CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 13, 2012

From: Mona Patel, Pharm.D., DOP2/OHOP/OND/CDER/FDA

Subject: Clinical Pharmacology Comments on exploratory analysis submitted on 1.10.2012

Product: NDA 203388: ERIVEDGE (vismodegib)

FDA has completed its review of your January 10, 2012 submission containing your exploratory analysis of the impact of pH altering drugs on systemic exposure of vismodegib. We have the following clinical pharmacology comments which were previously conveyed to you at the 1.11.12 telecon.

1. The plots for each patient who took a pH elevating agent and had relevant PK data for a visual comparison of pre- and post-administration of a pH elevating agent are not provided. Using the average PK data for the comparison between patients with and without pH altering agents may mask an effect of such agents on vismodegib exposure.

2. The retrospective and exploratory PK analysis on limited number of patients could not rule out the possible effects of pH elevating agents on vismodegib exposure. For example, there are large variations of the dose intervals between pH elevating agents and vismodegib. There is also considerable variability for the PK sampling time.

3. The analysis should separate the three classes of agents as PPI, H2 blockers and antacids because PPI/H_2 blockers have prolonged effect and high potency regarding the pH elevation relative to antacids.

4. We have identified some inconsistencies between the Figure 2 and Table 2 in your document submitted on 01/10/2011. For example, Table 2 (below) shows that Patient 13116 had the largest increase in concentration when vismodegib was administered with a pH-elevating agent, but Figure 2 (below) shows that this

patient had a decrease in vismodegib concentration when vismodegib was administered with a pH-elevating agent.

Figure 2: Intra-Patient Steady-State Concentrations of Total (A) and Unbound (B) Vismodegib for Patients Taking a pH Elevating Agent Concomitantly with Vismodegib

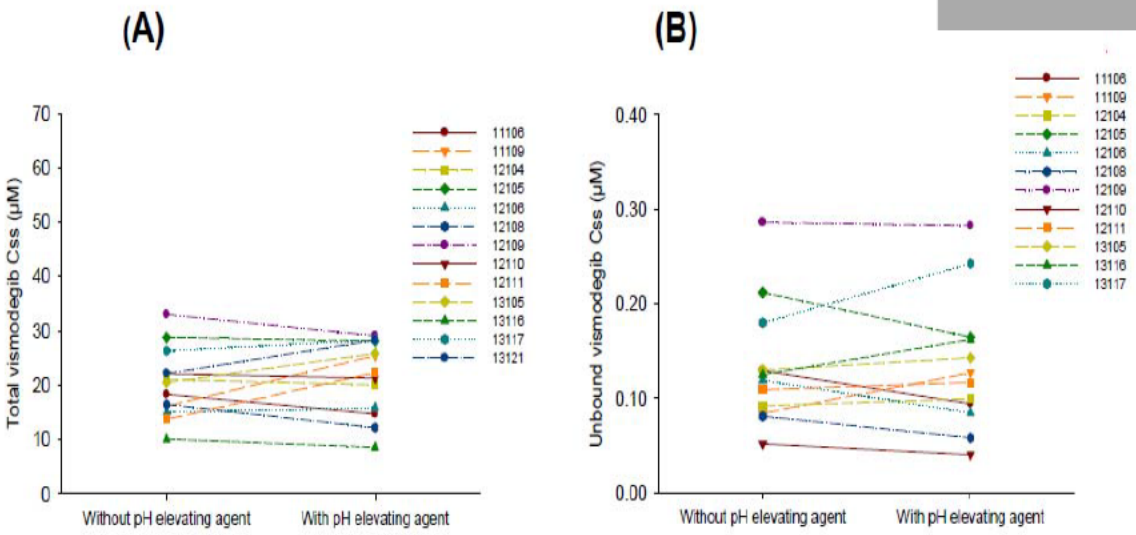

Table 2: Intra-Patient Fold Change in Vismodegib Total C_{ss} and AAG Post- and Pre-administration of a pH Elevating Agent

Subject ID	Fold Change in Vismodegib Mean C_{ss}	Fold Change in Mean AAG
13116	1.62	1.57
12104	1.58	1.15
14121	1.28	NA
13117	1.26	1.13
14112	1.08	1.01
12108	1.06	1.14
12106	0.98	1.11
13105	0.96	NA
12105	0.95	1.04
12111	0.88	0.90
13121	0.85	0.96
11106	0.80	1.04
12109	0.74	0.90

NA: AAG concentration not measured in this patient at the relevant timepoint.
Note: Values >1.0 indicate an increase in concentration when vismodegib was administered with a pH-elevating agent, relative to when vismodegib was given alone in the same patient. Similarly, values <1.0 indicate a decrease in concentration.

