impairment, depression, hypercholesterolemia, hypertension, insomnia, intermittent nausea, bladder spasms, permanent right foot drop, and "toenail issues." Concomitant medications during screening included acetaminophen/diphenhydramine hydrochloride and zolpidem tartrate for insomnia; folic acid and multivitamin supplementation; paroxetine hydrochloride for depression; bisoprolol for hypertension; tolterodine tartrate for bladder spasms; and atorvastatin calcium for hypercholesterolemia.

At screening, the subject's ECOG performance status was 0.

The subject received his first dose of 150 mg vismodegib on [redacted] (b) (4). Per the last study drug bottle returned by the subject, the last dose of vismodegib was on [redacted] (b) (4) [redacted] (b) (4) however, the safety report indicate that the last dose prior to the event of fatal myocardial infarction was taken [redacted] (b) (4)

On the evening of [redacted] (b) (4) the subject complained of coughing and shortness of breath after an earlier fall. He did not seek medical attention since he believed he had broken or bruised his ribs. On [redacted] (b) (4), the subject was found dead at home. The cause of death was reported to be acute myocardial infarction. An autopsy was not performed. The investigator assessed the event of fatal myocardial infarction as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included the subject's concurrent illness. On [redacted] (b) (4) dministration of vismodegib and participation in the study ended due to the fatal adverse event. Using the confirmed last dose date of [redacted] (b) (4) the subject had received a total of 508 doses of vismodegib.

Reviewer's comment: The subject did not have a medical history of cardiac disease or risk factors and the cause of death was not confirmed by autopsy. Vismodegib does not prolong QT making sudden death due to cardiac arrhythmia unlikely. This reviewer does not agree that acute myocardial infarction was the most likely cause of death labeling the death, but that the death should be considered related to vismodegib even with the recent history of trauma (fall) to his chest.

Subject 21080 was an 85 year old male with laBCC who died of Grade 5 hypovolemic shock [redacted] (b) (4) At the time of enrollment, the tumor on his nose was considered to be inoperable. Radiotherapy had been previously administered to at least one target lesion.

The subject was initially diagnosed with a basal cell carcinoma in 1982. Prior surgery included lesion excisions on the nose (5 times) in 1982, 1988, 1995, 1997, and 1999. Two courses of radiation directed to the left side of nose and the right jugal (zygomatic arch) region were administered; the first course (6500 cGy) ended in 2001, and the second course (6000 cGy) ended in 2008. No prior medical history or general surgical history was reported. Concurrent conditions at baseline included Alzheimer's disease, unspecified arteritis, depression, diabetes mellitus, hyperlipidemia, insomnia, ischemic cardiomyopathy, Grade 1 lymphopenia, pain related to basal cell carcinoma, pollakiuria, and keratoses on the trunk and face. Concomitant medications during screening included perindopril, nitroglycerin and trimetazidine hydrochloride

Reference ID: 3068456

for ischemic cardiomyopathy; citalopram hydrobromide /citalopram hydrochloride for depression; alfuzosin hydrochloride and trospium chloride for pollakiuria; risperidone for Alzheimer's disease; midazolam and zolpidem tartrate for insomnia; pravastatin sodium for hyperlipidemia; and acetaminophen/caffeine/opium for pain related to BCC.

At screening, the subject's ECOG performance status was 2.

The subject received his first dose of 150 mg vismodegib on January 28, 2010 [redacted] (b) (4) Per the last study drug bottle returned to the clinic, the last dose of vismodegib was administered on August 3, 2010 [redacted] (b) (4) however, the safety report indicate that August 4, 2010 [redacted] (b) (4) was the last dosing date.

On [redacted] (b) (4) the subject experienced a serious event of hypovolemic shock which resulted in the subject's death on [redacted] (b) (4) No further details were provided. An autopsy was not performed. The investigator assessed the event of hypovolemic shock as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included the subject's concurrent illness. On [redacted] (b) (4) administration of vismodegib and participation in the study ended due to the fatal adverse event. Using the confirmed last dose date of [redacted] (b) (4) the subject had received a total of 126 doses of vismodegib.

Reviewer's comment: The narrative does not contain enough information on the subject's concurrent illnesses or the hypovolemic shock event to reliably assess this case and whether or no vismodegib could have contributed to his death.

Subject 20821 was a 55 year old female with laBCC died of an adverse event described as "death." At the time of enrollment, the tumor on her forehead was considered to be inoperable. Radiotherapy had not been administered to a target lesion; radiotherapy was considered to be inappropriate due to the location of the lesion. The subject was initially diagnosed with a basal cell carcinoma in 1999. Prior surgery included excision of the lesion (four times) in [redacted] (b) (4) [redacted] (b) (4)

The subject's medical history included renal deficiency. General surgical history included skin transplant (twice), bilateral breast implant, with insertion a skin expander, scar excisions (twice). Concurrent conditions at baseline included an unspecified allergy, anxiety, constipation, depression, hyperuricemia, and insomnia. Concomitant medications during screening included bromazepam and hydroxyzine hydrochloride for anxiety; valproate sodium/valproic acid for epilepsy prophylaxis; amitriptyline hydrochloride and paroxetine hydrochloride for depression; allopurinol for hyperuricemia; alimemazine tartrate for allergy; polyethylene glycol for constipation; lormetazepam, zolpidem tartrate, and zopiclone for insomnia; and estradiol/norethindrone acetate for hormone therapy. Pregnancy testing was not required because of her post-menopausal status.

At screening, the subject's ECOG performance status was 0.

Reference ID: 3068456

The subject received her first dose of 150 mg vismodegib on October 8, 2009 [redacted] (b) (4) The last dose of vismodegib prior to the event of drug toxicity was taken on January 2, 2010 [redacted] (b) (4)

On [redacted] (b) (4) the subject experienced a serious Grade 1 event of drug toxicity described as diuretic intoxication; she was hospitalized on the same day. Blood tests were performed with results not provided. No treatment was administered for the event. The event resolved on [redacted] (b) (4) No action was taken with vismodegib in response to the event. The investigator assessed the event of drug toxicity as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included concomitant medications. The last dose of vismodegib prior to the first episode of hypokalemia was taken on July 5, 2010 [redacted] (b) (4) On [redacted] (b) (4), the subject presented to the hospital with dizziness, asthenia and was hospitalized for Grade 1 hypokalemia. It was reported that she took diuretics without a medical prescription. EKG, blood count, and blood biochemistry were performed with results not provided. She underwent an unspecified procedure/surgery for the event. The event resolved on the same day. No action was taken with vismodegib in response to the event. The investigator assessed the event of hypokalemia as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included concomitant medications.

The last dose of vismodegib prior to the second episode of hypokalemia was taken on [redacted] (b) (4) [redacted] (b) (4) On [redacted] (b) (4) the subject experienced the second episode of serious Grade 3 hypokalemia and was hospitalized on the same day. It was reported that she again took diuretics without a medical prescription. No relevant laboratory tests were reported. She received unspecified treatment for the event. The event resolved on the same day. No action was taken with vismodegib in response to the event. The investigator assessed the event of hypokalemia as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included concomitant medications.

The last dose of vismodegib prior to death was taken on [redacted] (b) (4) On [redacted] (b) (4), the subject died. The cause of death was unknown. An autopsy was performed with results not reported. The investigator assessed the death as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included concomitant medications. The suspected drug was aldactazine (althiazide, spironolactone). On [redacted] (b) (4) administration of vismodegib and participation in the study ended due to death. Using the confirmed last dose date of [redacted] (b) (4) the subject had received a total of 307 doses of vismodegib.

Reviewer's comment: The narrative does not contain enough information to assess a possible relationship between vismodegib and the cause of death, which was unknown even though an autopsy was performed.

Subject 20844 was a 55 year old male with laBCC who died of an adverse event described as "meningeal disorder." Surgery was medically contraindicated because of anticipated substantial morbidity and/or deformity from surgery to the lesions of the neck and skull base. Radiotherapy had been previously administered to at least one target lesion.

Reference ID: 3068456

The subject was initially diagnosed with a basal cell carcinoma in 2000. Prior surgery included excision of the lesion in (b) (4) and right postauricular skin excision (three times) in (b) (4) (b) (4) Radiation (2400 cGy) directed to the right face, jugular foramen and petrous apex ended in (b) (4)

The subject's medical history included hypertension, lethargy, right ankle fracture, and septal defect. General surgical history included repair of septal defect (heart) and gamma knife procedure for trigeminal neuralgia. Concurrent conditions at baseline included alopecia, anxiety, Bell's palsy, benign prostatic hyperplasia, blurry vision, complete 7th cranial nerve involvement, constipation, decreased appetite, dietary supplementation, fatigue, gold weight in right eye, arrhythmia, horizontal diplopia, hypokalemia, hyponatremia, mild photophobia, mood swings, multiple cranial nerve palsies, nausea and vomiting, nerve pain, night sweats, obesity, pain, reflux, right 5th cranial nerve "D2 signs", right 6th cranial nerve palsy, right dry eye, right eye infection, right facial pain, right keratopathy, right side facial paralysis, sleep apnea, squamous cell [lesions], swelling of the brain, transient ischemic attacks (TIA), trigeminal neuralgia, unstable walking/gait, and weight loss. Concomitant medications during screening included flecainide acetate for arrhythmia; carbamazepine for seizure prevention; clonazepam and escitalopram oxalate for anxiety; pregabalin for nerve pain; ondansetron hydrochloride for nausea and vomiting; alfuzosin hydrochloride for benign prostatic hyperplasia; aripiprazole for mood swings; ofloxacin and erythromycin for eye infection; lactulose for constipation; aspirin for heart/antiplatelet therapy; artificial tears for right dry eye; omeprazole for reflux; zolpidem tartrate for sleep aid; dexamethasone for swelling of brain; hydromorphone hydrochloride, morphine sulfate, and oxycodone hydrochloride for pain; morphine for breakthrough pain; oxycodone for face/head pain; mineral/multivitamins supplement; and multivitamins supplement.

At screening, the subject's ECOG performance status was 2.

The subject received his first dose of 150 mg vismodegib on November 19, 2009 (b) (4) The last dose of vismodegib prior to the event of viral meningitis was taken on January 29, 2009 (b) (4) On (b) (4) the subject presented with hypotension, fever of 104 °F, and altered mental status; he was hospitalized for Grade 4 viral meningitis. An MRI revealed a small acute left basal ganglia infarct and findings consistent with a prior right cerebellar stroke. A lumbar puncture (LP) revealed elevated protein and increased white blood cells. During hospitalization, he had a hypotensive stroke. He received broad-spectrum antibiotics intravenously, antiviral and fluid resuscitation with improvement of mental status, and underwent an unspecified procedure/surgery for the event. The event resolved on (b) (4) (b) (4) No action was taken with vismodegib in response to the event. The investigator assessed the event of viral meningitis as unrelated to vismodegib. No other possible etiological factors were reported.

The last dose of vismodegib prior to the event of meningeal disorder was not reported. On (b) (4) the subject presented with increased lower extremity muscle weakness, bowel and bladder incontinence, as well as difficulty voiding; he was hospitalized for

meningeal disorder. On the same day, a chest X-ray revealed bibasilar atelectasis; a CT scan of head revealed increase in edema in the right-sided middle cerebellar peduncle; and an MRI of the thoracic and lumbar spine revealed widespread leptomeningeal disease with cord edema likely from C3 through T6. On (b) (4) (b) (4) an MRI of the face and/or neck clearly revealed an "extensive ongoing tumor of a perineural mechanism well posteriorly into the brainstem," which may have led to the leptomeningeal disease. He received vancomycin and cefpodoxime proxetil for the event. On March 21, 2010 (b) (4) administration of vismodegib and participation in the study ended due to the subject's own decision. On (b) (4) (b) (4) the subject died due to the meningeal disorder. It was reported that the subject's death was most likely due to the progression of his disease. It was not possible to state whether or not the subject had the disease in his spine at the time he enrolled in this study. It was not known if an autopsy was performed. The investigator assessed the event of meningeal disorder as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included basal cell carcinoma and the subject's concurrent illness. Using the confirmed last dose date of March 21, 2010 (b) (4) the subject had received a total of 123 doses of vismodegib.

Reviewer's comment: The subject's narrative indicates that disease progression likely contributed to death and likely better describes the cause of death instead of the adverse event – meningeal disorder.

Subject 20940 was a 71 year old female with laBCC who died of progressive disease. At the time of enrollment, the tumor of her nose and skull was considered to be inoperable. Radiotherapy had not been administered to a target lesion; radiotherapy was considered contraindicated due to the massive involvement of tumor as well as recent history of brain abscess.

The subject was initially diagnosed with a basal cell carcinoma in 2009. Prior surgery included a biopsy of superficial scalp in (b) (4), and a biopsy of scalp in (b) (4) The subject's medical history included brain abscess. General surgical history included hysterectomy and left frontal burr hole with catheter drainage of abscess.

Concurrent conditions at baseline included alopecia, anorexia, anxiety, cough, dyspnea, fatigue, headaches, hypertension, occasional hemoptysis, taste changes, and weight loss. Concomitant medications during screening included chlordiazepoxide and amitriptyline hydrochloride for anxiety; naproxen sodium for headaches; and verapamil hydrochloride for hypertension.

Pregnancy testing was not required because of her hysterectomy.

At screening, the subject's ECOG performance status was 1.

The subject received her first dose of 150 mg vismodegib on November 17, 2009 (b) (4) On (b) (4) administration of vismodegib and participation in the study ended due to death related to disease progression. Using the confirmed last dose date of August 26, 2010 (b) (4) the subject had received a total of 275 doses of vismodegib.

Reference ID: 3068456

Reviewer's comment: As noted in Table 33*, Subject 20940 had two ongoing Grade 3 infectious related AEs – sinus infection and urinary tract infection at the time of death. The narrative does not contain enough information to assess whether or not the AEs or vismodegib contributed to the reported cause of death – progressive disease.*

Subject 20822 was a 53 year old male with mBCC who died of progressive disease. At screening, a target lesion was identified by radiography in the forehead, but had metastatic disease to the brain. The subject was initially diagnosed with a basal cell carcinoma in 2003. Prior surgery included skin and bone excision on the forehead in (b) (4) Radiation (unknown dose) directed to the forehead ended in (b) (4)

No prior medical history or general surgical history was reported. Concurrent conditions at baseline included arterial hypertension, mellitus diabetes, nausea, and pain. Concomitant medications during screening included irbesartan for arterial hypertension; metopimazine for nausea and vomiting; gliclazide and metformin hydrochloride for mellitus diabetes; and oxycodone hydrochloride for pain.

At screening, the subject's ECOG performance status was 0.

