

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203388Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

**NDA Number:** 203388  
**Drug Name:** Vismodegib  
**Indication(s):** Advanced basal cell carcinoma  
**Dosage Form:** Capsule, Hard Gelatin  
**Applicant:** Genentech, Inc.  
**Date(s):** Date Received: October 11, 2011  
Completion Date: December 22, 2011  
**Review Priority:** Priority  
**Biometrics Division:** VI  
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**Concurring Reviewers:** Yi Tsong  
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## 1. EXECUTIVE SUMMARY

This review describes statistical findings on Genentech, Inc.'s data from the stability study under long-term storage condition (30°C/65% RH) so that FDA office of New Drug Quality Assessment can make informed decisions on the proposed [REDACTED]<sup>(b) (4)</sup> drug product shelf life.

The reviewer conducted statistical analysis on the sponsor's 18-month long-term stability data in accordance with the 2004 ICH Q1E Guidance. Three test attributes – assay, [REDACTED]<sup>(b) (4)</sup>, and dissolution at [REDACTED]<sup>(b) (4)</sup> - are analyzed. Estimated shelf lives are longer than the proposed shelf life, [REDACTED]<sup>(b) (4)</sup> 12-month extrapolation beyond the period covered by the long-term data can be granted because the data shows little change over time and low variability. Therefore, the sponsor's stability data supports the proposed [REDACTED]<sup>(b) (4)</sup> shelf life of vismodegib capsules 150 mg.

## 2. INTRODUCTION

### 2.1 Overview

This review describes statistical findings on Genentech Inc.'s data from the stability study under long-term storage condition (30°C/65% RH) so that FDA office of New Drug Quality Assessment can make informed decisions on the proposed (b) (4) drug product shelf life.

The sponsor submitted the stability data set (stability-data.pdf) electronically but not in an electronic form. The data set contains average data per month from the dissolution test at (b) (4) (b) (4) FDA requested individual dissolution data to the sponsor through IR letter on November 16, 2011. In response to the agency's IR letter, the sponsor submitted the requested individual data in Excel format on November 23, 2011.

The sponsor conducted stability analysis on 18-month stability data under long-term storage condition and proposed (b) (4) shelf life. The reviewer evaluated the sponsor's study report and conducted independent stability analysis on the sponsor's data. The sponsor's submission and the reviewer's assessment can be found in Section 3 and Section 4, respectively.

### 2.2 Data Sources

The sponsor's study report is located in EDR: <\\cdsesub1\EVSPROD\NDA203388\0000\m3\32-body-data\32p-drug-prod\hard-capsules-150-mg\32p8-stab\stability-summary.pdf>.

The EDR location of the first submitted stability data set is <\\cdsesub5\EVSPROD\NDA203388\0000\m3\32-body-data\32p-drug-prod\hard-capsules-150-mg\32p8-stab\stability-data.pdf>

The EDR location of the stability data set containing individual data from the dissolution test is <\\cdsesub1\EVSPROD\NDA203388\0015\m1\us\111-info-amen\appendix-1-complete-stability-data.xls>

## 3. SPONSOR'S SUBMISSION

### 3.1 Data

The sponsor used 18-month data under long-term storage condition (30 °C/65% RH) and 6-month data under short-term condition (40 °C/75% RH) for stability analysis (see Table 1). The stability data were collected every 3 months over the first year, every 6 months thereafter until 18 months. Data from the following three stability tests (proposed commercial acceptance criterion in the parenthesis) are amenable to statistical analysis:

(b) (4)

**Table 1. Primary Stability Data**

Lot No.	Manufacture		Packaging			Date Placed on Stability	Data Available (months)	Storage Temperature
	Lot Size	Date	Site	Description	Site			
800526	(b) (4)	3 Oct 2009	(b) (4)	Primary 50 mL square white HDPE bottle with child-resistant cap (28 capsules/bottle)	(b) (4)	13 Nov 2009	18 6	30° C/65% RH. 40° C/75% RH.
800527	(b) (4)	6 Oct 2009	(b) (4)	50 mL square white HDPE bottle with child-resistant cap (28 capsules/bottle)	(b) (4)	13 Nov 2009	18 6	30° C/65% RH. 40° C/75% RH.
800528	(b) (4)	13 Oct 2009	(b) (4)	50 mL square white HDPE bottle with child-resistant cap (28 capsules/bottle)	(b) (4)	13 Nov 2009	18 6	30° C/65% RH. 40° C/75% RH.

Source: Table P.8.1-1 in Sponsor's stability report (page 3 of 17)

### 3.2 Sponsor's Analysis and Conclusion

First, the sponsor conducted stability analysis on assay (% label claim). Analysis of Covariance (ANCOVA) was performed to test batch poolability. Based on the test, three stability lots were pooled. Therefore, the linear regression lines with the same intercepts and slopes were fitted to the data to estimate the shelf life against the proposed NDA specification, (b) (4). The sponsor showed that two-sided 95% confidence limits for the mean response through 36 months are within the specification. Therefore, the sponsor concluded that statistical assessment supports the proposed shelf life of (b) (4).