5. The high protein binding to both human serum albumin and alpha-1 acid glycoprotein (AAG) does not rule out the possible effects of pH on vismodegib solubility and bioavailability. For example, binding of dasatinib to human plasma protein was 96%. Erlotinib is approximately 93% protein bound to plasma albumin and AAG. The bioavailability of both drugs is affected by pH elevating agents. In addition, the mechanism for the observed correlation between AAG levels and total vismodegib concentrations but not the unbound concentrations is not clear.

6. The co-medication listing in the Appendices received January 10, 2012 is not consistent with the co-medication listing provided in the NDA submission.

Other considerations:

7. The solubility of vismodegib is pH dependent (b) (4) between pH 7 (0.1μg/mL) and pH 1 (990 μg/mL).

8. pH dependent solubility has been seen in several other drugs such as dasatinib, erotinib and nilotinib. For dasatinib and erolitinib, *in vivo* studies have been conducted and the results led to the labeling recommendations on how to dose those agents. For nilotinib, a PMR has been issued.

9. The potential effect of pH elevating agents on vismodegib absorption is suggested by a PopPK analysis. The ka is 9.025 and 17.65 day^{-1} in cancer patients and healthy subjects, respectively. As you stated in the original NDA submission, the slower absorption in patients may be due to multiple factors such as slower gastrointestinal (GI) transit, higher GI pH, and co-medications affecting GI conditions, which in turn may affect vismodegib solubility and absorption *in vivo*.

10. FDA exploratory analysis:

Table 1 contains the FDA exploratory analysis of the primary efficacy endpoint from the registration trial SHH4476g. A trend towards lower objective response is observed among patients with locally advanced disease BCC who have been systemically exposed to a pH elevating agent while on vismodegib treatment, and a similar trend is observed for patients with metastatic BCC.

It is noted that this analysis is exploratory and could not exclude the confounding factors because of the nature of a single-arm trial. Nevertheless, this exploratory analysis provides supportive evidence for the necessity of a dedicated study on pH elevating agents.

Table 1: Objective Response by Exposure to pH Elevating Agents: Efficacy Evaluable patients in SHH4476g

Systemic Exposure to pH elevating agents	Metastatic BCC		Locally Advanced BCC		All Patients	
	n	Responders (%)	n	Responders (%)	n	Responders (%)
Yes	11	3 (27.2%)	16	4 (25.0%)	27	7 (25.9%)
No	22	7 (31.8%)	47	23 (48.9%)	69	30 (43.5%)
All Patients	33	10 (30.3%)	63	27 (42.9%)	96	37 (38.5%)

Taken together, FDA continues to request for a dedicated clinical trial as a PMR to evaluate if pH altering agents change the bioavailability of vismodegib. You may study the worst case scenario first in healthy volunteers, and then determine if further studies on other classes of gastric pH elevating agents are necessary. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents.

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/s/

MONA G PATEL
01/13/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203-388/ SDN: 29
Submission Date(s):	01/10/2012
Brand Name:	ERIVEDGE®
Generic Name:	Vismodegib
Submission Type:	Clinical pharmacology Response
PUDFA Date:	03/08/2012, 2/8/2012 (Target date)
Sponsor:	Genentech, Inc.
Relevant IND(s):	IND 74573
Formulation; Strength(s):	150 mg capsules
Proposed Indication:	Advanced basal cell carcinoma (BCC)
OND Division:	Division of Oncology Products 2 (DOP2)
OCP Division:	Division of Clinical Pharmacology 5 (DCP5)
Primary Reviewer:	Jian Wang, Ph.D.
Team Leader:	Hong Zhao, Ph.D.