The subject received his first dose of 150 mg vismodegib on January 21, 2010 (b) (4) The last dose of vismodegib prior to the event was taken on (b) (4) On (b) (4) (b) (4) the subject experienced a serious Grade 2 event of convulsion. A CT scan revealed infiltration of tumor into the left frontal and temporal lobes. He underwent an unspecified procedure/surgery and received valproate sodium/valproic acid for the event. The event resolved on (b) (4) No action was taken with vismodegib in response to the event. The investigator assessed the event of convulsion as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included basal cell carcinoma. On (b) (4) the subject died due to disease progression. An autopsy was not performed. Administration of vismodegib and participation in the study ended due to death. Using the confirmed last dose date of August 31, 2010 (b) (4) the subject had received a total of 222 doses of vismodegib.

Reviewer's comment: As noted in Table 33, Subject 20822 had a recent episode of Grade 2 convulsions, but the most likely cause of death was disease progression as evidenced by the CT scan showing infiltration of tumor into the left frontal and temporal lobes.

SHH4476 Deaths > 30 Days from Last Dose

Table 33 contains the subjects who died > 30 days after the last dose of vismodegib. Only three subjects had AEs within 90 days of death, 20720, 20540, and 20921 and had a cause of death other than disease progression. The other subjects all died of progressive disease except for Subject 20781 who stopped participating in SHH4476g due to her own decision, did not have any AEs within 90 days of death, and died on Day 197 after discontinuing vismodegib on Day 101. This section contains brief narratives of the three subjects who died > 30 days after the last dose of vismodegib, experienced AEs within 90 days of death, and died of a an adverse event.

Reference ID: 3068456

Subject 20720 was a 72 year old male with mBCC who died of an adverse event described as "death unknown cause." Metastatic lesions included mediastinum, skin, cervical lymph nodes, epidural space, frontal sinuses, brain, nose, and skull base.

The subject was initially diagnosed with a basal cell carcinoma in 1982. Prior surgery included excision of skin of the left ear in 1982 and 1985; radical resection of left ear region (1991); resection of the left scalp in 1997 and 1998; removal of the lower lobe of the right lung (1998); and radical resection of the left parotid gland and external left ear along with reconstruction in 2000. Two courses of radiation directed to ear/right lower eye lid were administered; the first course (4200 cGy) ended in 1991, and the second course (6000 cGy) ended in 1999.

No prior medical history was reported. General surgical history included appendectomy, excision of a cyst in right index finger, left inguinal hernia repair, left total hip replacement, and "brow lift". Concurrent conditions at baseline included alopecia, autonomic neuropathy, decreasing arterial blood pressure, depression, facial pain, fatigue, gout, hypotension, kidney stones, left eye blindness, loss of hearing, paroxysmal atrial fibrillation, and urinary incontinence. Concomitant medications during screening included imipramine hydrochloride for depression; colchicine/probenecid for gout; digoxin for atrial fibrillation; midodrine hydrochloride for low blood pressure; acetaminophen/hydrocodone bitartrate for pain; multivitamins supplement; and aspirin for "heart condition".

At screening, the subject's ECOG performance status was 1.

The subject received his first dose of 150 mg vismodegib on July 30, 2009 [redacted] (b) (4) Per the last study drug bottle returned by the subject, the last dose of vismodegib prior to the event was taken on June 4, 2010 [redacted] (b) (4) On [redacted] (b) (4) the subject died at home. It was not known if an autopsy was performed. The cause of death was unknown. The investigator assessed the event of death as unrelated to vismodegib. In the investigator's opinion, other possible causes for the event included the subject's concurrent illness.

On [redacted] (b) (4) administration of vismodegib and participation in the study ended due to death. Using the confirmed last dose date of June 4, 2010 [redacted] (b) (4) the subject had received a total of 308 doses of vismodegib.

Reviewer's comment: The narrative does not contain information on the on ongoing Grade 3 decreased performance status AE or any other possible contributing causes.

Subject 20540 was a 59 year old female with laBCC who died of ischemic stroke. She had lesions of the forehead, ear, and scalp. Radiotherapy had been previously administered to at least one target lesion.

The subject was initially diagnosed with a basal cell carcinoma in 1998. Two courses of radiation were directed to the areas described as "superior to hairline, medial to nose, lateral to hairline, inferior to orbit" and "3 cm diameter circle in center of chin," the first course (60 cGy) ended in 1998, and the second course (40 cGy) ended in 2001.

Reference ID: 3068456

No prior medical history was reported. General surgical history included femoral popliteal bypass of the right leg (twice). Concurrent conditions at baseline included hypertension and hypercholesterolemia. Concomitant medications during screening included hydrochlorothiazide/losartan potassium for hypertension; atorvastatin calcium for hypercholesterolemia; and aspirin for coronary artery disease prevention.

Pregnancy testing was not required at baseline because she was post-menopausal.

At screening, the subject's ECOG performance status was 1.

The subject received her first dose of 150 mg vismodegib on March 25, 2009 [redacted] (b) (4) Per the last study drug bottle returned by the subject, the last confirmed dose was on May 18, 2010 [redacted] (b) (4) [redacted] (b) (4); however, safety reports indicate that dosing continued until June 13, 2010 [redacted] (b) (4)

On [redacted] (b) (4) the subject presented to the emergency room with severe left upper and lower extremity weakness, and left arm numbness that progressed to the right leg. She was hospitalized for Grade 3 ischemic stroke on [redacted] (b) (4). A CT scan of the head without IV contrast revealed periventricular microvascular ischemic changes and mild generalized cortical atrophy. It revealed no evidence of acute intracranial hemorrhage or large vessel infarct. On [redacted] (b) (4) a transthoracic echocardiography (TTE) revealed normal ventricular size and function, dilated left atrium and no significant valvular disease. On [redacted] (b) (4), a CT angiography of the neck revealed complete occlusion of the right internal carotid artery. She underwent an unspecified procedure for the event. The event resolved on [redacted] (b) (4) No action was taken with vismodegib in response to the event. The investigator assessed the event of ischemic stroke as unrelated to vismodegib. No other possible etiological factors were reported.

On [redacted] (b) (4) the subject experienced the second episode of Grade 3 ischemic stroke. She complained of left leg numbness and droopy mouth. She was hospitalized on [redacted] (b) (4) [redacted] (b) (4) for the event. She underwent an unspecified procedure for the event. The event resolved on the same day. Vismodegib was permanently discontinued as a result of the event. The investigator assessed the event of ischemic stroke as unrelated to vismodegib. No other possible etiological factors were reported.

On [redacted] (b) (4) the subject presented to the emergency room with progressive left lower extremity weakness followed by increasing left upper extremity weakness. She experienced the third episode of ischemic stroke. A CT scan of the head revealed an acute/subacute infarct involving the right parietal and occipital regions. The subject was transferred to hospice, and on [redacted] (b) (4) the subject died as a result of the third episode of ischemic stroke. It was not known if an autopsy was performed. The investigator assessed the event of fatal ischemic stroke as unrelated to vismodegib. No other possible etiological factors were reported.

On June 19, 2010 [redacted] (b) (4) administration of vismodegib was discontinued due to the second episode of ischemic stroke. On [redacted] (b) (4) the subject ended participation in

Reference ID: 3068456

the study due to the fatal ischemic stroke. Using the confirmed last dose date of May 18, 2010 (b) (4) the subject had received a total of 409 doses of vismodegib.

Reviewer's comment: The presence of an occluded internal carotid artery and intracranial mBCC are likely contributors to the subject's fatal ischemic stroke and seem to be more probable causes of death than vismodegib.

Subject 20921 was a 89 year old female with laBCC who died of an adverse event described as "death unknown cause." At the time of enrollment, the tumor of her mediastium was considered to be inoperable. Radiotherapy had not been administered to a target lesion; radiotherapy was considered to be inappropriate due to large area of basal cell carcinoma involvement, toxicity of radiotherapy, and the subject's dementia.

The subject was initially diagnosed with a basal cell carcinoma in 2005. Prior surgery included lesion excision on the nose in 2005, lesion excision on the chin and left cheek on two occasions in 2006, and lesion excision on the upper lip in 2008. The subject's medical history included rectal polyps. General surgical history included ablation of rectal polyps. Concurrent conditions at baseline included aortic insufficiency, calcified myoma, chronic atrial fibrillation, coronary heart disease, type II diabetes mellitus, hypertension, incontinence, mitral insufficiency, osteoporosis, pancreatic cyst, reflux esophagitis, and urinary tract infection. Concomitant medications during screening included enalapril maleate, metoprolol succinate, amlodipine mesilate, and clopidogrel bisulfate for hypertension; isosorbide dinitrate for cardiac insufficiency; loperamide for diarrhea; solifenacin succinate for incontinence; acetyldigoxin and hydrochlorothiazide for chronic cardiac insufficiency; ciprofloxacin for urinary tract infection; and metformin hydrochloride/vildagliptin for diabetes mellitus.

Pregnancy testing was not required because of her post-menopausal status.

At screening, the subject's ECOG performance status was 2.

The subject received her first dose of 150 mg vismodegib on November 24, 2009 (b) (4) Per the last study drug bottle returned by the subject, the last confirmed dose was on January 28, 2010 (b) (4) however, safety reports indicate that the last dose of vismodegib prior to the events of cardiac failure and pneumonia was taken on (b) (4)

On (b) (4) the subject experienced serious Grade 3 events of cardiac failure and pneumonia and was hospitalized on the same day. A chest X-ray revealed moderate heart enlargement with cross compensation, and right basal infiltrate. An EKG revealed discrete ST reduction. An echocardiography showed pulmonary hypertension with right and left pleural effusion (each 700 ml). She received levofloxacin, cefuroxime, and clarithromycin for pneumonia, and torasemide and supplemental oxygen for cardiac failure. The events resolved on (b) (4) Vismodegib was temporarily withheld as a result of cardiac failure. The investigator assessed these events as related to vismodegib. In the investigator's opinion, other possible causes for the event of cardiac failure included the subject's concurrent illness and

Reference ID: 3068456

concomitant medications. No other possible etiological factors were reported for the event of pneumonia.

On [redacted] (b) (4) the subject experienced serious Grade 3 events of left ventricular systolic dysfunction and renal failure and was hospitalized on the same day. A chest X-ray revealed pleuropneumonia, and an EKG revealed non-ST segment elevation myocardial infarction. Relevant laboratory results included BUN of 76.59 (unit not provided) and creatinine of 4.7 mg/dL. She received heparin sodium, digitoxin, supplemental oxygen, and aspirin for left ventricular systolic dysfunction and torsemide for renal failure. The events resolved on [redacted] (b) (4) [redacted] (b) (4). Vismodegib continued to be temporarily withheld as a result of the events. The investigator assessed these events as unrelated to vismodegib. No other possible etiological factors were reported.

On March 9, 2010 [redacted] (b) (4) administration of vismodegib and participation in the study ended due to the subject's own decision. On [redacted] (b) (4) the subject died. The cause of death was unknown. No laboratory or diagnostic tests were reported. An autopsy was not performed. The investigator assessed the event of death as unrelated to vismodegib. No other possible etiological factors were reported. Using the confirmed last dose date of January 28, 2010 [redacted] (b) (4) the subject had received a total of 66 doses of vismodegib.

Reviewer's comment: The subject likely died of a cardiac related cause, congestive heart failure, which first developed when the subject was taking vismodegib. The lack of internal control and small trial size makes evaluation of this event and its relationship to vismodegib difficult.

Overall Reviewer's comments: This reviewer reviewed the applicant's assessment of the causes of death in Table 33, but does not agree that no deaths should be attributed to vismodegib. The lack of internal control complicates the ability to determine whether basal cell or vismodegib caused the adverse events. Because the half life of vismodegib is 4 days, this reviewer also examined Grade 3 or greater AEs occurring up to 90 days prior to the date of death. Subjects 20600, 21080, and 20921 highlight the difficulty attributing cardiac causes of death and their relationship to vismodegib, especially since vismodegib does not prolong QT duration.

In summary, the most common cause of fatal events after receiving vismodegib were disease progression and infections. Neither SHH4476g nor SHH3925g contain a comparison arm and the lack of internal control complicates the ability to determine whether basal cell cancer or vismodegib caused the adverse events.

7.3.2 Nonfatal Serious Adverse Events

Trials SHH3925g and SHH4476g defined a serious adverse event (SAE) as an AE that requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly or birth defect; is medically important; results in death; or is life threatening. *Reviewer's comment: This definition is in accordance with ICH E6 Good Clinical Practice Guidelines.*

Reference ID: 3068456

A total of 33 subjects experienced a total of 44 non fatal SAEs as described in the ISS ADAE dataset. Table 34 contains the total number of non-fatal SAEs, not by per subject incidence, by MedDRA SOC (System Organ Class) in SHH3925g, SHH4437g, and SHH4476g; in trial 4610g, the subject did not experience a SAEs.

Table 34: Non-Fatal Serious AEs by Trial

MedDRA SOC	SHH3925 n=33	SHH4437 n=13	SHH4476 n=104	Total n=138
CARDIAC DISORDERS	1	0	6	7
INFECTIONS AND INFESTATIONS	1	1	5	7
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	0	6	7
GASTROINTESTINAL DISORDERS	2	1	3	6
VASCULAR DISORDERS	1	0	4	5
NERVOUS SYSTEM DISORDERS	1	0	3	4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0	3	4
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	3	3
METABOLISM AND NUTRITION DISORDERS	1	0	2	3
HEPATOBILIARY DISORDERS	0	1	1	2
EYE DISORDERS	0	0	1	1
PSYCHIATRIC DISORDERS	1	0	0	1
RENAL AND URINARY DISORDERS	0	0	1	1

Abbreviations: MedDRA = medical dictionary for regulatory activities; SOC = system organ class

Table 35 contains the individual non-fatal SAEs on a per subject incidence. No individual SAE had an incidence greater than 3 occurrences, but as each SOC had less than 10 events per SOC, HGLT and HLT analyses were generally not more informative.