However, for dissolution at (b) (4) the sponsor did not conduct any statistical analysis but provided the plots of the data only. The sponsor concluded that these plots show drug product dissolution is comparable up to 18 months for primary stability samples because all individual dissolution data points (b) (4) are (b) (4) the proposed NDA specification, no less than (NLT) (b) (4), demonstrating the long-term stability of vismodegib drug product.

Similarly, the sponsor concluded 18-month shelf life for (b) (4) without statistical analysis. The sponsor noted that the analytical data do not show trending over an 18-month period based on the plot of the data.

In sum, the sponsor proposed the shelf life of (b) (4) for vismodegib capsules 150 mg based on the primary stability data and statistical assessment of dissolution at (b) (4).

## 4. REVIEWER'S ASSESSMENT

### 4.1 Statistical Evaluation

The FDA statistician evaluated the sponsor's 18-month stability data in accordance with the 2004 ICH Q1E Guidance. The reviewer conducted ANCOVA analysis to estimate a shelf life of the drug product for three stability test attributes – assay, (b) (4) and dissolution at (b) (4) – using Statistical Analysis Software, SAS.

First, the reviewer performed batch poolability tests. For all attributes, slopes and intercepts are pooled. Therefore, the regression lines with the same intercepts and slopes were fitted to the data. In Appendix, Figure 1 - 3 displays the stability data with both the fitted regression line (solid lines) and one-sided 95% prediction limit(s) of the regression mean (bands) for three test attributes.

Second, the reviewer estimated the shelf life against the proposed NDA specifications, (b) (4) NMT (b) (4) for (b) (4), and NLT (b) (4) for dissolution at (b) (4). Estimated shelf lives for assay and (b) (4) are (b) (4) and (b) (4) respectively. An estimated shelf life for dissolution (b) (4). In addition, the data shows little change over time and low variability. In this case, according to ICH guidance, a shelf life can be extrapolated up to 12 months beyond the period covered by long-term data, 18 months. Therefore, (b) (4) shelf life can be granted for assay, (b) (4), and dissolution at (b) (4).

#### 4.2 Summary and Conclusion

The FDA statistician conducted a stability analysis to estimate a shelf life of the drug product based on 18-month stability data. Three test attributes – assay, (b) (4), and dissolution at (b) (4) – are analyzed. Estimated shelf lives are longer than the proposed shelf life, (b) (4) 12-month extrapolation beyond the period covered by the long-term data can be granted because the data shows little change over time and low variability. Therefore, the sponsor's stability data supports the proposed (b) (4) shelf life of vismodegib capsules 150 mg.

## APPENDIX

(b) (4)



**Figure 1. Fitted Regression Line with Two One-Sided 95 % Prediction Limits for Assay**



**Figure 2. Fitted Regression Line with One-Sided 95 % Prediction Limit for**

(b) (4)



**Figure 3. Fitted Regression Line with One-Sided 95 % Prediction Limit  
For Dissolution at (b) (4)**

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/s/  
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01/12/2012

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01/18/2012



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA** 203388

**Serial Number:** N000

**Drug Name:** Erivedge (vismodegib)

**Indication:** For the treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate

**Applicant:** Genentech, Inc

**Submission Date:** September 08, 2011

**PDUFA Date:** March 8, 2012

**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics V

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**Keywords:** Exact binomial test; Exact confidence interval

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## 1. EXECUTIVE SUMMARY

In the new drug application (NDA), the applicant submitted the efficacy data collected from a single arm two cohort study to seek an approval of Vismodegib for the treatment of adult patients with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate. The pivotal study SHH4476g was a phase II, multicenter, single-arm, two-cohort trial. There were two cohorts in the study: the metastatic BCC cohort and the locally advanced BCC. Based on 96 efficacy-evaluable patients from the submitted pivotal single arm study, the estimated objective response rate (ORR), as assessed by an independent review facility (IRF) was 30.3% with 95% confidence interval (15.6; 48.2) for the metastatic BCC cohort and 42.9% with (30.5; 56.0) for the locally advanced BCC cohort. The estimated median response duration was 7.6 months for each cohort with 95% confidence interval (5.62; not available) for the metastatic BCC cohort and (5.65; 9.66) for the locally advanced BCC cohort. Objective response rate in the sensitivity analyses ranges from 38.0% to 43.7% for locally advanced BCC cohort. Because Study SHH4476g was a single arm non-comparative study, no statistical inferential conclusion can be drawn from the study. Whether the objective response rates demonstrated in the single pivotal study SHH4476g are clinically meaningful and provide a favorable benefit-risk profile of Vismodegib for the proposed indication are deferred to the clinical review team.