In the current submission, Genentech provides a response to FDA's request to conduct a clinical trial to evaluate if pH elevating agents (e.g. H2 antagonists, proton pump inhibitors and antacids) alter the bioavailability of vismodegib as a PMR. Genentech's response includes an exploratory analysis on the effects of pH elevating agents on vismodegib pharmacokinetics with the data retrospectively collected from clinical trials.

Reviewer's comments

Regarding the applicant's PK data analysis provided 1/10/2012:

- The concentration-time plots for each patient who took a pH elevating agent and with a relevant PK sample for a visual comparison of pre- and post-administration of a pH elevating agent are not provided. Using the average PK data for the comparison between patients with and without pH altering agents may mask an effect of such agents on vismodegib exposure if it truly exists.

- The retrospective and exploratory PK analysis on limited number of patients could not rule out the possible effects of pH elevating agents on vismodegib

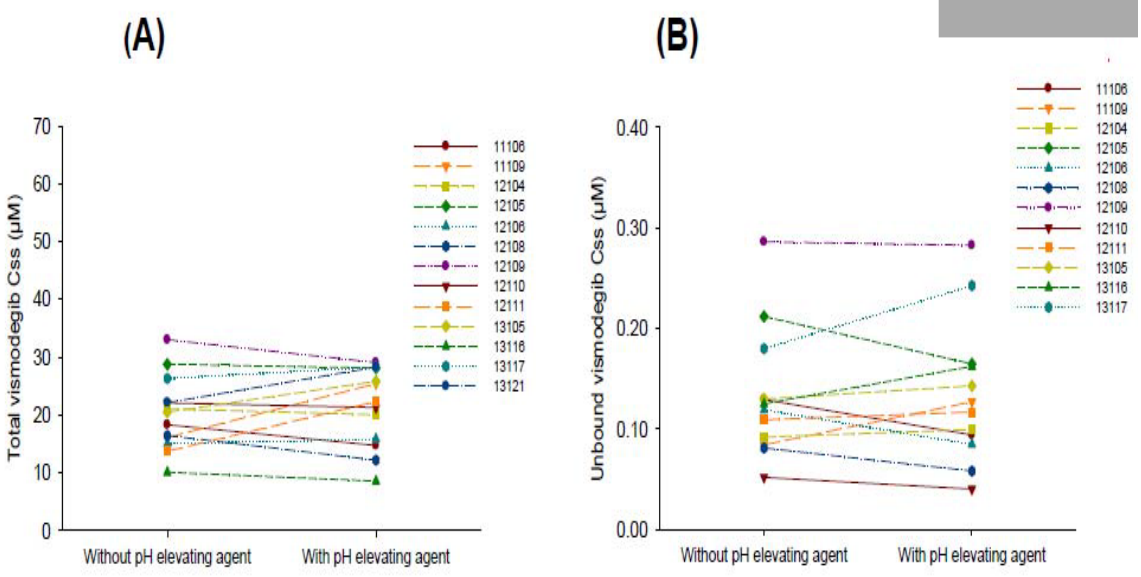
exposure. For example, there are large variations of the dose intervals between pH elevating agents and vismodegib. There is also considerable variability for the PK sampling time.

- The analysis should separate the three classes of agents as PPI, H2 blockers and antacids because PPI/H_2 blockers have prolonged effect and high potency regarding the pH elevation.

- The applicant's analysis shown in Figure 2(a) and Table 2 in the document submitted on 01/10/2011 is inconsistent. For example, Table 2 showed that Patient 13116 had the largest increase in concentration when vismodegib was administered with a pH-elevating agent. But it is not the case as shown in Figure 2(a).

The applicant's Figure 2:

Figure 2: Intra-Patient Steady-State Concentrations of Total (A) and Unbound (B) Vismodegib for Patients Taking a pH Elevating Agent Concomitantly with Vismodegib



The applicant's Table 2:

Table 2: Intra-Patient Fold Change in Vismodegib Total C_{ss} and AAG Post- and Pre-administration of a pH Elevating Agent

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Note: Values >1.0 indicate an increase in concentration when vismodegib was administered with a pH-elevating agent, relative to when vismodegib was given alone in the same patient. Similarly, values <1.0 indicate a decrease in concentration.