Table 35: Non-Fatal SAEs by Preferred Term by Trial

Non-Fatal SAE Preferred Term	SHH3925g n=33	SHH4437g n=13	SHH4476g n=104	Total n=138 (%)
PNEUMONIA	1	0	2	3 (2.2)
CARDIAC FAILURE	0	0	2	2 (1.4)
DEEP VEIN THROMBOSIS	0	0	2	2 (1.4)
GASTROINTESTINAL HAEMORRHAGE	0	1	1	2 (1.4)
HAEMORRHAGE	1	0	1	2 (1.4)
PULMONARY EMBOLISM	0	0	2	2 (1.4)
ADENOCARCINOMA PANCREAS	1	0	0	1 (0.7)
ANGINA PECTORIS	0	0	1	1 (0.7)
APHAGIA	0	0	1	1 (0.7)
ATRIAL FIBRILLATION	1	0	0	1 (0.7)
BILE DUCT OBSTRUCTION	0	1	0	1 (0.7)
CELLULITIS	0	0	1	1 (0.7)
CERVICAL VERTEBRAL FRACTURE	0	0	1	1 (0.7)

Reference ID: 3068456

Non-Fatal SAE Preferred Term	SHH3925g n=33	SHH4437g n=13	SHH4476g n=104	Total n=138 (%)
CHOLESTASIS	0	0	1	1 (0.7)
CONVULSION	0	0	1	1 (0.7)
DEHYDRATION	0	0	1	1 (0.7)
DRUG TOXICITY	0	0	1	1 (0.7)
DUODENAL ULCER	1	0	0	1 (0.7)
DYSPNOEA	1	0	0	1 (0.7)
EYE HAEMORRHAGE	0	0	1	1 (0.7)
HYPOKALAEMIA	0	0	1	1 (0.7)
HYPONATRAEMIA	1	0	0	1 (0.7)
IMPAIRED GASTRIC EMPTYING	1	0	0	1 (0.7)
ISCHAEMIC STROKE	0	0	1	1 (0.7)
LEFT VENTRICULAR DYSFUNCTION	0	0	1	1 (0.7)
MALIGNANT MELANOMA	0	0	1	1 (0.7)
MENINGITIS VIRAL	0	0	1	1 (0.7)
METASTATIC MALIGNANT MELANOMA	0	0	1	1 (0.7)
METASTATIC SQUAMOUS CELL CARCINOMA	0	0	1	1 (0.7)
MYOCARDIAL INFARCTION	0	0	1	1 (0.7)
OESOPHAGEAL CARCINOMA	0	0	1	1 (0.7)
ORTHOSTATIC HYPOTENSION	0	0	1	1 (0.7)
PARANOIA	1	0	0	1 (0.7)
PNEUMONIA ASPIRATION	0	0	1	1 (0.7)
PRESYNCOPE	1	0	0	1 (0.7)
RENAL FAILURE	0	0	1	1 (0.7)
RESTRICTIVE CARDIOMYOPATHY	0	0	1	1 (0.7)
SARCOMA	0	0	1	1 (0.7)
SMALL INTESTINAL OBSTRUCTION	0	0	1	1 (0.7)
SPINAL COMPRESSION FRACTURE	0	0	1	1 (0.7)
SQUAMOUS CELL CARCINOMA	0	0	1	1 (0.7)
SYNCOPE	0	0	1	1 (0.7)
TUBO-OVARIAN ABSCESS	0	1	0	1 (0.7)
URINARY TRACT INFECTION	0	0	1	1 (0.7)

Abbreviations: AE = adverse event

Infections and infestations

SAEs related to infections occurred in 7 subjects, 6 bacterial infections (hand phlegmon, pneumonia, tubo-ovarian abscess, and urinary tract infection) and 1 viral infection (viral meningitis). Subject 20921 experienced three Grade 2 urinary tract infections and one Grade 3 pneumonia. There were no Grade 4 infections.

Cardiac disorders

Five subjects experienced seven cardiac SAEs, atrial fibrillation, cardiac chest pain, global heart insufficiency, heart failure, left ventricular systolic dysfunction, myocardial infarction, and

restrictive cardiomyopathy. Each of these events were Grade 3. This reviewer reviewed all SAE reports (including fatal SAEs) for all cardiac SAEs included in the NDA, Table 36.

Table 36: Subject Narrative for Cardiac SAEs

Trial	Subject	Cohort	Event	Brief Description of Serious AE
4476	20681	LA	Restrictive cardiomyopathy; Cardiac failure; Myocardial infarction	76 year-old male with a PMH of hypertension and CAD with stent placement experienced Grade 3 asthenia and Grade 3 restrictive cardiomyopathy on (b) (4) with an echocardiogram showing LVEF had declined to 31%. The subject received carvedilol. On (b) (4) the subject experienced Grade 3 cardiac failure and Grade 3 NSTEMI. congestive heart failure after stopping diuretics. The subject discontinued vismodegib on (b) (4) due to Grade 3 asthenia. .
4476	20921	LA	Cardiac failure; Left ventricular dysfunction	89 year-old female with no cardiac PMH developed Grade 3 cardiac failure and Grade 3 pneumonia on (b) (4) after discontinuing vismodegib on (b) (4) (last confirmed day). An echocardiogram revealed pulmonary hypertension and a left pleural effusion. The subject received antibiotics and diuretics and the SAEs resolved by (b) (4) On (b) (4) the subject experienced Grade 3 left ventricular systolic dysfunction and Grade 3 renal failure, which resolved on (b) (4) (b) (4) the subject died on (b) (4) The applicant considered the (b) (4) events as related to vismodegib but the (b) (4) events as not related.
4476	20600	LA	Acute myocardial infarction	51 year-old male with no cardiac PMH died on (b) (4) (b) (4) after being found dead at home. The cause of death was reported as acute myocardial infarction and no autopsy was performed. The investigator assessed the death as not related to vismodegib; last confirmed dose of vismodegib was 512.
4476	20621	LA	Angina pectoris	76 year-old female with no cardiac PMH experience Grade 3 angina pectoris on (b) (4) Work up included a stress test that revealed pre-existing cardiac disease but the subject did not have a myocardial infarction. The SAE resolved on (b) (4) and the investigator did not take any action with vismodegib.
3925	11101	-	Atrial fibrillation	46 year-old man developed Grade 3 atrial fibrillation on (b) (4), but did not have myocardial infarction. He eventually received a pacemaker on (b) (4) and event resolved on (b) (4) Subject held vismodegib during SAE but resumed after resolution.

Reference ID: 3068456

Abbreviations: AE = adverse event; CAD = coronary artery disease; LA = locally advanced; LVEF = left ventricular ejection fraction; NSTEMI = non-ST elevation myocardial infarction; PMH = past medical history

Reviewer's comment: The applicant did not include warnings or adverse event information on cardiac adverse events. The lack of internal control makes it difficult to assess attribution of the above cardiac SAEs to vismodegib.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Six subjects experienced six neoplastic SAEs including melanoma (amelanotic and metastatic melanoma in one subject), metastatic squamous cell carcinoma (SQCC), infiltrative SQCC, esophageal carcinoma, and histiocytic sarcoma of the right cheek. This reviewer reviewed all SAE reports for all neoplastic SAEs included in the NDA, Table 37.

Table 37: Subject Narratives for Neoplastic SAEs

Trial	Subject	Cohort	Event	Brief Description of Serious AE
4467	20507	LA	Melanoma	59 year-old male with a PMH of amelanotic melanoma developed Grade 3 malignant melanoma in the right deltoid region on (b) (4) The subject underwent excision of the lesion on (b) (4) On (b) (4) the subject developed metastatic malignant melanoma and the subject discontinued vismodegib on (b) (4)
4467	20562	LA	SQCC	47 year old male with a PMH of actinic keratosis and a past surgical history (PSH) of removal of SQCC nine different times developed Grade 4 metastatic SQCC on (b) (4) The subject had also experienced a non-serious Grade 3 SQCC on (b) (4). The last confirmed dose of vismodegib was (b) (4)
4467	20661	LA	Sarcoma	84 year-old male with no prior history of sarcoma developed Grade 4 sarcoma of the right cheek on (b) (4) (b) (4) based on immunostaining of a biopsy of a right cheek mass. The investigators did not take action with vismodegib, but instead discontinued vismodegib on (b) (4) due to disease progression.
4467	20820	M	Esophageal Carcinoma	69 year-old male with no prior history of esophageal carcinoma developed serious Grade 3 aphagia on (b) (4) (b) (4) and was subsequently diagnosed with Grade 4 esophageal carcinoma on (b) (4) The investigator discontinued vismodegib due to esophageal carcinoma.
4467	20960	LA	SQCC	62 year-old female with a PMH of prior NMSC developed Grade 3 SQCC of the nose on (b) (4) and underwent rhinotomy on (b) (4) The investigator temporarily held vismodegib due to the SAE and resumed it after resolution of the SAE. The subject decided to stop vismodegib on (b) (4)
3925	13116	-	Adenocarcinoma pancreas	65 year old male with PMH of BCC, testicular cancer, and thyroid papillary thyroid carcinoma developed ca underwent biopsy of a pancreatic mass on (b) (4). The

Trial	Subject	Cohort	Event	Brief Description of Serious AE
				biopsy revealed Grade 4 pancreatic carcinoma and the subject underwent a Whipple procedure on (b) (4) The last day of vismodegib administration was (b) (4)

Abbreviations: AE = adverse event; LA = locally advanced; NMSC = non-melanomatous skin cancers; PMH = Past Medical History; PSH = Past Surgical History; SQCC = squamous cell carcinoma

Reviewer's comment: Three of the six subjects with neoplastic SAEs had a prior diagnosis of the same malignancy that reoccurred as a SAE. For the other three subjects, the investigators considered only the adenocarcinoma pancreas as related to vismodegib. The incidence of secondary malignancies in patients with BCC is not known, but given the median age of the safety population, subjects with second cancers would be expected. Vismodegib is not a mutagen and exposure to the drug for less than a year would not be expected to lead to malignancies that often take years to manifest themselves.

Respiratory, thoracic and mediastinal disorders
Four subjects experienced respiratory SAEs including aspiration pneumonia, dyspnea, and pulmonary embolisms. Subject 20780 (mBCC) experienced two Grade 4 pulmonary embolisms on (b) (4) but had no risk factors noted in the narratives. Subject 21081 (laBCC) experienced one Grade 2 pulmonary embolism on (b) (4). For both cases of pulmonary embolism, the investigators did not stop vismodegib. *Reviewer's comment: Subject 20660 had aspiration pneumonia, which falls under the respiratory SOC instead of the infection SOC. Inclusion in the respiratory SOC may be appropriate as the subject had had non-target BCC lung lesions and prior lung surgery, both of which confound the case.*

Gastrointestinal disorders
Five subjects experienced gastrointestinal SAEs including delayed gastric emptying, duodenal ulcer, gastrointestinal bleed, gastrointestinal hemorrhage, hospitalization for total aphagia for liquid and solid food, and small bowel blockage. Subject 20682 (laBCC) experienced gastrointestinal hemorrhage and small intestinal obstruction, otherwise the other terms occurred in single subjects.

Nervous System Disorders
Five subjects experienced nervous system SAEs including ischemic stroke, seizure, syncope, and vagal episode. Subject 20540 (laBCC) experienced two non-fatal ischemic strokes and one fatal ischemic stroke. Subject 20822 (mBCC) had disease involving his left frontal and temporal lobes making disease progression a more probable cause of death than Grade 2 convulsions.

Vascular Disorders
Five subjects experienced vascular SAEs including hemorrhage (one subject with bleeding from the neck and another with abdominal bleeding), orthostatic hypotension, and deep vein thrombosis (in two subjects). Subject 20800 (laBCC) had abdominal bleeding that was not related to his laBCC and the narrative does not provide the location of the abdominal bleeding or causative or concurrent factors that might have been related to the bleeding.

Reference ID: 3068456

Metabolism and nutrition disorders
Three subjects experience metabolism and nutrition SAEs including dehydration, hyponatremia, and hypokalemia. Subject 20821 (laBCC) experienced hypokalemia twice one Grade 1 event and one Grade 3 event. Subject 13105 experienced Grade 4 hyponatremia (Sodium 118, units not provided) that resolved 7 days later. *Reviewer's comment: The Grade 4 hyponatremia event is not captured in the ISS ADLBSI dataset, which contains only scheduled lab visits.*

Injury, poisoning and procedural complications
Two subjects experienced injury, poisoning and procedural SAEs including drug toxicity in Subject 20821(laBCC) and cervical vertebral fracture and spinal compression fracture in Subject 20543(mBCC). Subject 20821 (laBCC) had diuretic related toxicity and not vismodegib related toxicity.

Hepatobiliary disorders
Two subjects experienced hepatobiliary SAEs, bile duct obstruction and cholestasis. Subject 20682 (laBCC) had Grade 4 cholestasis in the setting of cholecystitis and had an endoscopic retrograde cholangiopancreatography (ERCP) with biliary stent placement. Subject 13005 developed Grade 3 bile duct obstruction at the same time as non-serious Grade 3 worsening pancreatic adenocarcinoma and received a biliary stent.

Eye disorders
Subject 20642 (mBCC) experienced Grade 1 hemorrhage on Day 1 of the trial likely related to his BCC.

Renal and urinary disorders
Subject 20921 (laBCC) experienced Grade 3 renal failure in the setting of Grade 3 left ventricular systolic dysfunction.

Psychiatric disorders
Subject 13120, who also had post traumatic stress disorder (PTSD) experienced Grade 4 paranoia

7.3.3 Dropouts and/or Discontinuations

Table 38 contains the reasons subjects withdrew from SHH3925g or SHH4476g; the single subject in SHH4610g did not withdraw from that trial.

Table 38: Reason for Discontinuation

Reason for Discontinuation	SHH3925	SHH4476		Total
	n =33	laBCC (n = 71)	mBCC (n = 33)	n = 138 (%)
MISSING	12	32	19	63 (45.6)
PROGRESSIVE DISEASE	18	5	6	29 (21)
SUBJECT DECISION TO DISCONTINUE TREATMENT	1	18	2	21 (15.2)

Reference ID: 3068456

Reason for Discontinuation	SHH3925	SHH4476		Total
	n =33	laBCC (n = 71)	mBCC (n = 33)	n = 138 (%)
ADVERSE EVENT	1	11	1	13 (9.4)
PHYSICIAN DECISION	1	1	2	4 (2.9)
LOST TO FOLLOW-UP	0	1	2	3 (2.1)
DEATH	0	2	1	3 (2.1)
OTHER	0	1	0	1 (0.7)
TOTAL	33	71	33	138

Percentage is out of 138, total pooled safety population. The subject in SHH4610g did not have a flag for study or treatment discontinuation. Table ADSL selecting the TRTDCR column for SSHH4476g and the STDDCFL column for SHH3925. Abbreviations: laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma

Table 39 contains adverse events by Grade that lead to discontinuation of vismodegib in 15 subjects. The two additional subjects are Subject 13005, originally enrolled in SHH3925 and continued to received vismodegib in the extension trial SHH4437g, who discontinued for an adverse event and Subject 20720 whose discontinuing AE was death and is included in the death column in Table 38.

Table 39: Adverse Events Leading to Discontinuation By Trial By Grade

Trial	Subject	Adverse Event	Grade
3925	13116	IMPAIRED GASTRIC EMPTYING	3
4437	13005	ADENOCARCINOMA PANCREAS	3
4476	20507	METASTATIC MALIGNANT MELANOMA	4
	20540	ISCHAEMIC STROKE	3
	20545	FATIGUE	3
	20562	METASTATIC SQUAMOUS CELL CARCINOMA	4
	20585	MUSCLE SPASMS	3
	20600	ACUTE MYOCARDIAL INFARCTION	5
	20680	DYSGEUSIA	1
		MUSCLE SPASMS	1
		WEIGHT DECREASED	2
	20681	ASTHENIA	3
	20720	DEATH	5
	20820	APHAGIA	3
	20880	PARAESTHESIA	2
	20924	CELLULITIS	3
	21080	HYPOVOLAEMIC SHOCK	5

See Section 7.3.2 for discussion of the subjects with malignancies. Table 40 contains AEs that led to discontinuation in SHH4489g, a trial in subjects with ovarian cancer; no subject who received placebo discontinued treatment due to an AE.