## 2. INTRODUCTION

### 2.1 Overview

Vismodegib is a small-molecule Hedgehog (Hh) pathway inhibitor. Vismodegib targets Smoothened, a key protein within the Hh signaling pathway, and thereby inhibits Hh signaling, which has been implicated in the development of BCC and other cancers. The applicant provided data from a single arm two cohort Study SHH4476g along with supportive safety data from other Phase I and II studies of vismodegib in patients with advanced BCC or solid tumors or in healthy volunteers to support the proposed indication: “*Vismodegib is for the treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate*”. Study SHH4476g was a phase II, multicenter, single-arm, two-cohort trial evaluating the efficacy and safety of Vismodegib in patients with advanced basal cell carcinoma. The primary endpoint was objective response rate (ORR) assessed by an independent review facility (IRF). All patients received 150 mg of vismodegib until evidence of progression, intolerable toxicities most probably attributable to vismodegib, or withdrawal from the study. The study was conducted at 31 sites in Australia, Belgium, France, Germany, the United Kingdom, and the United States. The data collected from the study were from February 10, 2009 to November 26, 2010 (data cutoff; follow-up ongoing). The study population consisted of patients  $\geq 18$  years old with a histologically confirmed diagnosis of advanced BCC (metastatic or locally advanced BCC). One hundred and four patients were enrolled into either the metastatic (33 patients) or locally advanced BCC cohort (71 patients). In the metastatic BCC cohort, tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) and images were reviewed by an independent review facility (IRF). In the locally advanced BCC cohort, a composite endpoint was utilized to incorporate external tumor dimensions, ulceration (for patients whose tumors were ulcerated at baseline), and RECIST (for patients with radiographically measurable disease). Histology of tumor biopsies obtained at baseline and during the study was also used to determine response. Standardized digital photographs, tumor biopsies, and radiographic images (for patients with RECIST-measurable disease) were reviewed by independent reviewers.

The applicant submitted a special protocol assessment (SPA) for Study SHH4476g in November 2008. FDA issued the SPA-No Agreement letter with responses to the applicant.

### 2.2 Data Sources

Data used for this review were from the electronic submission received on September 8, 2011. The E-CTD link was “[\\CDSESUB5\EVSPROD\NDA203388\203388.enx](#)”.

## 3. STATISTICAL EVALUATION

This section will be focused on major efficacy results in the pivotal Study SHH4476g.

### 3.1 Data and Analysis Quality

The quality of data in this NDA submission was such that it was not too difficult for this reviewer to reproduce the primary analysis dataset and to trace the primary endpoint from some raw datasets.

### 3.2 Evaluation of Efficacy

#### Study Design and Endpoints

Study SHH4476g was a Phase II, single-arm, two-cohort, multicenter clinical trial. The primary objective of this study 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). A total of 104 patients were enrolled into either the metastatic or the locally advanced BCC cohort. There were 33 patients in the metastatic BCC cohort and 71 patients in the locally advanced BCC cohort.

The primary endpoint was ORR assessed by an independent review facility (IRF). During treatment, tumor assessments were performed every 8 weeks and at the study completion or early termination visit. An objective response was defined as a complete or partial response determined on two consecutive assessments at least 4 weeks apart. Objective response rate was defined as the proportion of responders. Patients without a post-baseline tumor assessment were considered non-responders. In the metastatic BCC cohort, tumor response was assessed by the IRF according to the Response Evaluation Criteria in Solid Tumors (RECIST). In the locally advanced BCC cohort, tumor response was assessed by the IRF according to the composite criteria based on radiographic IRF, photographic IRF, and pathology IRF. For patients in the locally advanced BCC cohort, best overall response was determined according to the following table:

**Table 1: Best Confirmed Response Based on Subsequent Assessments**

First TPR	Second TPR	Best Confirmed Response*
CR	CR	CR
CR/PR	SD/PD	SD
PR	CR/PR	PR
SD	CR/PR/SD/PD	SD
PD	No further evaluation	PD

\* Best Confirmed Response, other than PD, could only be made after the subject was on-study for a minimum of eight (8) weeks (56 days). Tumor assessments before eight (8) weeks (56 days) would have a Best Confirmed Response of UE. CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate. TPR=time point response.

For a responder, duration of objective response was defined as the time from the initial confirmed CR or PR to the earlier of documented disease progression or death within 30 days of last exposure to study treatment. The duration of response for the responder without disease progression who had not died within 30 days of last exposure to study treatment was censored at the time of the last tumor assessment. Patients who discontinued study drug treatment were

followed for survival approximately every 3 months until death, loss to follow-up, or study termination by the applicant.

The secondary endpoints in the study included duration of objective response, progression-free survival (PFS), and overall survival (OS).

### **Patient Disposition, Demographic and Baseline Characteristics**

There were a total of 104 patients enrolled in Study SHH4476g. Among the 104 patients, 33 were in metastatic BCC cohort and 71 patients in the locally advanced BCC cohort. As shown in Table 2, a little more than half (52.9%) of patients were still in study at the time of the data cut-off (November 26, 2010). Among the study discontinuation reasons, disease progression and subject decision to withdraw were the top 2 reasons for discontinuation from the study.