- The high protein binding to both human serum albumin and alpha-1 acid glycoprotein (AAG) does not rule out the possible effects of pH on vismodegib solubility and bioavailability. For example, binding of dasatinib to human plasma protein was 96%. Erlotinib is approximately 93% protein bound to plasma albumin and AAG. The bioavailability of both drugs is affected by pH elevating agents. In addition, there is a correlation between AAG levels and total vismodegib concentrations, but not the unbound concentrations; the mechanism of this finding is not clear.

- The co-medication listing of the Appendices (received 1/10/2012) is not consistent with the co-medication listing provided in the NDA submission?.

Other considerations:

- The solubility of vismodegib is pH dependent; the solubility in water at pH 7 is 0.1µg/mL and is 990 µg/mL at pH 1. (b) (4)

- pH dependent solubility has been seen in several other drugs such as dasatinib, erotinib and nilotinib. For dasatinib and erolitinib, *in vivo* studies have been conducted and the results lead to the labeling recommendations on how to dose those agents. For nilotinib, a PMR has been issued. The proposed PMR reflects the FDA current thinking.

- The potential effect of pH elevating agents on vismodegib absorption is suggested by a PopPK analysis. The ka is 9.025 and 17.65 day^{-1} in cancer patients and healthy subjects, respectively. As you stated in the original NDA submission, the slower absorption in patients may be due to multiple factors such as slower gastrointestinal (GI) transit, higher GI pH, and co-medications affecting GI conditions, which in turn may affect vismodegib solubility and absorption *in vivo*.

- Efficacy exploratory analysis:

Table 1 contains the FDA exploratory analysis of the primary efficacy endpoint from the registration trial SHH4476g. A trend towards lower objective response is observed among patients with locally advanced disease BCC who have been systemically exposed to a pH elevating agent while on vismodegib treatment, and a similar trend is observed for patients with metastatic BCC.

It is noted that this analysis is exploratory and could not exclude the confounding factors because of the nature of a single-arm trial. Nevertheless, the results provide supportive evidence for the necessity of a dedicated study on pH elevating agents.

Table 1: Objective Response by Exposure to pH Elevating Agents: Efficacy Evaluable patients in SHH4476g

Systemic Exposure to pH elevating agents	Metastatic BCC		Locally Advanced BCC		All Patients	
	n	Responders (%)	n	Responders (%)	n	Responders (%)
Yes	11	3 (27.2%)	16	4 (25.0%)	27	7 (25.9%)
No	22	7 (31.8%)	47	23 (48.9%)	69	30 (43.5%)
All Patients	33	10 (30.3%)	63	27 (42.9%)	96	37 (38.5%)

Overall Conclusion:
Taken together, FDA continues to request for a dedicated clinical trial as a PMR to evaluate if pH altering agents change the bioavailability of vismodegib. You may study the worst case scenario first in healthy volunteers, and then determine if further studies on other GI pH elevating drugs are necessary. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents. For example, separating the doses between those drugs and EVRIEDGE by several hours may be an option of practical solutions.

Discussion at Teleconference Held on January 11, 2012
The major points of the above comments were conveyed to the sponsor at the teleconference held on January 11, 2012. The sponsor agreed to propose milestone timelines for the PMR to study the effect of gastric pH elevating agents on vismodegib bioavailability. FDA suggested that the sponsor could study the worst case scenario first

and the results will determine whether additional studies are required. The sponsor will submit the draft protocol for FDA review and comment.

With regard to the proposed organ dysfunction PMR studies, FDA agreed with the sponsor's proposal to remove the statement of balancing demographics among the study arms from the PMR language. However, FDA reminded the sponsor to follow the pertinent FDA guidance and make efforts to balance age, gender and body weight among study arms to reduce inter-subject variability.

Recommendation: Please convey the above comments to the sponsor in writing and incorporate the discussion points into the meeting minutes.