Table 40: AEs Leading to Discontinuation in SHH4489G

Subject	Adverse Event	Grade

Reference ID: 3068456

Subject	Adverse Event	Grade
18153	MUCOSAL INFLAMMATION	3
18351	MUSCLE SPASMS	3
18450	DYSGEUSIA	1
18801	HEPATIC ENZYME INCREASED	3
19252	ALOPECIA	1
	DRY MOUTH	1
	DYSGEUSIA	1
	MUSCLE SPASMS	2
19450	DIARRHOEA	2

Table 41 contains AE that lead to discontinuation of vismodegib or placebo in SHH4429g, a trial in subjects with mCRC. *Reviewer's comment: The applicant did not submit datasets for SHH4429g.*

Table 41: AEs Leading to Discontinuation in SHH4429g
(copied from submission with minor modifications)

AE Term	Placebo n = 98		Vismodegib n = 98	
	Grade 3-5	Overall (%)	Grade 3-5	Overall (%)
Fatigue	(0.0)	(0.0)	2 (2.0)	4 (4.1)
Mucosal Inflammation	(0.0)	(0.0)	2 (2.0)	2 (2.0)
Diarrhea	(0.0)	(0.0)	1 (1.0)	2 (2.0)
Asthenia	(0.0)	(0.0)	1 (1.0)	2 (2.0)
Dehydration	(0.0)	(0.0)	1 (1.0)	2 (2.0)
Coagulopathy	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Weight Decreased	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Pneumonia	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Sepsis	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Hypoglycemia	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Ascites	(0.0)	(0.0)	1 (1.0)	1 (1.0)
Decreased Appetite	(0.0)	(0.0)	(0.0)	1 (1.0)
Muscle Spasms	(0.0)	(0.0)	(0.0)	1 (1.0)
Gait Disturbance	(0.0)	(0.0)	(0.0)	1 (1.0)
Drug Hypersensitivity	(0.0)	(0.0)	(0.0)	1 (1.0)
Neutropenia	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)
Nausea	(0.0)	1 (1.0)	(0.0)	1 (1.0)
Proctalgia	1 (1.0)	1 (1.0)	(0.0)	(0.0)
Small Intestinal Obstruction	1 (1.0)	1 (1.0)	(0.0)	(0.0)
Small Intestinal Perforation	1 (1.0)	1 (1.0)	(0.0)	(0.0)
Thrombocytopenia	1 (1.0)	1 (1.0)	(0.0)	(0.0)
Abdominal Abscess	1 (1.0)	1 (1.0)	(0.0)	(0.0)

Reviewer's comment: Muscle spasms, fatigue, and dysgeusia were the only AEs that led to discontinuation that occurred in both the pooled safety database and the expanded pooled safety database (SHH4489 and SHH4429g) and are the most common AEs.

Reference ID: 3068456

Twenty two subjects, all in SHH4476g, who discontinued vismodegib for reasons other than AE had an adverse events that occurred within 90 days of discontinuing vismodegib, Table 42.

Table 42: AEs Occurring within 90 Days of Discontinuation of Vismodegib in Subjects who Discontinued Vismodegib for Reasons other than AE

Subject	AE Term	TG	AE Start Date*
20500	INTERMITTENT STIFFNESS IN HANDS	1	-86
	LEG CRAMPING	1	-70
	DECREASED ENERGY	1	-58
	HAIR LOSS	1	-58
	INCREASED PAIN IN L ARM	1	-58
	PAIN AND STIFFNESS IN HIP	1	-58
	DYSURIA	1	-55
	IRRITATED MOLE ON L FLANK (UNK DIAGNOSIS)	1	-55
	INDIGESTION	1	-53
	DECREASED APPETITE	1	0
	LOSS OF TASTE	1	0
20501	CANDIDA ON TONGUE	1	-83
	PAIN IN HAND, LEG, & FOOT	3	-58
	TREMORS IN HANDS AND KNEES	1	-15
	CRAMPS IN HANDS	1	-13
	INCREASED FREQUENCY OF LEG CRAMPS	1	-7
	DECREASED ABILITY TO TASTE	1	-3
	DECREASED APPETITE	1	-3
	DECREASED ENERGY	1	0
20502	DECREASED ABILITY TO TASTE	1	-33
	MOUTH DRYNESS	1	-2
20508	INCREASED APPETITE	1	-18
	LOSS OF HAIR	1	-8
	THINNING OF HAIR	1	-8
	NAUSEA	2	-6
20522	ALTERED SENSE OF SMELL	1	-7
	INFECTION BIOPSY SITE	1	0
20523	MUSCLE CRAMPS	1	-49
20561	COUGHING UP BLOOD	1	-41
	BRUISE ON CHEST	1	-40
	CUT ON LEFT #2 FINGER	1	-40
	CUT ON LEFT ARM	1	-40
	FALL	2	-40
	HURT LEFT THUMB	1	-40
	SWOLLEN LIP	1	-40
	DECREASED APPETITE	1	-39
	INNER EAR INFECTION	2	-39
	NAUSEA	1	-39
	LEG CRAMPS	1	-32

Reference ID: 3068456

Subject	AE Term	TG	AE Start Date*
	BLEEDING AREA OF RIGHT CHEEK	1	-14
	WATERING OF LEFT EYE	1	-14
	BURNING SENSATION OF LIPS AND GUMS	3	-10
	SORENESS OF LIPS AND GUMS	3	-10
	NIGHTMARES	2	-9
	INCREASED NERVOUSNESS	2	-7
	DAILY HEADACHES	2	-6
20563	PUSUTULES ON BACK	1	-56
	LEG CRAMPS	1	-46
	DECREASED APPETITE	1	-41
	METALIC TASTE IN MOUTH	2	-41
20581	ALOPECIA	1	-63
	SORENESS AT TUMOR SITE	1	-63
	LEG CRAMPS	1	-32
	TASTE ALTERATION	1	-17
	INDIGESTION	1	-16
20583	NAUSEA	1	-55
	ANXIETY	1	-52
	ALOPECIA	1	-41
	VOMITING	1	-41
	COUGH	1	-13
	SINUS CONGESTION	1	-13
	SORE THROAT	1	-13
	TASTE ALTERATION	1	-13
	LEG CRAMPS	1	-8
20641	MUSCLE CRAMPS	1	-57
	DYSARTHRIA	1	-28
	TASTE ALTERATION	1	-28
20660	DEPRESSED MOOD	2	-56
	INCREASED FATIGUE	2	-56
	LOSS OF APPETITE	1	-56
	WEIGHT LOSS	1	-56
	TASTE CHANGES	1	-27
	CONJUNCTIVITIS	2	0
20781	FATIGUE	3	-89
	BASCAL CELL CARCINOMA ULCUS	1	-31
	CRAMPS IN THE FINGERS OF BOTH HANDS	1	0
20844	VIRAL MENINGITIS	4	-72
20846	FATIGUE	1	-86
	CONSTIPATION	1	-58
	LEG CRAMPS	1	-56
	JOINT PAIN	1	-14
	LOSS OF APETITE	1	-7
	DECREASE IN SENSE OF TASTE	1	0

Reference ID: 3068456

Subject	AE Term	TG	AE Start Date*
20847	HAIR LOSS	1	-83
	LEG AND FLANK CRAMPS	1	-54
	LOSS OF TASTE	1	-54
	WEIGHT LOSS	1	-28
	FATIGUE	1	-3
20921	GLOBAL HEART INSUFFIZIENZ	3	-66
	PNEUMONIA - INFECTION WITH UNKNOWN ANC	3	-66
	DIARRHEA INTERMITTENT	1	-57
	NAUSEA INTERMITTENT	1	-16
20923	LEG CRAMPS	1	-39
20925	HAIRLOSS HEAD AND EYEBROWS	1	-85
	PAIN HIP AND SHOULDER JOINTS	1	-85
	TASTE DISTURBANCE	1	-84
	CALF CRAMPS RIGHT AND LEFT LEG	1	-59
	FATIQUE	1	-2
20960	LOSS OF TASTE AND APPETITE	1	-31
	NAUSEA	1	-17
	CONSTIPATION	2	-16
	TIREDNESS	1	-7
20961	ACTINIC KERATOSIS	1	-84
	WRIST FRACTURE	2	-72
	DIARRHOEA	1	-17
21100	CONSTIPATION	1	-10
	INDIGESTION	2	-4
	INTERMITTANT HEADACHES	1	-2

*AE Start Date relative to discontinuation date
Abbreviations: AE = adverse event; TG = toxicity grade

Reviewer's comment: The majority of these subjects discontinued vismodegib for "subject decision to discontinue treatment." Most of the AEs in these subjects within 90 days of discontinuing vismodegib were Grade 1 or 2. The only Grade 3 or greater AEs within 30 days of discontinuation occurred in Subject 20651 who had Grade 3 burning sensation of lips and gums and soreness of lips and gums and discontinued vismodegib for "subject decision to discontinue treatment."

7.3.4 Significant Adverse Events

Infections and infestations: In the pooled safety database a total of 7 subjects experienced 7 infectious SAEs. In SHH4429g, a trial comparing vismodegib to placebo in subjects with metastatic ovarian cancer trial, only one subject, who received placebo, had an infectious SAE, a Grade 3 urinary tract infection. In addition the number of Infections and Infestations were the same in each arm, regardless of Grade. In SHH4489g, which combined placebo or vismodegib with FOLFOX/FOLFIRI plus bevacizumab in subjects with metastatic colon cancer, the applicant did not provide a AE dataset and the SHH4489g CSR contains SAE comparisons for

Reference ID: 3068456

events that occurred at ≥ 3 incidence. Pneumonia was the only infectious SAE occurring in 2 subjects in the placebo arm and 3 subjects in the vismodegib arm, one of which was fatal.

Reviewer's comment: The low rate of infectious SAEs in SHH4429 and SHH4489g and the small numerical difference between subject who received vismodegib compared to placebo suggests infectious SAEs may be related more to the underlying malignancy or factors other than vismodegib. Comparisons across trials should be considered exploratory and not definitive due to the differences in the trial designs, the small number of events, and the lack of internal control in the pooled safety population with BCC.

Thrombotic Events: In the pooled safety database a total of 4 subjects experienced 5 thrombotic events, 3 pulmonary embolism and 2 DVTs. In SHH4429g there were a total of 16 thrombotic events, 5 in the placebo arm and 11 in the vismodegib arm, Table 43.

Table 43: 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%)

In SHH4489g, one subject in the vismodegib arm (1/52, 1.9%) experienced a DVT and PE compared to none in the placebo arm (0/58).

Reviewer's comment: There were numerically more thrombotic events in the vismodegib arms in SHH4429g and SHH4489, but the differences in baseline malignancy, concomitant chemotherapy, and different baseline demographics, make interpretation of cross trial comparisons difficult.

Cardiac disorders: A total of five subjects experience a total of 7 cardiac SAEs in the pooled safety population. In SHH4429g, there were no cardiac SAEs that occurred at an incidence of ≥ 3, but one subject in the vismodegib arm died of "probable acute myocardial infarction." In SHH4489g, there were two Grade 3 cardiac SAEs, "cardiac failure congestive" and "chest pain," which both occurred in the vismodegib arm. No subject in SHH4489g died of a cardiac AE.

Reviewer's comment: The low numbers of total subjects and cardiac events in the placebo controlled trials and the different types of cardiac SAEs make it difficult to interpret the relationship between cardiac SAEs and vismodegib.

7.3.5 Submission Specific Primary Safety Concerns

A specific primary safety concern is the risk of vismodegib to a developing fetus. The applicant proposed (b) (4) The basis for the proposal comes from evidence that vismodegib, an inhibitor of the hedgehog pathway, was teratogenic, embryotoxic and fetotoxic in an embryo-fetal developmental toxicology study. Inhibitors of the

Reference ID: 3068456

hedgehog pathway, an essential pathway for embryogenesis and fetal development, are known to be teratogenic in multiple animal species often causing craniofacial malformations. In the embryo-fetal development toxicology study, vismodegib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 60 or 300 mg/kg/day, respectively. Doses of ≥ 60 mg/kg/day (≥ 2-fold the human exposure at the recommended dose of 150 mg/day base on AUC) resulted in 100% embryo-fetal lethality. Teratogenic findings at 10 mg/kg/day (corresponding to approximately 16% the human exposure at the recommended dose of 150 mg/day based on AUC) included absent and/or fused digits in 21/70 (30%) fetuses examined and identified in 4 of the 5 litters with additional findings of, open perineum (1 fetus) and multiple craniofacial anomalies (1 fetus). The incidence of retardations or variations (dilated renal pelvis, dilated ureter, incompletely or unossified sternal elements, centra of vertebrae or proximal phalanges and claws) was also increased at 10 mg/kg/day, which indicates fetal toxicity.

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

On October 20, 2011 FDA held a teleconference with the applicant (b) (4) (b) (4) FDA asked the applicant to (b) (4) (b) (4) (b) (4) address two issues: (*copied from meeting minutes with minor modifications*)

(b) (4)

The applicant agreed to address the above issues and re-examine their proposed (b) (4) (b) (4) On November 4, 2011, the applicant submitted a revised plan to address the risk of vismodegib to a developing fetus. The applicants (b) (4) proposed additional physician and patient educational efforts and pharmacovigilance: (*copied from submission with minor modifications*)

- To inform healthcare professionals (HCPs) and patients about the serious risks associated with vismodegib, including the risk of embryo-fetal and postnatal developmental toxicity.

Reference ID: 3068456

- To inform HCPs and patients about the importance of pregnancy prevention.
- To allow treatment of patients with severe and life-threatening disease for whom the benefits of therapy would outweigh the potential risks to a developing embryo/fetus.
- To collect information on pregnancy outcomes through routine pharmacovigilance

On November 18, 2011 the applicant submitted detailed revisions to the risk management plan

(b) (4)

On December 13, 2011, the FDA and the applicant held a teleconference to clarify the applicant's pharmacovigilance plan. FDA informed the applicant that the pregnancy pharmacovigilance plan would be conducted under a PMR and requested the applicant revise (b) (4) (b) (4). The applicant submitted their plan on January 4, 2011.

Overall Reviewer's comment: On December 9, 2011 the review team presented the vismodegib application in a regulatory briefing to discuss the risks of oncology drugs with respect to pregnancy labeling. Feedback from this discussion was not binding, but included support that the teratogenicity risk of vismodegib likely did not warrant a REMS and labeling and a medication guide would likely be sufficient to communicate the risk of teratogenicity.