**Table 2: Disposition of Patients (All Enrolled Patients)**

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

All enrolled patients were Caucasian. The majority (72.7%) of patients in were male in the metastatic BCC cohort. Table 3 shows the major demographics for 104 enrolled patients.

**Table 3: Demographics of All Enrolled Patients**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=71)</b>	<b>Total (n=104)</b>
<b>Age (yr), n(%)</b>	33 (100)	71 (100)	104 (100)
<b>Mean (SD)</b>	61.6 (11.4)	61.2 (16.8)	61.4 (15.2)
<b>Median</b>	62	62	62
<b>Range</b>	38 - 92	21 - 101	21 - 101
<b>Age group (yr), n(%)</b>	33 (100)	71 (100)	104 (100)
<b>&lt;65</b>	19 (57.6)	38 (53.5)	57 (54.8)
<b>&gt;= 65</b>	14 (42.4)	33 (46.5)	47 (45.2)
<b>Sex, n(%)</b>	33 (100)	71 (100)	104 (100)
<b>Male</b>	24 (72.7)	39 (54.9)	63 (60.6)
<b>Female</b>	9 (27.3)	32 (45.1)	41 (39.4)
<b>Ethnicity, n(%)</b>	33 (100)	71 (100)	104 (100)
<b>Not Hispanic or Latino</b>	33 (100.0)	69 (97.2)	102 (98.1)
<b>Weight (kg), n(%)</b>	33 (100)	70 (100)	103 (100)
<b>Mean (SD)</b>	76.50 (15.3)	84.94(21.1)	82.23 (19.8)
<b>Median</b>	74.8	81.87	79
<b>Range</b>	54.2-122.0	42.0-170.0	42.0-170.0

**Reviewer's Comments:**

- [1] *The applicant's primary analysis population (called the efficacy-evaluable population) was defined as all enrolled patients and who had a confirmed biopsy of BCC at baseline. There were 8 patients who did not have a confirmed biopsy of BCC at baseline. According to the FDA response dated on January 5, 2009 in the SPA-No agreement letter, FDA agreed with excluding patients who did not have a confirmed biopsy of BCC at baseline from the primary analysis. Therefore, there were 96 patients in the primary analysis. The 8 patients excluded were all in the locally advanced BCC cohort.*

Table 4 shows patient demographics for 96 efficacy-evaluable patients.

**Table 4: Demographics of Efficacy-Evaluable Patients**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=63)</b>	<b>Total (n=96)</b>
<b>Age (yr), n(%)</b>	33 (100)	63 (100)	96 (100)
<b>Mean (SD)</b>	61.6 (11.4)	61.4 (16.9)	61.5 (15.2)
<b>Median</b>	62	62	62
<b>Range</b>	38-92	21-101	21-101
<b>Age group (yr), n(%)</b>	33 (100)	63 (100)	96 (100)
<b>18-40</b>	1 (3.0)	7 (11.1)	8 (8.3)
<b>41-64</b>	18 (54.5)	26 (41.3)	44 (45.8)
<b>&lt;65</b>	14 (42.4)	30 (47.6)	44 (45.8)
<b>&gt;= 65</b>	14 (42.4)	33 (46.5)	47 (45.2)
<b>Sex, n(%)</b>	33 (100)	63 (100)	96 (100)
<b>Male</b>	24 (72.7)	35 (55.6)	59 (61.5)
<b>Female</b>	9 (27.3)	28 (44.4)	37 (38.5)
<b>Ethnicity, n(%)</b>	33 (100)	63 (100)	96 (100)
<b>Not Hispanic or Latino</b>	33 (100.0)	61 (96.8)	94 (97.9)
<b>Weight (kg), n(%)</b>	33 (100.0)	62 (100.0)	95 (100.0)
<b>Mean (SD)</b>	76.50 (15.30)	86.13 (21.49)	82.78 (20.02)
<b>Median</b>	74.8	82.2	79.5
<b>Range</b>	54.2-122.0	52.0-170.0	52.0-170.0

As shown in Table 5, among 96 efficacy-evaluable patients, majority (94.8% and 91%) of patients had prior therapies and prior surgery for cancer, respectively, but most (89.6%) patients did not have any prior Chemo/Non-Anthracycline therapy when they entered the study.