Signatures

_____

Jian Wang, Ph.D
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

_____

Hong Zhao, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 5

Cc: DOP2: CSO – **M Patel**; MTL – **J Summers**; MO – **M Axelson**
DCP5: Reviewers – **J Wang**; TL – **H Zhao**; Division Deputy Director – **B Booth**; Division Director - **A Rahman**

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/s/

JIAN WANG
01/12/2012

HONG ZHAO
01/12/2012
I concur.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203-388
Submission Date(s):	09/08/2011
Brand Name:	ERIVEDGE®
Generic Name:	Vismodegib
Submission Type; Code:	NME NDA; Priority review
PUDFA Date:	03/08/2012, 2/8/2012 (Target date)
Sponsor:	Genentech, Inc.
Relevant IND(s):	IND 74573
Formulation; Strength(s):	150 mg capsules
Proposed Indication:	Advanced basal cell carcinoma (BCC)
OND Division:	Division of Oncology Products 2 (DOP2)
OCP Division:	Division of Clinical Pharmacology 5 (DCP5)
Primary Reviewer:	Jian Wang, Ph.D.
Team Leader:	Hong Zhao, Ph.D.
Pharmacometric Reviewer:	Bahru Habtemariam, Pharm.D.
Pharmacometric Team Leader:	Christine Garnett, Pharm.D.
Pharmacogenomics Reviewer:	Christian Grimstein, Ph.D.
Pharmacogenomics Team Leader:	Rosane Charlab Orbach, Ph.D. (Acting)

OCP Briefing was held on January 4th, 2012. The attendees at the briefing include: Shiew Mei Huang, NAM Atiqur Rahman, Brian Booth, Michael Axelson, John Lazor, Mehul Mehta, Issam Zineh, Lei Zhang, Darrell Abernethy and others.

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1 EXECUTIVE SUMMARY

ERIVEDGE (vismodegib) is a new molecular entity and the first in the class that binds to and inhibits smoothened, a transmembrane protein involved in Hedgehog signal transduction. The proposed indication is for the treatment of adult patients with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate. The proposed dose regimen is 150 mg (1 capsule) administered orally once daily.

A single-arm, multi-center, open-label, 2-cohort registrational trial conducted in 104 patients with advanced BCC supports the efficacy claim. This trial demonstrated durable tumor shrinkage with an objective response rate (ORR) of 43% (95% CI: 30%, 56%) in patients with locally advanced disease and of 30% (95% CI: 16%, 48%) in patients with metastatic disease, with a median duration of response (DoR) of 7.6 months in both cohorts. In uncontrolled trials with vismodegib, the most common adverse events (AEs) reported (incidence ≥ 30%) were muscle spasms (75%), alopecia (63%), dysgeusia (55%), weight decreased (52%), fatigue (45%), diarrhea (31%) and nausea (31%). The most common serious adverse events (SAEs) identified (incidence ≤2%) were dyspnea, pneumonia, urinary tract infections, pulmonary embolism, cardiac failure, deep vein thrombosis, gastrointestinal hemorrhage, and hypokalemia. While high incidence and unusual nature of many of the common, non-serious AEs make attribution to the drug likely, the causal relationship of the SAEs to vismodegib treatment is uncertain due to the single arm study design of the clinical trial.

The pharmacokinetic (PK) profile of vismodegib can be explained by a saturable absorption, saturable binding to AAG, minor metabolism and major hepatic elimination. Vismodegib exhibits nonlinear PK as evidenced by dose- and concentration-dependent changes in PK parameters following daily dosing. Exposure-response relationships were not identified for efficacy or safety based on the limited data. The proportion of patients with ORR (efficacy) and with Grade 3+ weight loss or fatigue (safety) did not increase with increasing total or unbound plasma vismodegib concentrations. In a thorough QTc study in 60 healthy subjects, no QTc interval prolongation was observed with the therapeutic dose regimen of vismodegib.

1.1 Recommendation

This NDA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language and the identified clinical studies under the post marketing requirements (PMRs). The Office of Clinical Pharmacology recommends approval of this NDA.

Please see Section 3 for Detailed Labeling recommendations.