Reference ID: 3068456

The REMS programs are intended to provide safeguards to permit approval of a drug, which absent a REMS, would not be approved because of the risk of the drug would outweigh the benefits. This reviewer finds that despite the serious nature of the teratogenic risk of vismodegib, a REMS should not be required for the following reasons:

1. *The standard of medical care in oncology when prescribing drugs like vismodegib provides adequate safe guards through the familiarity with the risk, risk communication, and patient monitoring. In the treatment of cancer, oncologist have a long history with administration of highly toxic and teratogenic drugs dating back to the 1940's. The assumption in oncology is that all oncology drugs are teratogenic and carry serious potential for risks if administered incorrectly. Oncologists who prescribe these drugs have completed specialized training that incorporates the administration of these drugs and the management of their toxicities. Oncologists discuss with their patients the side effects of chemotherapy and require patients sign informed consent in order to receive approved chemotherapy drugs outside of REMS programs. These risk discussions can include teratogenic risks and the impact on fertility such as those encountered in the treatment of breast cancer, testicular cancer, or Hodgkin's lymphoma.*
2. *Oncology drugs have a de facto limited distribution. Due to the side effects, cost, need for special pharmacists, and history of intravenous administration, oncology drugs have a de facto restricted distribution to oncologist and specialty pharmacies.*
3. *The risk of teratogenicity is common in oncology drugs and recent approvals have not required REMS with ETASU. A review of recent approvals of other oral drugs in the Office of Hematology and Oncology Products include several drugs (vandetanib, crizotinib, and vemurafenib) with similar teratogenic findings as those of vismodegib and do not have associated REMS for risks to embryo-fetal development or pregnancy.*
4. *Specific to the NDA 203388, the size of the population, duration of treatment, and lack of alternative therapies support a decision not to implement a REMS with ETASU. The indicated population of patients with BCC who are no longer candidates for surgery or radiation is small, estimated at 2300 cases per year in the United States. Of those 2300 patients, only ten percent (230 patients) is likely to be of child bearing potential. The duration of treatment is limited with a median of 10 months. There are currently no other available therapies for the proposed indication. A REMS program has the potential to limit access to vismodegib as most prescribing oncologists would not be expected to treat many patients with advanced BCC due to the small incidence and registration in a REMS program would likely be for a very small number of patients.*

For these reasons, this reviewer believes that a REMS with or without an ETASU is not necessary to communicate and mitigate the teratogenic risks of vismodegib (b) (4) *. The applicant's plan* (b) (4) *is adequate to communicate the teratogenic risks of vismodegib. For this reviewer's detailed recommendations* (b) (4) (b) (4) *see Section 9.*

Reference ID: 3068456

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This reviewer analyzed the safety databases of SHH4476g, SHH3925g, SHH4437g, SHH4610g, and SHH4489 as well as the ISS safety database (pooled from SHH4476g, SHH3925g, SHH4437g, and SHH4610g) at each level of the MedDRA hierarchy for common adverse events (AEs). In each of the tables below, this reviewer included subjects who received placebo from SHH4489g, a trial in subjects with ovarian cancer. *Reviewer's note: FDA previously agreed to use subjects from SHH4489 as part of the safety analysis and inclusion into the safety database submissions.*

For the adverse reactions table in the product labeling, this reviewer recommended the inclusion of adverse reactions reported in at least 10% of subjects who received vismodegib. Adverse reactions meeting these criteria were muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, nausea, diarrhea, decreased appetite, constipation, cough, arthralgias, vomiting, headache, ageusia, insomnia, upper respiratory tract infection.

Table 44 contains all treatment emergent AEs, at the preferred term (PT) level, occurring at an incidence rate greater than 5% in for the pooled population (N=138), including SHH3925.

Table 44: All TEAEs by PT (per subject incidence of ≥5%)

Adverse Event	All AEs	All%	G3-4 AEs	G3-4 AEs%
MUSCLE SPASMS	99	71.7%	5	3.6%
ALOPECIA	88	63.8%	0	0.0%
DYSGEUSIA	76	55.1%	0	0.0%
WEIGHT DECREASED	62	44.9%	10	7.2%
FATIGUE	55	39.9%	8	5.8%
NAUSEA	42	30.4%	1	0.7%
DIARRHOEA	40	29.0%	1	0.7%
DECREASED APPETITE	35	25.4%	3	2.2%
CONSTIPATION	29	21.0%	0	0.0%
COUGH	26	18.8%	0	0.0%
ARTHRALGIA	22	15.9%	1	0.7%
VOMITING	19	13.8%	0	0.0%
HEADACHE	18	13.0%	0	0.0%
AGEUSIA	15	10.9%	0	0.0%
INSOMNIA	15	10.9%	0	0.0%
UPPER RESPIRATORY TRACT INFECTION	14	10.1%	0	0.0%
DYSPEPSIA	13	9.4%	0	0.0%
PRURITUS	13	9.4%	0	0.0%
DYSPNOEA	12	8.7%	3	2.2%
HYPOGEUSIA	12	8.7%	0	0.0%
NASOPHARYNGITIS	12	8.7%	0	0.0%

Reference ID: 3068456

Adverse Event	All AEs	All%	G3-4 AEs	G3-4 AEs%
PAIN	12	8.7%	2	1.4%
PAIN IN EXTREMITY	12	8.7%	1	0.7%
ANXIETY	11	8.0%	0	0.0%
ASTHENIA	11	8.0%	2	1.4%
BACK PAIN	11	8.0%	1	0.7%
ERYTHEMA	11	8.0%	0	0.0%
RASH	11	8.0%	0	0.0%
SQUAMOUS CELL CARCINOMA	11	8.0%	2	1.4%
ANAEMIA	9	6.5%	0	0.0%
DEPRESSION	9	6.5%	0	0.0%
DRY SKIN	9	6.5%	0	0.0%
FLATULENCE	9	6.5%	0	0.0%
MUSCULOSKELETAL CHEST PAIN	9	6.5%	0	0.0%
OEDEMA PERIPHERAL	9	6.5%	1	0.7%
RHINORRHOEA	9	6.5%	0	0.0%
ABDOMINAL PAIN UPPER	8	5.8%	0	0.0%
MYALGIA	8	5.8%	0	0.0%
PARAESTHESIA	8	5.8%	0	0.0%
ABDOMINAL PAIN	7	5.1%	0	0.0%
CHEST PAIN	7	5.1%	0	0.0%
DIZZINESS	7	5.1%	0	0.0%
DYSPHAGIA	7	5.1%	0	0.0%
HYPOAESTHESIA	7	5.1%	0	0.0%
HYPOKALAEMIA	7	5.1%	1	0.7%
RHINITIS	7	5.1%	0	0.0%
URINARY TRACT INFECTION	7	5.1%	2	1.4%

Abbreviations: AE = adverse events; G = grade

The most common Grade 3 or greater AEs were weight decreased, fatigue, muscle spasms, and dysgeusia, which are among the most common TEAEs in pooled safety population. *Reviewer's note: There is no Grade 3 alopecia.*

Table 45 contains the most common AEs in the fifty two subjects who received vismodegib in SHH4489g compared to the fifty two subjects who received placebo.

Table 45: Most Common (≥ 10%) AEs in SHH4489g

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%**
FATIGUE	15	14	27%	6	12%
CONSTIPATION	**5**	**12**	**23%**	-	**0%**
ABDOMINAL PAIN	**7**	**10**	**19%**	**5**	**10%**

Reference ID: 3068456

Adverse Events 4489	Placebo	Vismodegib		Vismodegib	
	N= 52	N = 52	All AEs%	AEs G3-4	AEs G3-4 %
DECREASED APPETITE	**1**	**10**	**19%**	**5**	**10%**
ABDOMINAL PAIN UPPER	**3**	**9**	**17%**	**4**	**8%**
VOMITING	**5**	**8**	**15%**	**4**	**8%**
ARTHRALGIA	8	8	15%	1	2%
DIARRHOEA	8	6	12%	2	4%
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%**
COUGH	5	5	10%	4	8%
MUSCULOSKELETAL PAIN	**3**	**5**	**10%**	**2**	**4%**
HEADACHE	6	5	10%	2	4%

Bolded Terms indicate a numerically higher incidence subjects who received vismodegib compared to placebo.
Abbreviations: AE = adverse events; G = grade

The most common AEs in SHH4489g were similar to the most common AEs in the pooled safety population, including Grade 3 or 4 events. "Muscle spasms," "dysgeusia," "alopecia," "weight decreased," "nausea," "decreased appetite," "constipation," and "vomiting" were the most common AEs in both the pooled safety population and were more common in subjects who received vismodegib when compared to placebo in SHH4489. The terms "fatigue," "cough," "arthralgias," and "headache" were not more common in subjects who received vismodegib when compared to placebo in SHH4489. *Reviewer's comment: Analysis from SHH4489 is suggestive that fatigue, cough, arthralgias, and headache may not be directly related to vismodegib, but since SHH3925, SHH4433, SHH4476, and SHH4610g did not contain internal controls there is no reliable way to make that determination. The applicant did not include* [redacted] (b) (4)*, or arthralgias* [redacted] (b) (4) *of the proposed* [redacted] (b) (4) *for vismodegib, but did include fatigue which they state may be related to the mechanism of action of vismodegib.*

Table 46 contains TEAEs (≥5%)by high level term (HLT) for the pooled safety population.

Table 46: Table 28: All TEAEs by HLT (per subject incidence of ≥5%)

High Level Term	All AEs	All%	G3-4 AEs	G3-4 AEs%
MUSCLE RELATED SIGNS AND SYMPTOMS NEC	99	71.7%	5	3.6%
SENSORY ABNORMALITIES NEC	98	71.0%	0	0.0%
ALOPECIAS	92	66.7%	0	0.0%
ASTHENIC CONDITIONS	63	45.7%	10	7.2%
PHYSICAL EXAMINATION PROCEDURES	63	45.7%	10	7.2%
NAUSEA AND VOMITING SYMPTOMS	47	34.1%	1	0.7%
DIARRHOEA (EXCL INFECTIVE)	40	29.0%	1	0.7%
APPETITE DISORDERS	37	26.8%	3	2.2%

High Level Term	All AEs	All%	G3-4 AEs	G3-4 AEs%
UPPER RESPIRATORY TRACT INFECTIONS	35	25.4%	1	0.7%
MUSCULOSKELETAL AND CONNECTIVE TISSUE PAIN AND DISCOMFORT	34	24.6%	2	1.4%
COUGHING AND ASSOCIATED SYMPTOMS	32	23.2%	0	0.0%
GASTROINTESTINAL ATONIC AND HYPOMOTILITY DISORDERS NEC	31	22.5%	1	0.7%
JOINT RELATED SIGNS AND SYMPTOMS	26	18.8%	1	0.7%
UPPER RESPIRATORY TRACT SIGNS AND SYMPTOMS	21	15.2%	0	0.0%
PAIN AND DISCOMFORT NEC	20	14.5%	2	1.4%
HEADACHES NEC	19	13.8%	0	0.0%
INFECTIONS NEC	17	12.3%	0	0.0%
DERMAL AND EPIDERMAL CONDITIONS NEC	17	12.3%	0	0.0%
DISTURBANCES IN INITIATING AND MAINTAINING SLEEP	15	10.9%	0	0.0%
PRURITUS NEC	15	10.9%	0	0.0%
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	14	10.1%	0	0.0%
ANXIETY SYMPTOMS	14	10.1%	0	0.0%
RASHES, ERUPTIONS AND EXANTHEMS NEC	14	10.1%	0	0.0%
DYSPEPTIC SIGNS AND SYMPTOMS	13	9.4%	0	0.0%
FLATULENCE, BLOATING AND DISTENSION	13	9.4%	0	0.0%
BREATHING ABNORMALITIES	13	9.4%	3	2.2%
GENERAL SIGNS AND SYMPTOMS NEC	12	8.7%	1	0.7%
NEOPLASMS MALIGNANT SITE UNSPECIFIED NEC	12	8.7%	2	1.4%
ERYTHEMAS	12	8.7%	0	0.0%
GASTROINTESTINAL SIGNS AND SYMPTOMS NEC	11	8.0%	1	0.7%
BACTERIAL INFECTIONS NEC	11	8.0%	2	1.4%
SKIN STRUCTURES AND SOFT TISSUE INFECTIONS	11	8.0%	0	0.0%
PARAESTHESIAS AND DYSAESTHESIAS	11	8.0%	1	0.7%
ANAEMIAS NEC	10	7.2%	0	0.0%
OEDEMA NEC	10	7.2%	1	0.7%
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	9	6.5%	4	2.9%
NEUROLOGICAL SIGNS AND SYMPTOMS NEC	9	6.5%	2	1.4%
DEPRESSIVE DISORDERS	9	6.5%	0	0.0%
APOCRINE AND ECCRINE GLAND DISORDERS	9	6.5%	1	0.7%
PILAR DISORDERS NEC	9	6.5%	0	0.0%
ORAL DRYNESS AND SALIVA ALTERED	8	5.8%	0	0.0%
FEELINGS AND SENSATIONS NEC	8	5.8%	0	0.0%
URINARY TRACT INFECTIONS	8	5.8%	2	1.4%
SKIN INJURIES NEC	8	5.8%	0	0.0%
POTASSIUM IMBALANCE	8	5.8%	1	0.7%
MUSCLE PAINS	8	5.8%	0	0.0%
BLADDER AND URETHRAL SYMPTOMS	8	5.8%	0	0.0%
BRONCHOSPASM AND OBSTRUCTION	8	5.8%	0	0.0%

Reference ID: 3068456

High Level Term	All AEs	All%	G3-4 AEs	G3-4 AEs%
ACNES	8	5.8%	0	0.0%
INNER EAR SIGNS AND SYMPTOMS	7	5.1%	1	0.7%
EYE AND EYELID INFECTIONS	7	5.1%	0	0.0%
BONE RELATED SIGNS AND SYMPTOMS	7	5.1%	0	0.0%

Abbreviations: AE = adverse events; G = grade

Asthenic conditions combines the PTs "fatigue" and "asthenia," but the overall percentage of the HLT asthenic conditions NEC is not notably different than the PT "fatigue." *Reviewer's comment: This reviewer does not recommend combining the terms fatigue and asthenia under the HLT asthenic conditions to put in the label as the percentage difference does not appear to be large and the comparison to subjects in SHH4489 indicates that the background incidence of fatigue in an advanced cancer population is high; see above comment under PT analysis.*

Sensory Abnormalities consists of several different lower level terms (LLT), the most common being *dysgeusia*, *taste alteration*, *loss of taste* , *taste diminished*, *tasted altered*, *taste changed*, and *taste metallic*. *Reviewer's comment: This reviewer recommends using the PT dysgeusia at the incidence in Table 44 which captures the adverse reaction appropriately.*

Table 47 contains all TEAEs by high level group term (HLGT) for the pooled safety population.