**Table 5: Baseline Characteristics (Efficacy-Evaluable Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=63)</b>	<b>Total (n=96)</b>
<b>Time from Initial Diagnosis of any BCC until Study Treatment (months)</b>			
<b>Mean (SD)</b>	98.6 (108.4)	196.0 (151.7)	162.5 (145.4)
<b>Median</b>	66.1	169.4	117.8
<b>Range</b>	1 - 522	1 - 512	1 - 522
<b>Number of Target Lesions, n(%)</b>			
<b>1</b>	9 ( 27.3)	40 ( 63.5)	49 ( 51.0)
<b>2</b>	4 ( 12.1)	12 ( 19.0)	16 ( 16.7)
<b>3</b>	9 ( 27.3)	6 ( 9.5)	15 ( 15.6)
<b>3+</b>	11 ( 33.3)	5 ( 7.9)	16 ( 16.7)
<b>ECOG performance status, n(%)</b>			
<b>0</b>	13 ( 39.4)	48 ( 76.2)	61 ( 63.5)
<b>1</b>	19 ( 57.6)	13 ( 20.6)	32 ( 33.3)
<b>2</b>	1 ( 3.0)	2 ( 3.2)	3 ( 3.1)
<b>Any Prior Treatment, n(%)</b>			
<b>Yes</b>	32 ( 97.0)	59 ( 93.7)	91 ( 94.8)
<b>Prior Surgery for Cancer, n(%)</b>			
<b>Yes</b>	32 ( 97.0)	56 ( 88.9)	88 ( 91.7)
<b>No</b>	1 ( 3.0)	7 ( 11.1)	8 ( 8.3)
<b>Prior Radiotherapy for Cancer, n(%)</b>			
<b>Yes</b>	19 ( 57.6)	17 ( 27.0)	36 ( 37.5)
<b>No</b>	14 ( 42.4)	46 ( 73.0)	60 ( 62.5)
<b>Prior Systemic Therapy, n(%)</b>			
<b>Yes</b>	10 ( 30.3)	7 ( 11.1)	17 ( 17.7)
<b>No</b>	23 ( 69.7)	56 ( 88.9)	79 ( 82.3)
<b>Prior Chemo/Non-Anthracycline, n(%)</b>			
<b>Yes</b>	9 ( 27.3)	1 ( 1.6)	10 ( 10.4)
<b>No</b>	24 ( 72.7)	62 ( 98.4)	86 ( 89.6)

### Statistical Methodologies

Per the statistical analysis plan (SAP), the primary endpoint ORR would be formally tested using one-sided exact binomial tests in the metastatic and locally advanced BCC cohorts. Specifically, the following hypothesis would be tested at the one-sided  $\alpha = 0.025$  level in the mBCC cohort:

$$H_0: \text{ORR} \leq 0.10 \text{ versus } H_1: \text{ORR} > 0.10;$$

And the following hypothesis would be tested at the one-sided  $\alpha = 0.025$  level in the locally advanced BCC cohort:

$$H_0: \text{ORR} \leq 0.20 \text{ versus } H_1: \text{ORR} > 0.20;$$

Ninety-five percent Blyth–Still–Casella exact confidence intervals for the ORR would be calculated for each patient cohort.

For handling missing data, the SAP specified that patients who had received at least one dose of vismodegib and who discontinued for any reason prior to undergoing one post-baseline response evaluation would be considered non-responders in the primary analysis and disease progression would be censored at the date of baseline tumor assessment + 1 day.

Per the SAP, with 100 patients, this study would have at least 80% probability of detecting an RR of 37% or higher in the mBCC cohort (with 20 treated patients) and 34% or higher in the locally advanced BCC cohort (with 80 treated patients).

The Kaplan–Meier method was used to estimate the median duration in each cohort for duration of response, PFS and OS.

**Reviewer’s Comments:**

[2] *A formal hypothesis test--one sample test was pre-specified as the primary analysis for each cohort in the SAP. However, without a comparative arm, no inferential conclusion of statistical strength can be drawn. Descriptive statistics are more appropriate in reporting the results for a non-comparative study.*

**Results and Conclusions**

Per the applicant, the cutoff date for the primary data analysis was November 26, 2010, which was at least 9 months after first treatment of the last enrolled patient which was the same timing for the primary analysis as specified in the protocol. Table 6 shows the applicant’s primary analysis of ORR assessed by IRF for the two cohorts of BCC.

**Table 6: Applicant’s ORR Results (IRF, Efficacy Evaluated Patients)**

	Metastatic BCC (n=33)	Locally Advanced BCC (n=63)	All Patients (n=96)
Patients with objective response	10 (30.3%)	27 (42.9%)	37 (38.5%)
Complete response	0	13	13
Partial response	10	14	24
Stable disease	21	24	45
Progressive disease	1	8	9
Missing (no post-baseline tumor assessment)	1	4	5
95% CI for objective response <sup>a</sup>	(15.6%, 48.2%)	(30.5%, 56.0%)	(28.8%, 48.9%)
p-value for objective response <sup>b</sup>	0.0011	<0.0001	—

*[Source: Table 10.2/1 in the Clinical Study Report for Study SHH4476g] <sup>a</sup> The 95% CI for response rate was computed using Blyth–Still–Casella method. <sup>b</sup> Complete response as best objective response required a CR confirmed by a CR, otherwise the best objective response was a partial response. <sup>c</sup> The p-value was derived from*

an exact binomial test of overall response  $\leq 10\%$  in the metastatic BCC cohort and  $\leq 20\%$  in the locally advanced BCC cohort.