1.2 Post Marketing Requirements

1. To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function -Study Design, Data Analysis and Impact on Dosing and Labeling" The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on 17 October 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248
Final Protocol Submission Date: 31 January 2012
Trial Completion Date: 30 September 2014
Final Report Submission: 31 March 2015

2. To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling". A "reduced" renal impairment study could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

   The timetable you submitted on 17 October 2011 states that you will conduct this trial according to the following schedule:

   Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248
   Final Protocol Submission Date: 31 January 2012
   Trial Completion Date: 30 September 2014
   Final Report Submission: 31 March 2015

3. To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone).

   The timetable you submitted on 17 October 2011 states that you will conduct this trial according to the following schedule:

   Trial Completion Date: March 30, 2012
   Final Report Submission: March 31, 2012

4. Conduct a clinical trial to evaluate if proton pump inhibitors, H_2 antagonists and antacids alter the bioavailability of vismodegib. You may study the worst case scenario first, and then determine if further studies on other drugs are necessary. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents. Submit the study protocol and final reports following the agreed upon milestone timelines:

   Protocol Submission Date:
   Trial Completion Date:
   Final Report Submission:

With regard to PMR#4, FDA accepted the applicant's proposal to submit the exploratory analysis results based on the available data by January 10 for FDA review before discussing the milestone timelines.

1.3 Post Marketing Commitments

None.

1.4 Comments to the Applicants

(b) (4)

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Proposed Dose and Indication: ERIVEDGE (vismodegib) is a hedgehog pathway inhibitor. The proposed indication is for the treatment of adult patients with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate. The proposed dosage of ERIVEDGE is 150 mg (1 capsule) given orally once daily (QD).

ADME: The single dose absolute bioavailability of vismodegib at 150 mg is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg or 540 mg vismodegib. ERIVEDGE may be taken without regard to meals because the systemic exposure of vismodegib at steady state is not affected by food. Vismodegib plasma protein binding is greater than 99%. Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG), and binding to AAG is saturable. The parent drug is the predominant component (> 98%) in the circulation. Metabolic pathways of vismodegib include oxidation, glucuronidation, and pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5. Vismodegib and its metabolites are eliminated primarily by the hepatic route with 82% of the administered dose recovered in the feces and 4.4% recovered in the urine with 56 days. The estimated elimination half-life ($t_{1/2}$) of vismodegib is 4 days after continuous once-daily dosing and 12 days after a single dose.

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

Dose Selection: Vismodegib plasma concentrations after a single oral dose increased with dose escalation from 150 mg to 270 mg; however, at 540 mg, the mean total and unbound plasma vismodegib concentrations were similar to that observed at 270 mg, suggesting saturable absorption. Increasing the daily dose from 150 mg to 270 or 540 mg did not result in higher steady-state plasma vismodegib concentrations. The PK results of the dose-scheduling study in cancer patients suggested that patients receiving less frequent dosing of vismodegib, either as a twice a week (TIW) or once a week (QW) regimen or a lower QD dose, would be at risk of not achieving unbound vismodegib concentrations that associated with efficacy in advanced BCC. The 150-mg vismodegib QD regimen has been well tolerated to date and shown to be effective in patients with advanced BCC. Taken together, these data support the selection of the 150 mg QD vismodegib regimen.

Drug-Drug Interaction: *In vitro* study results indicate that vismodegib is an inhibitor of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19 and transporter BCRP. *In vivo* studies indicate that there was no clinically meaningful difference in the pharmacokinetics of rosiglitazone, a CYP2C8 substrate, ethinyl estradiol, or norethindrone when co-administered with vismodegib. Vismodegib was identified to be a substrate of CYP2C9 and CYP3A4; however, CYP inhibition would unlikely alter vismodegib concentrations because of its slow elimination via multiple pathways, including minor metabolism by several CYPs and main excretion of unchanged drug. In clinical trials, similar steady-state plasma vismodegib concentrations were observed in patients concomitantly treated with CYP3A4 inducers (i.e., carbamazepine, modafinil, phenobarbital) and in those concomitantly treated with CYP3A4 inhibitors (i.e., erythromycin, fluconazole). *In vitro* studies results also indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp).