Table 47 All TEAEs by HLGT (per subject incidence of ≥5%)

High Level Group Term	All AEs	All%	G3-4 AEs	G3-4 AEs%
NEUROLOGICAL DISORDERS NEC	105	76.1%	4	2.9%
MUSCLE DISORDERS	102	73.9%	6	4.3%
SKIN APPENDAGE CONDITIONS	100	72.5%	1	0.7%
GENERAL SYSTEM DISORDERS NEC	76	55.1%	13	9.4%
GASTROINTESTINAL SIGNS AND SYMPTOMS	70	50.7%	2	1.4%
INFECTIONS - PATHOGEN UNSPECIFIED	69	50.0%	8	5.8%
PHYSICAL EXAMINATION TOPICS	63	45.7%	10	7.2%
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	61	44.2%	2	1.4%
RESPIRATORY DISORDERS NEC	49	35.5%	3	2.2%
EPIDERMAL AND DERMAL CONDITIONS	44	31.9%	0	0.0%
APPETITE AND GENERAL NUTRITIONAL DISORDERS	37	26.8%	3	2.2%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	34	24.6%	2	1.4%
JOINT DISORDERS	28	20.3%	1	0.7%
HEADACHES	19	13.8%	0	0.0%
BACTERIAL INFECTIOUS DISORDERS	16	11.6%	2	1.4%
ELECTROLYTE AND FLUID BALANCE CONDITIONS	16	11.6%	6	4.3%
SLEEP DISORDERS AND DISTURBANCES	16	11.6%	0	0.0%
INJURIES NEC	14	10.1%	1	0.7%
ANXIETY DISORDERS AND SYMPTOMS	14	10.1%	0	0.0%

Reference ID: 3068456

High Level Group Term	All AEs	All%	G3-4 AEs	G3-4 AEs%
UPPER RESPIRATORY TRACT DISORDERS (EXCL INFECTIONS)	13	9.4%	0	0.0%
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLASMS MALIGNANT AND UNSPECIFIED	12	8.7%	2	1.4%
ORAL SOFT TISSUE CONDITIONS	11	8.0%	1	0.7%
ANAEMIAS NONHAEMOLYTIC AND MARROW DEPRESSION	10	7.2%	0	0.0%
OCULAR INFECTIONS, IRRITATIONS AND INFLAMMATIONS	10	7.2%	2	1.4%
BONE AND JOINT INJURIES	10	7.2%	1	0.7%
DEPRESSED MOOD DISORDERS AND DISTURBANCES	10	7.2%	0	0.0%
URINARY TRACT SIGNS AND SYMPTOMS	10	7.2%	0	0.0%
CARDIAC ARRHYTHMIAS	9	6.5%	1	0.7%
EYE DISORDERS NEC	9	6.5%	0	0.0%
VISION DISORDERS	9	6.5%	0	0.0%
FUNGAL INFECTIOUS DISORDERS	9	6.5%	0	0.0%
BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)	9	6.5%	0	0.0%
SALIVARY GLAND CONDITIONS	8	5.8%	0	0.0%
VIRAL INFECTIOUS DISORDERS	8	5.8%	1	0.7%
BRONCHIAL DISORDERS (EXCL NEOPLASMS)	8	5.8%	0	0.0%
INNER EAR AND VIIITH CRANIAL NERVE DISORDERS	7	5.1%	1	0.7%
CRANIAL NERVE DISORDERS (EXCL NEOPLASMS)	7	5.1%	0	0.0%

Abbreviations: AE = adverse events; G = grade

Skin appendage conditions appears more frequently in the HLGT analysis, which mainly consists of the PT *alopecia.*

Table 48 contains all TEAEs by System Organ Class (SOC) for the pooled safety population.

Table 48: All TEAE by SOC

System Organ Class	All AEs	All%	G3-4 AEs	G3-4 AEs%
NERVOUS SYSTEM DISORDERS	109	79.0%	4	2.9%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	109	79.0%	1	0.7%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	108	78.3%	9	6.5%
GASTROINTESTINAL DISORDERS	103	74.6%	7	5.1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	79	57.2%	13	9.4%
INFECTIONS AND INFESTATIONS	78	56.5%	11	8.0%
INVESTIGATIONS	70	50.7%	15	10.9%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	60	43.5%	5	3.6%
METABOLISM AND NUTRITION DISORDERS	50	36.2%	10	7.2%

Reference ID: 3068456

System Organ Class	All AEs	All%	G3-4 AEs	G3-4 AEs%
PSYCHIATRIC DISORDERS	33	23.9%	1	0.7%
EYE DISORDERS	30	21.7%	2	1.4%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	25	18.1%	2	1.4%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	25	18.1%	7	5.1%
VASCULAR DISORDERS	24	17.4%	5	3.6%
CARDIAC DISORDERS	14	10.1%	4	2.9%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	12	8.7%	1	0.7%
RENAL AND URINARY DISORDERS	12	8.7%	1	0.7%
EAR AND LABYRINTH DISORDERS	11	8.0%	1	0.7%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6	4.3%	0	0.0%
HEPATOBILIARY DISORDERS	2	1.4%	2	1.4%
IMMUNE SYSTEM DISORDERS	2	1.4%	0	0.0%
ENDOCRINE DISORDERS	1	0.7%	0	0.0%
SOCIAL CIRCUMSTANCES	1	0.7%	1	0.7%

Abbreviations: AE = adverse events; G = grade

The most common SOCs were Nervous System Disorders and Skin and Subcutaneous Tissue Disorders. The most common Grade 3 or 4 SOC AEs were investigation, representing lab abnormalities, see Section 7.4.2.

7.4.2 Laboratory Findings

The ISS ADLBSI dataset contained only serum chemistry parameters and only values collected on scheduled study visits. The ALBSI datasets for SHH4476g, SHH3925g, SHH4610g contained both serum chemistry and hematology parameters. All three trials (4476g, 3925g, and 4610g) collected laboratory parameters every 4 weeks and at end of trial visit. Shift tables below show per-patient incidence rates of worsening laboratory values during the trials and show the pooled population. The shifts correspond to baseline NCI CTCAE grade to worse post-baseline NCI CTCAE. *Reviewer's comment: The number differ slightly from the applicant as this reviewer did not exclude subjects with at least one baseline value or sort by direction (high or low) for sodium and potassium, neither of which affect the most important changes from < Grade 3 to ≥ Grade 3.*

Table 49 shows shifts from baseline toxicology Grade to highest toxicology Grade on a per subject basis. There were no Grade 4 laboratory toxicities based on screening visit laboratories 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%)

Reference ID: 3068456

Table 49: Shift Table for Serum Chemistries

Baseline Toxicology Grade	Max Toxicology Grade			
	0	1	2	3
Sodium				
0	80	37	0	**5**
1	0	13	0	**1**
2	0	0	0	**0**
3	0	0	0	**0**
Potassium				
0	82	36	6	**2**[a]
1	0	7	1	**1**
2	0	0	1	**0**
3	0	0	0	**0**
Magnesium				
0	94	32	0	**1**
1	0	4	0	**0**
2	0	0	1	**0**
3	0	0	0	**0**
Creatinine				
0	109	13	1	**0**
1	0	7	4	**0**
2	0	0	2	**0**
3	0	0	0	**0**
BUN				
0	87	24	3	**1**
1	0	9	4	**1**
2	0	0	3	**1**
3	0	0	0	**1**
Bilirubin				
0	122	9	1	**0**
1	0	1	0	**0**
2	0	0	1	**1**
3	0	0	0	**0**
Alk Phos				
0	100	15	1	**1**
1	0	14	3	**0**
2	0	0	1	**0**
3	0	0	0	**1**
ALT				
0	106	18	4	**1**
1	0	3	1	**0**
2	0	0	2	**0**
3	0	0	0	**0**
AST				
0	95	30	3	**0**
1	0	6	1	**0**

Reference ID: 3068456

Baseline Toxicology Grade	Max Toxicology Grade			
	0	1	2	3
2	0	0	0	0
3	0	0	0	0

[a] One hypokalemia and one hyperkalemia

Error! Reference source not found. contains a listing of all the Grade 3 laboratory abnormalities from the most common Grade 3 lab abnormality to the least common, by subject.

Table 50: Grade 3 Lab Abnormalities from SHH4476g with baseline Toxicity Grade

Lab	Subject	Baseline Lab Toxicity Grade	Max Lab Toxicity Grade
Glucose	20560	1	3
	20562	0	3[a]
	21100	3	3
	20603	2	3
BUN	20762	1	3
	20763	2	3
	20821	0	3
	20545	3	3
Sodium	20583	0	3
	20504	0	3
	20721	0	3
	20844	0	3
Lymphocyte	20681	2	3
	20740	3	3
	20700	3	3
	20660	0	3
Albumin	20860	3	3
	20861	3	3
	20862	3	3
Potassium	20521	0	3
	20842	1	3
Alk Phos	20802	0	3
ALT	20802	0	3
Magnesium	20780	0	3
Hemoglobin	20545	2	3
Urine Protein	20640	3	3

[a] Grade 3 hypoglycemia
Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; BUN = blood urea nitrogen

The applicant did not submit a separate lab data set for SHH4610g or SHH4437g.

Reference ID: 3068456

7.4.3 Vital Signs

SHH4476g measured vitals signs every 4 weeks and at end of study visit. SHH3925g measured vital signs every two weeks and at end of study visit. The applicant did not submit a dataset containing vital signs for the single BCC subject from SHH4610g.

Temperature: On one subject, 20980, in SHH4476g developed a temperature of ≥ 38 degrees Celsius at week 16 visit. No subject on SHH3925g had an elevated temperature.

Hypotension: Nine subjects in SHH4476g experienced systolic blood pressure less than 90 mm Hg during the conduct of SHH4476g. Of these nine subjects, three subjects (20504, 20720, 20660) also experienced tachycardia (heart rate ≥ 100 beats per minute) The ISS ADAE dataset recorded Subject 20720 as having two Grade 2 AEs of hypotension and recorded Subject 20660 as having one Grade 1 event of tachycardia.

Hypertension: In SHH4476g, A total of 45 subjects experienced at least one episode of hypertension with a systolic blood pressure (SBP) > 150 mmHg. Of those 45 subjects, at total of 29/104 (28%) did not have a SBP greater than 150 mm/Hg at the time of the screening visit. Of these instances of hypertension, investigators deemed 2 subjects as having hypertension related AEs, both Grade 2. In SHH3925g, a total of 19 subjects experienced at least one episode of hypertension. A total of 13/33 (40%) subjects did not have a SBP > 150 mm Hg at the time of screening visit. Of these instances of hypertension, investigators deemed 3 subjects as having hypertension related AEs, two Grade 2 and one Grade 3 events. In SHH4489g, a total of 13/104 (13%) subjects had a SBP greater than 150 mm/Hg that was not present at their screening visit; 5 subjects received vismodegib compared to 8 who received placebo. *Reviewer's comment: The comparison of subjects with hypertension in SHH4489g suggests the higher incidence of hypertension in SHH4476g and SHH3925g may be due to factors other than vismodegib.*

Weight: Weight decreased was the fourth most common AE in the ISS pooled population occurring in 48% of subjects (for any Grade) and 7% (10/138) of the subjects had Grade 3 weight loss, Table 51. CTCAE Grade 3 weight loss is ≥ 20% loss from baseline or tube feeding or total parenteral nutrition indicated.

Table 51: Subjects with Grade 3 Weight Decrease

Subject	Baseline (kg)	Min (kg)	Difference	Final (kg)	Notes
12111	98.7	91.4	7.4%	91.4	AE not in CRF, Grade 2 Ageusia; Grade 1 Hypogeusia
13005	98	78.2	20.2%	83.8	Dose held: no taste related AEs
13105	85.1	69.8	18.0%	69.8	No CRF; Grade 2 Dysgeusia
13111	79.8	76.9	3.6%	80	AE not in CRF; no taste related AEs
13117	93.7	81.4	13.1%	83.9	AE in CRF Grade 2; no taste related AEs
20506	101.1	77.36	23.5%	77.36	Continued vismodegib: Grade 1 Hypogeusia
20621	83.91	56.2	33.0%	57.2	Continued vismodegib; no taste related AEs

Reference ID: 3068456

Subject	Baseline (kg)	Min (kg)	Difference	Final (kg)	Notes
20763	70	52.3	25.3%	54	Continued vismodegib; Grade 2 Dysgeusia
20800	63.5	49.6	21.9%	49.9	Continued vismodegib; Grade 2 Ageusia
20920	85	74	12.9%	76	AE not in CRF; Grade 1 Dysgeusia

Of the ten subjects with Grade 3 weight loss, only five had 20% or greater weight loss from baseline.

Reviewer's comment: The CRFs and narratives did not contain specific information for subjects with less than 20% loss to determine whether or not the subject required supplemental feedings. Six of the ten subject had taste related AEs, which may be one contributing factor to weigh loss. The applicant provided information on the severity of weight after FDA asked the applicant to confirm the severity in these 10 subjects: (copied with minor modifications from December 21, 2011 email)

> *Genentech left this number at "10" since that is what was reported by investigators. However, the requested data are as follows:*
>
> *Three of these [subjects] do not have documented decrease of 20% or more from baseline. [Subjects] 20920 and 13111 have weight measurements before and after or on the same date as the reported AE. [Subject] 13105 is missing weight at the date of AE and does not have weight recorded thereafter. However, [the subject] continued on treatment for another 2 months. The month before reporting G3 weight loss, the patient had an 18% decrease in weight.*

The applicant did not propose to change the number of Grade 3 weight loss AEs in the proposed (b) (4) *which is appropriate as the severity of weight loss could not be confirmed and 10 represents what was reported by investigators.*

7.4.4 Electrocardiograms (ECGs)

The applicant submitted SHH4683g, a phase 1, single-center, three-arm, randomized, double-blind, active- and placebo-controlled trial evaluating the effect of vismodegib on the QT/QTc interval. Subjects were healthy female subjects of non-childbearing potential. The applicant reported that there were no "changes or trends of clinical significance for the heart rate, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval."

7.4.5 Special Safety Studies/Clinical Trials

There was no separate "special" safety study submitted to the NDA.

7.4.6 Immunogenicity

Vismodegib is a small molecule and not expected to illicit immunogenicity.

Reference ID: 3068456

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A formal analysis of dose dependency for adverse events was not possible. All subjects SHH4476g received the same dose of vismodegib. Subjects in SHH3925g received either 150 mg or 270 mg, but there were too few at each dose level to conduct any formal comparisons.

7.5.2 Time Dependency for Adverse Events

The median start day for TEAE in the pooled ISS AE data base was Day 126 (range 1-783) and the mean start day was 153 (SD 125), Figure 12 and Table 52.

Figure 12: AE Count By Relative AE Start Date

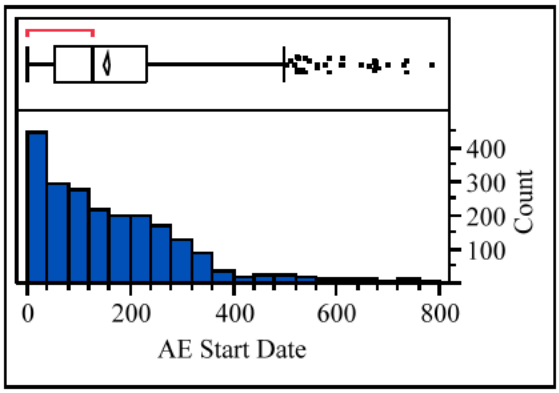


Table 52: TEAE Statistics

TEAE Statistics	
Median	126
Maximum	783
Minimum	1
Mean	153.86
Standard Deviation	125.29

Table 53 shows the relative TEAE start date by toxicology Grade.