**Reviewer’s Comments:**

- [3] *This reviewer has replicated the ORR results for the two cohorts respectively in Table 6.*
- [4] *It is not appropriated to combine the two cohorts to conduct the response analysis for all patients in the study because the response criterion were not the same in the two cohorts.*
- [5] *As shown in Table 6, the applicant reported one-sided p-values from the exact binomial tests in the ORR primary analysis. The applicant pre-specified a formal hypothesis testing—one sample test (whether the specification of ORR is clinically meaningful will be deferred to the clinical review team). However, without a comparative arm, no inferential conclusion of statistical strength can be drawn. Descriptive statistics are more appropriate in reporting the results for a non-comparative study.*

The following Table 7 shows the applicant’s result of response duration assessed by IRF.

**Table 7: Applicant’s Results of Duration of Response (IRF)**

	Metastatic BCC	Locally Advanced BCC	All Patients
Patients with objective response	10	27	37
Number of events	3 (30.0%)	13 (48.1%)	16 (43.2%)
Earliest contributing event:			
Disease progression	3	12	15
Death	0	1	1
Number censored	7 (70.0%)	14 (51.9%)	21 (56.8%)
Duration of objective response (mo)			
Median	7.6	7.6	7.6
(95% CI)	(5.62, NE)	(5.65, 9.66)	(5.65, 9.66)
25th–75th Percentile	5.7–NE	5.7–9.5	5.7–9.7
Minimum–maximum	2.1+ to 11.1+	1.0+ to 12.9+	1.0+ to 12.9+

*[Source: Table 13 in the Clinical Study Report for Study SHH4476g]  
 BCC = basal cell carcinoma; CI = confidence interval; IRF = independent review facility;  
 NE = not estimable; + = censored value.*

### **Reviewer's Comments:**

- [6] *This reviewer has replicated the results of response duration for the two cohorts respectively in Table 7.*
- [7] *It is not appropriate to combine the two cohorts to conduct the response analysis for all patients in the study because the response criterion were not the same in the two cohorts.*
- [8] *The primary analysis of ORR excluded 8 patients who did not have a confirmed biopsy of BCC at baseline. According to the SPA-No agreement letter in January 2009, FDA agreed with the exclusion in the primary analysis. This reviewer conducted an ORR analysis and duration of ORR analysis based on all enrolled patients. Since the 8 patients who were excluded from the primary analysis of ORR were in the locally advanced BCC cohort and there were 4 responders, the ORR for the metastatic BCC cohort remains unchanged but increases from 42.9% to 43.7% in the locally advanced BCC cohort. Table 8 shows the reviewer's analysis.*

**Table 8: ORR Sensitivity Analysis 1 (IRF, All Enrolled Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=71)</b>
<b>Confirmed ORR, n (%) (95%CI)</b>	10 (30.3) (15.6, 48.7)	31 (43.7) (31.9, 55.2)
<b>Complete response</b>	0 (0.0)	14 (19.7)
<b>Partial response</b>	10 (30.3)	17 (23.9)
<b>Median Response Duration (month) (95%CI)</b>	7.62 (5.62, NA*)	7.49 (4.70, 9.46)

\*NA=not available due to small number of events

### **Reviewer's Comments:**

- [9] *There were 8 patients who were excluded from the primary analysis of ORR. Among the 8 patients, there were 4 responders. The results of ORR and duration of ORR shown in Table 8 were conducted based on all enrolled patients, including the 4 responders. According to the FDA SPA-No Agreement letter of November 2009, patients who did not have confirmed biopsy at baseline should be considered as non-responders. The ORR analysis shown in Table 9 was conducted by considering the 4 responders who did not have confirmed biopsy at baseline as the non-responders.*

Table 9 shows another sensitivity analysis of ORR conducted by the reviewer.

**Table 9: ORR Sensitivity Analysis 2 (IRF, All Enrolled Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=71)</b>
<b>Confirmed ORR, n (%) (95%CI)</b>	10 (30.3) (15.6, 48.7)	27 (38.0) (26.7, 49.3)
<b>Complete response</b>	0 (0.0)	14 (19.7)

### **Reviewer's Comments:**

[10] *As shown in Table 9, the ORR for the locally advanced BCC cohort decreases from 42.9% in the primary ORR analysis to 38%.*

Per the SAP, the duration of response for the responder without disease progression who had not died within 30 days of last exposure to study treatment was censored at the time of the last tumor assessment. There was a patient in mBCC cohort who did not die 30 days after the last exposure to study treatment and was censored in the applicant's analysis of duration of ORR (IRF). This reviewer conducted a sensitivity analysis of response duration by considering the patient having an event at the date of death. Table 10 shows the sensitivity analysis for the duration of response.