E-R Relationship: No exposure-response relationship for efficacy was identified. The proportion of patients with over all response rate (ORR) did not increase with increasing total or unbound vismodegib concentrations. Similarly, no trend of exposure-response for safety was found. The proportion of patients with Grade 3+ weight loss or fatigue did not increase with increasing total or unbound vismodegib concentrations. In a thorough QTc study in 60 healthy subjects, there was no effect of therapeutic doses of ERIVEDGE on the QTc interval.

***Product Comparability*:** The pharmacokinetic analysis of the Phase I product (b) (4) (b) (4) and Phase II product (b) (4) showed a difference in exposure after single-dose administration, but not at steady-state after continuous daily dosing.

Signatures

Jian Wang, Ph.D
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Division of Clinical Pharmacology 5

Bahru Habtemariam, Pharm.D..
Pharmacometrics Reviewer
Division of Pharmacometrics

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Christine Garnett, Pharm.D.
Pharmacometrics Team Leader

Christian Grimstein, Ph.D.
Pharmacogenomics Reviewer

Nam Atiqur Rahman, Ph.D.
Division Director, Division of Clinical Pharmacology V

Rosane Charlab Orbach, Ph.D.
Pharmacogenomics Team Leader (Acting)

Cc: DOP2: CSO – **M Patel**; MTL – **J Summers**; MO – **M Axelson**
DCP5: Reviewers – **J Wang**; TL – **H Zhao**; Division Deputy Director – **B Booth**; Division Director - **A Rahman**

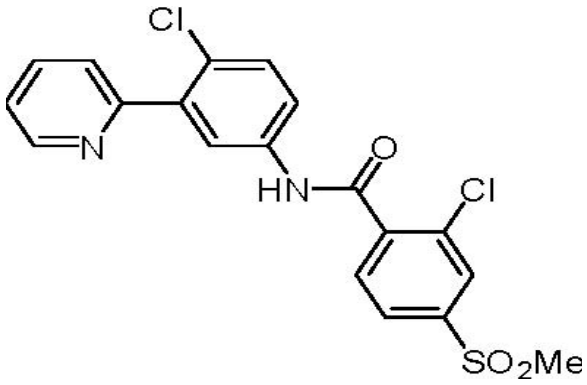
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

(Do not include full details of formulation here. Details go in Biopharmaceutics section.)

Established name: Vismodegib
Molecular Formula: $C_{19}H_{14}Cl_2N_2O_3S$
Molecular Weight: 421 g/mol
Chemical Name (CAS): 2-chloro-N-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonyl-benzamide
Chemical Structural:



Vismodegib, (b) (4) is used in clinical trials. The solubility of vismodegib is pH dependent, 0.1 µg/mL in water at pH 7 and 0.99 mg/mL at pH 1. Vismodegib melts at approximately (b) (4). The pKa (b) (4) and the partition coefficient in (b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Vismodegib is a low molecular weight, orally available inhibitor of the Hedgehog (Hh) pathway. Vismodegib binds to and inhibits the smoothened transmembrane protein (SMO) thereby preventing Hh signal transduction. Hh pathway activation caused by mutations or by Hh ligand overexpression has been implicated in cancer. Inhibition of the Hh pathway in pre-clinical models of cancer leads to tumor shrinkage or tumor growth delay.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose regimen for vismodegib is 150 mg given orally once daily (QD), with or without food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Eight trials in healthy subjects or patients with advanced cancers were completed to support the clinical pharmacology and biopharmaceutics portion of the NDA (see Table 1). In addition to the clinical pharmacology studies, the sponsor performed a population PK analysis which included PK data from the registrational trial.

Table 1: Trials Supporting the Clinical Pharmacology and Biopharmaceutics of Vismodegib