Table 53: Median AE Start Date by Toxicity Grade

AE Toxicity Grade	Median Start Date
1	113
2	154
3	156
4	155
5	261.5

For the median AE start date for dysgeusia was 65.5 days, muscle spasms or cramps was 113 days, and alopecia was 119.5 days, which are all slightly less than the median start days for all AEs.

Reference ID: 3068456

7.5.3 Drug-Demographic Interactions

Race: All the subjects in the pooled safety population were White and thus explorations of differences in AEs based on race is not possible.

Gender: Table 54 shows the incidence of AEs by PT and by gender for AEs where there was a 5% or greater difference between genders, sorted by female > male difference to male > female difference. Most AEs had similar per-patient incidence rates between genders. Women had a higher rate of anemia, amenorrhea, urinary tract infections, nausea, vomiting, diarrhea, decreased appetite, and pain in extremity. Men had a higher rate constipation, flatulence, dizziness, dyspnea, cough, dry skin, musculoskeletal chest pain, acne, hair growth abnormal, weight decreased, back pain, rash, squamous cell carcinoma, parathesia, arthralgia, hyponatremia, pain in jaw. As the pooled safety population did not have an internal control, such comparisons should be considered exploratory. There were not large differences observed in the per-patient incidence of ≥ Grade 3 events.

Table 54: Adverse Event by Gender with Differences ≥ 5%

Adverse Event	Female AG%	Female ≥ G3 AE %	Male AG%	Male ≥ G3 AE %	Difference
	N=49		N=89		
CONSTIPATION	14.3%	0.0%	24.7%	0.0%	-10.4%
FLATULENCE	0.0%	0.0%	10.1%	0.0%	-10.1%
DIZZINESS	0.0%	0.0%	7.9%	0.0%	-7.9%
DYSPNOEA	4.1%	0.0%	11.2%	3.4%	-7.2%
COUGH	14.3%	0.0%	21.3%	0.0%	-7.1%
DRY SKIN	2.0%	0.0%	9.0%	0.0%	-6.9%
MUSCULOSKELETAL CHEST PAIN	2.0%	0.0%	9.0%	0.0%	-6.9%
ACNE	0.0%	0.0%	6.7%	0.0%	-6.7%
HAIR GROWTH ABNORMAL	0.0%	0.0%	6.7%	0.0%	-6.7%
WEIGHT DECREASED	40.8%	4.1%	47.2%	9.0%	-6.4%
BACK PAIN	4.1%	0.0%	10.1%	1.1%	-6.0%
RASH	4.1%	0.0%	10.1%	0.0%	-6.0%
SQUAMOUS CELL CARCINOMA	4.1%	2.0%	10.1%	1.1%	-6.0%
PARAESTHESIA	2.0%	0.0%	7.9%	0.0%	-5.8%
ARTHRALGIA	12.2%	2.0%	18.0%	0.0%	-5.7%
HYPONATRAEMIA	0.0%	0.0%	5.6%	4.5%	-5.6%
PAIN IN JAW	0.0%	0.0%	5.6%	0.0%	-5.6%
ANAEMIA	10.2%	0.0%	4.5%	0.0%	5.7%
AMENORRHOEA	6.1%	0.0%	0.0%	0.0%	6.1%
ERYTHEMA	12.2%	0.0%	5.6%	0.0%	6.6%
URINARY TRACT INFECTION	10.2%	2.0%	2.2%	1.1%	8.0%
NAUSEA	36.7%	2.0%	27.0%	0.0%	9.8%
VOMITING	20.4%	0.0%	10.1%	0.0%	10.3%

Reference ID: 3068456

Adverse Event	Female AG%	Female ≥ G3 AE %	Male AG%	Male ≥ G3 AE %	Difference
	N=49		N=89		
DIARRHOEA	36.7%	2.0%	24.7%	0.0%	12.0%
DECREASED APPETITE	34.7%	4.1%	20.2%	1.1%	14.5%
PAIN IN EXTREMITY	18.4%	2.0%	3.4%	0.0%	15.0%

Difference with negative values represent AEs with a greater incidence in males compared to females; differences with positive values represent AEs with a greater incidence in females compared to males.
Abbreviations: AE = adverse event; AG = all Grades; G = grade

Age: A total of 54/138 (39%) subjects of the pooled safety population was ≥ 65 years in age. Because the total number of patients ≥ 65 years of age was less than 100 (and because there was no comparison to an internal control in the pooled safety population), no definitive conclusions can be made regarding the safety of vismodegib in older patients. Table 55 shows an exploratory analysis of AEs by MedDRA PT in subjects 65 years or older compared to subjects younger than 65, sorted by AE difference. Subjects < 65 had more alopecia, cough, musculoskeletal chest pain, muscle spasms, hypokalemia, nasopharyngitis, diarrhea, upper respiratory tract infection, nausea, acne, erythema, parathesia, hypomagnesemia, influenza, productive cough, sinus congestion, wheezing, insomnia, and dysphagia. Subjects ≥ 65 had more dehydration, asthenia, rash, hemorrhage, squamous cell carcinoma, constipation, weight decreased, and decreased appetite.

Table 55: Adverse Event by Age Group with Differences ≥ 5%

Adverse Event	< 65 AG%	<65 ≥ G3%	≥ 65 AG%	≥ 65 ≥ G3%	Difference
	N=84		N=54		
ALOPECIA	75.0%	0.0%	48.1%	0.0%	26.9%
COUGH	23.8%	0.0%	11.1%	0.0%	12.7%
MUSCULOSKELETAL CHEST PAIN	10.7%	0.0%	0.0%	0.0%	10.7%
MUSCLE SPASMS	76.2%	3.6%	66.7%	3.7%	9.5%
HYPOKALAEMIA	8.3%	1.2%	0.0%	0.0%	8.3%
NASOPHARYNGITIS	11.9%	0.0%	3.7%	0.0%	8.2%
DIARRHOEA	32.1%	1.2%	24.1%	0.0%	8.1%
UPPER RESPIRATORY TRACT INFECTION	13.1%	0.0%	5.6%	0.0%	7.5%
NAUSEA	33.3%	1.2%	25.9%	0.0%	7.4%
ACNE	7.1%	0.0%	0.0%	0.0%	7.1%
FOLLICULITIS	7.1%	0.0%	0.0%	0.0%	7.1%
PYREXIA	7.1%	1.2%	0.0%	0.0%	7.1%
ERYTHEMA	10.7%	0.0%	3.7%	0.0%	7.0%
PARAESTHESIA	8.3%	0.0%	1.9%	0.0%	6.5%
HYPOMAGNESAEMIA	6.0%	0.0%	0.0%	0.0%	6.0%
INFLUENZA	6.0%	0.0%	0.0%	0.0%	6.0%
PRODUCTIVE COUGH	6.0%	0.0%	0.0%	0.0%	6.0%
SINUS CONGESTION	6.0%	0.0%	0.0%	0.0%	6.0%
WHEEZING	6.0%	0.0%	0.0%	0.0%	6.0%
INSOMNIA	13.1%	0.0%	7.4%	0.0%	5.7%

Adverse Event	< 65 AG%	<65 ≥ G3%	≥ 65 AG%	≥ 65 ≥ G3%	Difference
	N=84		N=54		
DYSPHAGIA	7.1%	0.0%	1.9%	0.0%	5.3%
DEHYDRATION	2.4%	1.2%	7.4%	1.9%	-5.0%
ASTHENIA	6.0%	0.0%	11.1%	3.7%	-5.2%
RASH	6.0%	0.0%	11.1%	0.0%	-5.2%
HAEMORRHAGE	0.0%	0.0%	5.6%	1.9%	-5.6%
SQUAMOUS CELL CARCINOMA	4.8%	2.4%	13.0%	0.0%	-8.2%
CONSTIPATION	16.7%	0.0%	27.8%	0.0%	-11.1%
WEIGHT DECREASED	40.5%	4.8%	51.9%	11.1%	-11.4%
DECREASED APPETITE	20.2%	1.2%	33.3%	3.7%	-13.1%

Abbreviations: AE = adverse event; AG = all Grades; G = grade

Reviewer's note: These age and sex comparisons should be considered exploratory and limited by the small number of subjects.

7.5.4 Drug-Disease Interactions

None

7.5.5 Drug-Drug Interactions

On December 6, 2011, the applicant submitted an interim report for Study CSS SHH4593g a phase 1b PK DDI study with vismodegib and rosiglitazone or combined oral contraceptive in subjects with laBCC or mBCC. The applicant concluded in the interim CSR, "Overall, the results from this study 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. Rosiglitazone and ethinyl estradiol exposure were unchanged and a trend for increased exposure to norethindrone was observed with vismodegib co-administration. The latter result is the opposite of an enzyme induction-mediated effect, thereby demonstrating that the efficacy of oral contraceptives would not be compromised by co-administration of vismodegib." See clinical pharmacology review for full discussion.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant submitted results of GLP genetic toxicology studies that consisted of *in vitro* (with and without metabolic activation) and *in vivo* systems. The applicant claimed that "vismodegib did not induce mutagenic or clastogenic responses in a *Salmonella typhimurium/Escherichia coli* reverse mutation assay (Study 05-1451), a chromosome aberration assay in human peripheral blood lymphocytes (Study 05-1452), or a rat micronucleus assay (Study 05-1453)."

Reference ID: 3068456

7.6.2 Human Reproduction and Pregnancy Data

The applicant did not submit formal studies of vismodegib in pregnant or breastfeeding women. The applicant excluded pregnant subjects from receiving vismodegib and required two forms of birth control and a separate informed consent due to the findings of teratogenic effects in animals in pre-clinical testing.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant has not conducted clinical studies with vismodegib in children. The only data comes from a single subject who received vismodegib for medulloblastoma. Data from studies in animals suggest that the use of vismodegib results in irreversible alteration/loss of incisors (erupting teeth) and closure of the femoral epiphysis (growth plate) in rats (Study 07-1224). (b) (4) [redacted] The FDA Pediatric Review Committee (PeRC) granted a full waiver for vismodegib for studies required under PREA (Pediatric Research Equity Act) because the disease/condition does not exist in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with overdose of vismodegib. The applicant studied doses up to 540 mg daily in subjects with advanced cancer with no acute harm observed. No data suggests that vismodegib can lead to dependence.

7.7 Additional Submissions / Safety Issues

Safety Update

On December 6, 2011 the applicant submitted the results of the safety update. This update was a 90 day update in lieu of the 120-day safety update. FDA agreed to the timing and did not object to omission of datasets during the application orientation meeting on October 11, 2011. The safety data included new and updated safety summaries and narratives for SHH4476g (cut off date May 26, 2011; n = 104), updated safety data for SHH44811g (cut off date July 7, 2011; n = 53), and new and updated safety narratives for SHH4437g (cut off date May 26, 2011; n = 13). As the safety update did not contain datasets, this reviewer did not incorporate the updated safety information in Sections 7.1 through 7.6.

Safety Update Disposition: (SHH4476g)

At the time of data cut-off for the safety update, eight additional subjects discontinued therapy due to disease progression, four subjects discontinued to adverse events, and two subjects discontinued due to subject decision, Table 56.

Reference ID: 3068456

Table 56: SHH4476g Updated Disposition
(copied from safety update submission with minor modifications)

Disposition	mBCC (n = 33)	laBCC (n = 71)	Total (n = 104)
On treatment	11	26	37 (35.6%)
Discontinued treatment	22	45	67 (64.4%)
Adverse event	2	14	16 (15.4%)
Death	1	2	3 (2.9%)
Lost to follow-up	2	1	3 (2.9%)
Physician's decision to discontinue treatment	2	1	3 (2.9%)
Subject's decision to discontinue treatment	3	19	22 (21.2%)
Disease progression	12	7	19 (18.3%)
Other	0	1	1 (1.0%)

Exposure: (SHH4476g)

The median cumulative dose of vismodegib increased from 43.2 grams to 57.6 grams. The median treatment duration increased from 9.8 months to 12.9 months.

Overview of Adverse Events: (SHH4476g)

The following list contains AE comparisons on a per-subject incidence comparing the safety update information compared to the original NDA submission:

- ≥ Grade 3 AEs (48.1% versus 42.3%);
- SAEs (30.8% versus 25.0%);
- AE leading to discontinuation (15.4% versus 9.6%);
- Fatal AEs (6.7% versus 6.7%);
- Muscle spasms (70.2% versus 71.7%);
- Alopecia (64.4% versus 63.8%);
- Dysgeusia (52.9% versus 55.1%);
- Weight decreased (50.0% versus 44.9%);
- Fatigue (38.5% versus 39.9%);
- Nausea (32.7% versus 30.4%);

The applicant added two common AEs (≥ 10% incidence), amenorrhea, 2 of 6 (33%) subjects who were of child bearing potential, and nasopharyngitis, 12 subjects (11.5%) that had previously been reported in only 10 subjects (9.6%). Table 57 contains the updated per-subject incidence of AEs for SHH4476g.

Reference ID: 3068456

Table 57: Updated Common AEs SHH4476g
(copied from submission with minor modifications)

MedDRA Preferred Term	mBCC (n = 33)	laBCC (n = 71)	Total (n = 104)
Any adverse events	33	71	104 (100.0%)
Muscle spasms	21	52	73 (70.2%)
Alopecia	20	47	67 (64.4%)
Dysgeusia	21	34	55 (52.9%)
Weight decreased	16	36	52 (50.0%)
Fatigue	14	26	40 (38.5%)
Nausea	11	23	34 (32.7%)
Decreased appetite	11	17	28 (26.9%)
Diarrhea	9	18	27 (26.0%)
Constipation	6	12	18 (17.3%)
Cough	9	9	18 (17.3%)
Vomiting	6	11	17 (16.3%)
Arthralgia	4	13	17 (16.3%)
Headache	4	10	14 (13.5%)
Nasopharyngitis	3	9	12 (11.5%)
Squamous cell carcinoma	3	9	12 (11.5%)
Ageusia	2	10	12 (11.5%)
Hypogeusia	3	8	11 (10.6%)

The applicant reported the per-subject incidences of AEs by sex and age (<65 versus ≥ 65 years) were similar with no additional AEs with ≥ 10% incidence between male and females. Nasopharyngitis (17.5% versus 4.3%), nausea (38.6% versus 25.5%), and upper respiratory tract infection (12.3% versus 2.1%) were new additional AEs occurring with ≥ 10% incidence between <65 versus ≥ 65 years, respectively.