**Table 10: Sensitivity Analysis of Response Duration (IRF)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=63)</b>
<b>Median Duration of response (month)</b>	7.76	7.62
<b>(95%CI)</b>	(5.62, NA*)	(5.65, 9.66)
<b>25th-75th Percentile</b>	5.7-NA*	5.7-9.5

\*NA=not available due to small number of events

### **Reviewer's Comments:**

[11] *Table 10 shows that changing the censoring date to the event date increases the median duration for the mBCC cohort.*

In Study SHH4476g, ORR was also assessed by the investigators. Table 11 shows the ORR results based on the investigators' assessments.

**Table 11: ORR Results (INV, Efficacy Evaluated Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=63)</b>
<b>Confirmed ORR, n (%)</b>	15 (45.5)	38 (60.3)
<b>(95%CI)</b>	(28.1, 62.2)	(47.2, 71.7)
<b>Complete response</b>	0 (0.0)	20 (31.7)
<b>Partial response</b>	15 (45.5)	18 (28.6)
<b>Median Response Duration (month)</b>	12.9	7.6
<b>(95%CI)</b>	(5.56, 12.9)	(7.43, NA*)

\*NA=not available due to small number of events

### **Reviewer's Comments:**

[12] *As shown in Table 11, the ORR assessed by (INV) is higher than the ORR assessed by IRF. The following Table 12 shows the concordance of INV and IRF ORR assessment, which were about 79% for metastatic BCC and 60% for local advanced BCC.*

**Table 12: Concordance of INV and IRF ORR Assessment**

ORR Assessed by IRF	ORR Assessed by INV	
	Responder	Non-Responder
<b>Metastatic BCC, n (%)</b>		
Responder	9 (27.3)	1 (3.0)
Non-responder	6 (18.2)	17 (51.5)
<b>Locally advanced BCC, n (%)</b>		
Responder	20 (31.7)	7 (11.1)
Non-responder	18 (28.6)	18 (28.6)

**Reviewer's Comments:**

- [13] *Per the applicant, the discordances between INV and IRF assessments in the locally advanced BCC cohort were mostly attributed to the IRF not assessing response in cases where the investigator had assessed a response. For the locally advanced BCC patients, according to the applicant's explanation, the lower concordance rate was owing to the multiple components of the composite endpoint definition, which included assessment of response by visible dimension for all patients and response by ulceration and/or according to RECIST for a subset of patients. The applicant also explained that for a small number of locally advanced BCC patients, the radiographic IRF identified additional sites of RECIST-measurable disease other than the target lesions that had been specified by the investigator, which could contribute to differences in the RECIST response assessment.*
- [14] *This reviewer broke down the concordance of INV and IRF ORR assessment using the categories of ORR: complete response (CR), partial response (PR) stable disease (SD) and progression disease (PD). As shown in the following Table 13, four PDs assessed by IRF in locally advanced BCC were CR assessed by INV. Six SDs in the metastatic BCC cohort and 9 SDs in the locally advanced BCC cohort assessed by IRF were considered to be PRs according to INV assessment.*

**Table 13: Concordance of INV and IRF ORR Assessment**

ORR Assessed by IRF, n	ORR Assessed by INV, n			
	CR	PR	SD	PD
<b>Metastatic BCC</b>				
CR				
PR		9	1	0
SD		6	14	1
PD		0	0	1
<b>Locally Advanced BCC</b>				
	0	1	0	1
CR	9	1	2	1
PR	3	7	3	0
SD	4	9	9	1
PD	4	0	1	3

The endpoints PFS and OS were also evaluated in Study SHH4476g. Table 14 shows PFS results for all enrolled patients.

**Table 14: PFS Results (IRF, All Enrolled Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=71)</b>
<b>Number of Events</b>	15	33
<b>Median PFS (month) (95%CI)</b>	9.5 (7.36, NA*)	9.5 (7.40, 11.90)

\*NA=not available due to small number of events

Table 15 shows OS results for all enrolled patients.

**Table 15: Overall Survival Results (All Enrolled Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=71)</b>
<b>Number of events</b>	7	9
<b>Median OS (month) (95%CI)</b>	NA* (13.86, NA*)	NA* (17.6, NA*)

\*NA=not available due to small number of events

### **Reviewer's Comments:**

[15] *The results of time-to-event endpoints such as PFS and OS are not interpretable in a single arm study.*

### **3.3 Evaluation of Safety**

Please refer to FDA's clinical review for safety evaluation of vismodegib.

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

The reviewer's results of subgroup analyses will be provided in this section.

### **4.1 Gender, Race, Age, and Geographic Region**

This reviewer performed the ORR subgroup analyses by age (greater than 65 versus less than or equal to 65 years), gender and region (US versus non-US) for two cohorts. Table 16 shows the summary of the subgroup analyses.

**Table 16: Subgroup ORR Results (IRF)**

Subgroup	Responders/Total Patients, n (%)	
	MBCC (n=33)	LaBCC (n=71)
<b>Age (yr)</b>		
<=65	6/19 (31.6)	19/33 (57.8)
>65	4/14 (28.6)	8/30 (26.7)
<b>Gender</b>		
Male	7/24 (29.2)	15/35 (42.9)
Female	3/9 (33.3)	12/28 (42.9)
<b>Region</b>		
Non-United States	1/7 (14.3)	7/21 (33.3)
United States	9/26 (34.6)	20/42 (47.6)

**Reviewer's Comments:**

[16] *The results of the subgroup analyses in Table 16 are considered to be exploratory.*

**4.2 Other Special/Subgroup Populations**

Besides the subgroup analyses based on patients demographics, this reviewer conducted the other subgroup analyses based on patient baseline characteristics. Since more than 90% of patients in the study had prior treatment and had prior surgery for cancer, there is no need to conduct the subgroup analyses for the patients who had prior treatment and had prior surgery for cancer respectively. Table 17 shows the baseline characteristics subgroup ORR analyses.

**Table 17: Baseline Characteristics Subgroup ORR Results (IRF)**

Subgroup	Responders/total Patients, n (%)	
	MBCC (n=33)	LaBCC (n=63)
<b>ECOG Performance Status</b>		
0	4/13 (30.8)	22/48 (45.8)
1 or 2	6/20 (30.0)	5/13 (38.5)
<b>Number of Target Lesions at Baseline</b>		
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)

## **Reviewer's Comments:**

[17] *As shown in Table 17, the 10 responders in metastatic BCC cohorts were the patients who had at least 3 target lesions at baseline. For that subgroup in the locally advanced BCC cohort, the observed ORR seems to be better than the other subgroups based on numbers of target lesions at baseline. However, the interpretation of results based on the small sample size subgroups should be viewed cautiously.*

[18] *The results of the subgroup analyses in Table 17 are considered exploratory.*

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

Based on the efficacy data collected from Study SHH4476g, the applicant claimed that the administration of vismodegib to patients with advanced BCC demonstrated evidence of single-agent activity, with ORRs assessed by the IRF of 30.3% (95% CI: 15.6%, 48.2%) in patients with metastatic BCC and 42.9% (95% CI: 30.5%, 56.0%) in patients with locally advanced BCC. The ORRs were significantly greater than the protocol-specified minimal clinical benefit threshold of 10% ( $p = 0.0011$ ) and 20% ( $p < 0.0001$ ), respectively; 2) the applicant also claimed that response was durable in both patient cohorts, with a median IRF-determined duration of objective response of 7.6 months in each cohort.

This reviewer has identified some issues and has the following findings.

#### **Issues:**

- Although a formal hypothesis test was pre-specified as the primary analysis for each cohort in the SAP of Study SHH4476g, without a control arm in the study, the statistical strength of efficacy can not be evaluated. Therefore, no inferential conclusion of statistical analysis can be drawn from a non-comparative study. *Descriptive statistics are more appropriate in reporting the results for a single arm study.*

#### **Findings:**

- A total of 104 patients were enrolled in the pivotal study SHH4476g. Based on a total of 96 patients who had confirmed biopsy of BCC at baseline in the study: the primary analysis results of ORR based on IRF assessment data are shown in the following Table 18.
- In sensitivity analyses conducted by this reviewer, ORR ranges from 38.0% to 43.7% for the locally advanced BCC cohort.

**Table 18: ORR Results (IRF) (Efficacy-Evaluable Patients)**

	<b>MBCC (n=33)</b>	<b>LaBCC (n=63)</b>
<b>Confirmed ORR, n (%) (95%CI)</b>	10 (30.3) (15.6, 48.2)	27 (42.9) (30.5, 56.0)
<b>Complete response</b>	0 (0.0)	13 (20.6)
<b>Partial response</b>	10 (30.3)	14 (22.2)
<b>Median Response Duration (month) (95%CI)</b>	7.6 (5.62, NA*)	7.6 (5.65, 9.66)

\*NA=not available due to small number of events

## 5.2 Conclusions and Recommendations

Since the pivotal study SHH4476g was a single arm study, no conclusion of statistical strength of efficacy evidence and statistical inference can be drawn from the non-comparative study. Whether the objective response rates demonstrated in the single pivotal Study SHH4476g are clinically meaningful and provide a favorable benefit-risk profile of Vismodegib for the proposed indication are deferred to the clinical review team.

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/s/  
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XIAOPING JIANG  
01/06/2012

KUN HE  
01/06/2012

THOMAS E GWISE  
01/06/2012

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 203388**

**Applicant: Genentech**

**Stamp Date:**

**September 8, 2011**

**Drug Name: Vismodegib**

**NDA/BLA Type: Type 1- New  
Molecular Entity**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?   Yes**

If the NDA/BLA is not fileable from the statistical 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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.			×	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			×	
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	×			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

File name: Statistics Filing Checklist for NDA203388

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Xiaoping (Janet) Jiang, Ph.D.	10/04/2011
Reviewing Statistician	Date
Kun He, Ph.D.	10/04/2011
Team Leader	Date

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10/04/2011

KUN HE  
10/04/2011