Grade 3 or Greater AEs (SHH4476g)

The applicant reported no new Grade 5 AEs. The safety update reported that 58 subjects (48.1%) of subjects had a Grade 3-5 AE compared with 44 subjects (42.3%) in the original submission. Weight loss (5.8%), muscle spasms (5.8%), and fatigue (4.8%) remained the most common Grade 3-5 AEs. The applicant reported new Grade 3-4 AEs occurring in 2 or more subjects, weight decreased (n = 2), muscle spasms (n = 2), and syncope (n = 2). The applicant revised one prior case of Grade 3 weight decreased to Grade 2. Table 58 contains the updated Grade 3-5 AEs for SHH4476g occurring in 2 or more subjects.

Reference ID: 3068456

Table 58: Updated Grade 3-5 AEs SHH4476g
(copied from submission with minor modifications)

MedDRA Preferred Term	mBCC (n = 33)	laBCC (n = 71)	Total (n = 104)
Any Grade 3–5 adverse events	12	38	50 (48.1%)
Weight decreased	1	5	6 (5.8%)
Muscle spasms	0	6	6 (5.8%)
Fatigue	2	3	5 (4.8%)
Asthenia	1	2	3 (2.9%)
Death	1	2	3 (2.9%)
Decreased appetite	1	2	3 (2.9%)
Syncope	2	1	3 (2.9%)
Pain	1	1	2 (1.9%)
Cellulitis	1	1	2 (1.9%)
Deep vein thrombosis	1	1	2 (1.9%)
Cardiac failure	0	2	2 (1.9%)
Pneumonia	0	2	2 (1.9%)
Squamous cell carcinoma	0	2	2 (1.9%)

Serious AEs (SHH4476g):

The applicant reported an additional 5 subjects experienced SAEs in the safety update, 32 subjects (30.8%) compared to 26 subjects (25.0%). During the additional reporting period, a total of 9 subjects experienced 15 new serious AEs. The following list, adapted from safety update submission, contains brief narratives of the 9 subjects who experienced SAEs. (*copied from safety submission with minor modifications*)

Subject 20506, a 75-year-old female in the laBCC cohort, developed Grade 3 diarrhea due to food poisoning on [redacted] (b) (4) (b) (4) In [redacted] (b) (4), the subject experienced Grade 3 cardiac flutter and Grade 3 atrial fibrillation. Treatment with warfarin and amiodarone was initiated. Subsequently, the subject experienced a Grade 4 overdose of zolpidem on Study [redacted] (b) (4) None of these serious adverse events were considered related to vismodegib. Vismodegib treatment began on November 12, 2009 and was not interrupted.

Subject 20564, a 61-year-old female in the laBCC cohort, experienced Grade 2 pain in extremity after she twisted her left leg, and she was hospitalized on [redacted] (b) (4) No fracture was noted at the time. The investigator did not consider the adverse event related to vismodegib did not interrupt vismodegib.

Subject 20621, a 71-year-old female in the laBCC cohort, experienced a Grade 4 cerebral hemorrhage on [redacted] (b) (4), which was confirmed with CT scan. At the time of diagnosis, the subject was receiving treatment with warfarin, with an INR of 3.4, for the treatment of atrial fibrillation. The subject was treated with vitamin K, fresh frozen plasma, and

Reference ID: 3068456

factor IX complex. The investigator attributed the event to supratherapeutic INR but also considered the event related to vismodegib. The investigator interrupted vismodegib and the event lasted (b) (4) days.

Subject 20763, an 86-year-old male in the laBCC cohort, experienced Grade 2 pneumothorax on (b) (4) and was hospitalized on (b) (4). The subject's relevant past medical history included chronic obstructive pulmonary disease. The investigator did not consider the event related to vismodegib, and the event resolved on (b) (4) (b) (4) The investigator interrupted vismodegib as a result of the pneumothorax and subsequently discontinued vismodegib because of disease progression on (b) (4) (b) (4)

Subject 20780, a 74-year-old male in the laBCC cohort, experienced Grade 3 syncope on (b) (4) (b) (4) and was hospitalized. The investigator considered the event elated to vismodegib; however, did not interrupt vismodegib.

Subject 20841, a 59-year-old female in the laBCC cohort, experienced Grade 3 osteomyelitis, initially reported as "possible CNS infection," on (b) (4) and was hospitalized. An MRI demonstrated the direct invasion of BCC into the brain and evidence of edema suggesting possible infection. Antibiotic treatment was initiated. The investigator considered the event related to vismodegib, interrupted vismodegib on (b) (4) (b) (4) (b) (4) and subsequently discontinued vismodegib on (b) (4) As of May (b) (4), the event was ongoing.

Subject 20861, a 61-year-old male in the mBCC cohort, experienced Grade 3 asthenia and Grade 2 ankle fracture on (b) (4) and Grade 2 pneumonia on (b) (4) (b) (4) The investigator interrupted vismodegib and begun additional therapy with antibiotics and splint. On (b) (4) the subject experienced Grade 3 syncope, which resolved the same day. The evaluation was unremarkable for metastatic disease and cerebral hemorrhage. The investigator considered the event of ankle fracture not related to vismodegib, but did consider the events of asthenia, pneumonia, and syncope related to vismodegib. The investigator resumed administration of vismodegib on (b) (4)

Subject 21081, a 52-year-old female in the laBCC cohort, experienced Grade 4 depression and was hospitalized on (b) (4) The adverse event lasted 59 days and resolved on (b) (4) The investigator considered the adverse event not related to vismodegib, but interrupted and subsequently discontinued vismodegib because of the adverse event.

Subject 21140, 38-year-old male in the laBCC cohort, experienced Grade 4 suicidal ideation and was hospitalized after making "suicidal threats" on (b) (4) The event resolved (b) (4) The investigator considered the event not related to vismodegib and did not interrupt vismodegib.

Reference ID: 3068456

Adverse Events leading to Discontinuation (SHH4476g):

The applicant reported an additional 4 subjects who discontinued vismodegib due to adverse events, Table 59. An additional subject discontinued after experiencing muscles spasms (2.9% versus 1.9%). An additional subject discontinued for weight decreased (1.9% versus 1.0%). Osteomyelitis was the only new adverse event, not previously contained in the original submission, to lead to discontinuation of vismodegib.

Table 59: Updated SHH4476g AEs leading to Discontinuation
(copied from safety submission with minor modifications)

MedDRA Preferred Term	mBCC (n = 33)	laBCC (n = 71)	Total (n = 104)
Any adverse events	3	14	17 (16.3%)
Muscle spasms	1	2	3 (2.9%)
Weight decreased	2	0	2 (1.9%)
Acute myocardial infarction	0	1	1 (1.0%)
Aphagia	0	1	1 (1.0%)
Asthenia	0	1	1 (1.0%)
Death	1	0	1 (1.0%)
Fatigue	0	1	1 (1.0%)
Cellulitis	0	1	1 (1.0%)
Osteomyelitis	0	1	1 (1.0%)
Metastatic malignant melanoma	0	1	1 (1.0%)
Metastatic squamous cell carcinoma	0	1	1 (1.0%)
Dysgeusia	1	0	1 (1.0%)
Ischemic stroke	0	1	1 (1.0%)
Paresthesia	0	1	1 (1.0%)
Depression	0	1	1 (1.0%)
Hypovolemic shock	0	1	1 (1.0%)

Labs and Vital Signs (SHH4476g):

The applicant stated there were no new ≥ Grade 3 laboratory abnormalities. The applicant stated "no clinically meaningful changes were observed in vital signs except for weight loss, which showed an increase in the median weight loss from baseline from 5.7 kg to 7.4 kg."

Deaths (SHH4476g):

The applicant reported an additional 5 deaths for the safety update for a total of 21 (20.2%) compared to 16 (15.5%) in the original submission. No additional subjects died within 30 days of last vismodegib use. The cause of death for the additional 5 subjects was disease progression for 4 subjects and metastatic melanoma for Subject 20800. The applicant provided safety

Reference ID: 3068456

narratives for the two of the additional subjects who died, but did not include AE information on these subjects.

8 Postmarket Experience

Vismodegib is a new molecular entity and thus there is no postmarket experience with vismodegib.

Reference ID: 3068456

9 Appendices

9.1 Literature Review/References

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Reference ID: 3068456

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Wong H, Alicke B, West K, et al, 2011, Pharmacokinetic–pharmacodynamic analysis of vismodegib in preclinical models of mutational and ligand-dependent Hedgehog pathway activation using vismodegib, Clin Cancer Res 17:4682–92.

9.2 Labeling Recommendations

This reviewer recommended the following key labeling changes. Numbering below is consistent with the applicable sections in product labeling. This reviewer will not comment on all sections (for example, if only minor edits were made to a section) of product labeling.

1. Indication

- This reviewer recommends changing the indication statement to include information about radiation and reflect the eligibility criteria of the pivotal trial.

  ERIVEDGE capsule is indicated for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and that has recurred following radiation or who are not candidates for radiation.

2. Dosage and Administration

- This reviewer recommends revision of the instruction on how to administer vismodegib to use the active voice instead of passive.

4. Contraindications

- This reviewer recommends there be no contraindications.

5. Warnings and Precautions

- This reviewer recommends revision of the Warnings and Precautions section to instruction physicians to verify pregnancy status, advise patients of the risk of vismodegib, counsel on the need for contraception, and inform pregnant women exposed of the risk :

  Verify pregnancy status prior to the initiation of ERIVEDGE. Advise male and female patients of the risks of embryo-fetal death and severe birth defects and the need for

Reference ID: 3068456

contraception. Advise patients to contact their healthcare provider immediately if they suspect they (or, for males, their female partner) may be pregnant. Female and male patients of reproductive potential should be counseled regarding pregnancy prevention and planning. If ERIVEDGE is used during pregnancy or if the patient becomes pregnant while taking (or for males, if his female partner is exposed to) ERIVEDGE, the patient should be apprised of the potential hazard to the fetus [see Boxed Warnings, Use in Specific Populations (8.1, 8.5)]

- This reviewer recommends revising the Warnings and Precautions for blood donation to use active voice.

6. Adverse Reactions

- This reviewer recommends addition of a description of the trials contained in the safety database, patient characteristics for those trials, and a list of the most common adverse reactions (≥ 10%) [redacted] (b) (4) to Section 6.1
- This reviewer recommends removing [redacted] (b) (4)
- This reviewer recommends changing the description of amenorrhea as a an adverse event developed by 3 of 10 premenopausal women instead of an by removing [redacted] (b) (4)
- This reviewer recommends changing the description of laboratory abnormalities to use the clinical terms associated with the laboratory abnormality instead of [redacted] (b) (4)

8. Use in Specific Populations:

- This reviewer recommends rewording Section 8.5 Geriatric Use to read:
  Clinical studies of ERIVEDGE capsule did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

10. Overdoasge

- This reviewer recommends removing the statement [redacted] (b) (4) and replacing it with the statement "there is no information on overdosage in humans" to be more factually accurate.
- This reviewer recommends adding information about dosing up to 540 mg, as was done in the phase 1 trial, and including the statement "exposure did not increase between 150 mg and 540 mg" to be more factually accurate.

14. Clinical Studies

- This reviewer recommends revision of the Clinical Studies section to contain details from SHH4476g, the pivotal trial, to include demographic data for the efficacy population a description of the two cohorts (laBCC and mBCC) with respect to the eligibility criteria and the response and progression criteria.

Reference ID: 3068456

- This reviewer recommends including the percentage of patients from SHH4476g who had Gorlin syndrome.
- This reviewer recommends revision of the efficacy outcome table to include only INV ORR, 95% CI, CR and PR, and median duration of response only.

17. Patient Counseling Information

- This reviewer recommends including the following instructions:

  Advise patients that ERIVEDGE exposure during pregnancy can cause embryo-fetal death or severe birth defects.

  Instruct female patients of reproductive potential to use a highly effective form of contraception (failure rate of less than 1%) while taking ERIVEDGE and for at least 7 months after the last dose of ERIVEDGE.

  Instruct male patients to use condoms with spermicide, during sexual intercourse with female partners while taking ERIVEDGE and for at least 2 months after the last dose of ERIVEDGE.

  Instruct patients to immediately contact their healthcare provider if they (or, for males, their female partner) becomes pregnant or if pregnancy is suspected following exposure to ERIVEDGE. Advise pregnant women who were exposed to ERIVEDGE to enroll in the "pregnancy registry".

  Advise patients not to donate blood while taking and for at least 7 months after the last dose of ERIVEDGE.

  Advise patients to swallow ERIVEDGE capsules whole and not to crush or open the capsules

The applicant responded to the FDA label recommendations on December 21, 2011. Labeling negotiations were still ongoing at the time of completion of this review.

9.3 Advisory Committee Meeting

This reviewer did not recommend presentation of NDA 203388 at an advisory committee due to the magnitude of benefit of response rate and duration of response in a population with no available therapy with the and the main safety risk being limited to developing fetuses.

9.4 Other Supportive Tables and Figures

None

Reference ID: 3068456

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL AXELSON
01/13/2012

JEFFERY L SUMMERS
01/13/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			(eCTD)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			On initial review, the label appears to be in acceptable PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: SHH3925g Study Title: An Open label, Phase 1 Study of Systemic Hedgehog Pathway Antagonist, GDC-0449, in Patients with Locally Advanced or Metastatic Solid Tumors that are Refractory to Standard Therapy or for Whom No Standard Therapy Exists. Sample Size:68 cohorts: 7 Location in submission: CSR SHH3925g (5.3.5.2)	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	FDA commented on May 5, 2011 that

Reference ID: 3022967

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Study Number: SHH4476g Study Title: Pivotal Phase 2, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma Sample Size: 104 Arms: 1 Indication: Treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate				submission of a single, pivot trial did not appear to be a significant filing issue.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	See comment to 14
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			FDA commented that the efficacy analyses would consist of the all-treated population and the efficacy-evaluable population, but accepted response rate as the primary endpoint.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Trial SHH4476g was conducted in the US and abroad with 69% US enrollment.
	SAFETY				
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			On initial review
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			On initial review, Study SHH4871g is a QT interval study in health women with ECG data.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			On initial inspection.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			The safety database contains safety information on 983 subjects according to

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

Reference ID: 3022967

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					the ISS.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		All verbatim and preferred terms are included in the CRF and xpt files according to MedRA dictionary.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		X		The application does not contain renal or hepatic impairment studies.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			On initial inspection of Trials SHH476g and SHH3925g
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	The application does not contain renal or hepatic impairment studies.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A request for pediatric waiver was submitted with the NDA
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Trial SHH4476g was conducted in the US and abroad with 69% US enrollment.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Appears acceptable during initial safety review
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			On initial review
34.	Are all datasets to support the critical safety analyses available and complete?	X			On initial review
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			On initial review
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms	X			On initial review

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3022967

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			On initial inspection
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		The individual clinical summary reports contain this statement for the individual trials????

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

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Michael Axelson September 30, 2011

Reviewing Medical Officer Date

Ke Liu September 30, 2011

Clinical Team Leader Date

Reference ID: 3022967

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL AXELSON
09/30/2011

KE LIU
09/30/2011