Trial Number	Study Type	Population	Dose
SHH4433g	Single-dose	Healthy women of non-childbearing potential	150 mg single oral
SHH4683g			
Part A	Single-dose IV/PO	Healthy women of non-childbearing potential	single 14C tracer IV dose administered 2 hr after a single 150 mg PO dose
Part B	Single-dose PO	Healthy women of non-childbearing potential	150 mg single oral Suspension dose labeled with 14C tracer
Part C	Multi-dose PO, single-dose IV	Healthy women of non-childbearing potential	150 mg PO QD x 7 days with single 14C tracer IV 2 hr after PO dose on Day 7
Part D	Multi-dose PO	Healthy women of non-childbearing potential	150 mg PO QD x 6 days with single 14C tracer PO suspension dose on Day 7
SHH4610g	Two-period (loading and maintenance), randomized	Cancer patients	150 mg PO QD, TIW, QW
SHH8395g	Two-part, single- and multi-dose, with or without food	Cancer patients	150 mg PO QD
SHH4871g	Randomized, double-blind, 3-arm parallel with positive and placebo controls	Healthy women of non-childbearing potential	Vismodegib: 150 mg PO QD x 7 days Moxifloxacin: single 400 mg PO
SHH3925g	Single- and multi-dose	Advanced solid tumor patients	150, 270, and 540 mg PO QD
SHH4476g	Multi-dose	BCC patients	150 mg PO QD
SHH4429g	Multi-dose, sequential	Metastatic CRC (first-line)	Vismodegib: 150 mg or placebo PO QD in combination with FOLFOX plus bevacizumab or FOLFIRI plus bevacizumab

Table 2: Trials contributing to Population Pharmacokinetics

Study	Enrolled	N*	Population	Vismodegib Dose
SHH3925g Phase I	68	68	Patients with advanced solid tumors including 33 advanced BCC patients	Stage 1 cohorts: single PO on Day 1 + continuous PO QD from Day 8 at 150, 270, or 540 mg Stage 2 BCC cohort: 150 or 270 mg PO QD Stage 2 safety cohort: 150 mg PO QD Stage 2 new formulation cohort: 150 mg PO QD
SHH4610g Phase Ib	67	63	Patients with advanced solid tumors	Single 150 mg PO on Day 1 + continuous PO QD Day 4-14, followed by 150 mg PO QD, TIW, or QW from Day 14
SHH4476g Phase II	104	73	Advanced BCC patients	150 mg PO QD
SHH4433g Phase I	3	3	Healthy WONCBP	150 mg single PO
SHH4683g Phase I	24	18	Healthy WONCBP	A: Single 150 mg PO + single 100 µg IV labeled with 14C** C: 150 mg PO QD×7 dose with single 100 µg IV labeled with 14C on Day 7** D: 150 mg PO QD×6 dose with single 150 mg oral solution labeled with 14C on Day 7**

WONCBP = women of non-childbearing potential, * Number of patients included in the PopPK analysis, ** PK data obtained from trials with IV and oral suspension not included in the PopPK analysis

To support the efficacy claims , the sponsor submitted the results from a single-arm, multi-center, open-label, 2-cohort registrational trial conducted in 104 patients with BCC, including metastatic BCC (mBCC, n = 33) and locally advanced BCC (laBCC, n = 71). Patients were treated with oral dosing of vismodegib at 150 mg daily. The median age was 62 years for all patients with 45% of patients being older than 65 years.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Efficacy Endpoint

The primary efficacy endpoint was objective response rate (ORR) defined as a complete or partial response (CR or PR) determined on two consecutive assessments separated by at least 4 weeks. In the mBCC cohort, tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. In the laBCC cohort, tumor response was assessed based on visual assessment of external tumor and ulceration, tumor imaging (if appropriate), and tumor biopsy. A patient with locally advanced BCC was considered a responder if at least one of the following three criteria was met and the patient did not experience disease progression: (1) ≥ 30% reduction in lesion size [sum of the longest diameter (SLD)] from baseline in target lesions by radiography; (2) ≥ 30% reduction in SLD from baseline in externally visible dimension of target lesions; (3) complete resolution of ulceration in all target lesions.

Biomarkers

Biomarker *GLI1* expression in hair follicle cells from pulled hair and skin-punch biopsies prior to and during vismodegib treatment was measured by quantitative real-time polymerase chain

reaction in a dose-scheduling trial SHH3925g. When SMO signaling is inhibited, the transcription factor GLI remains inactive, thus preventing the expression of genes that mediate the role of Hh on tumor growth.

2.2.3 ***Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Yes. Total and unbound vismodegib in plasma were analyzed by validated methods for several clinical trials to explore the exposure-response relationship. Refer to 2.6, Analytical Section

2.2.4 Exposure-Response

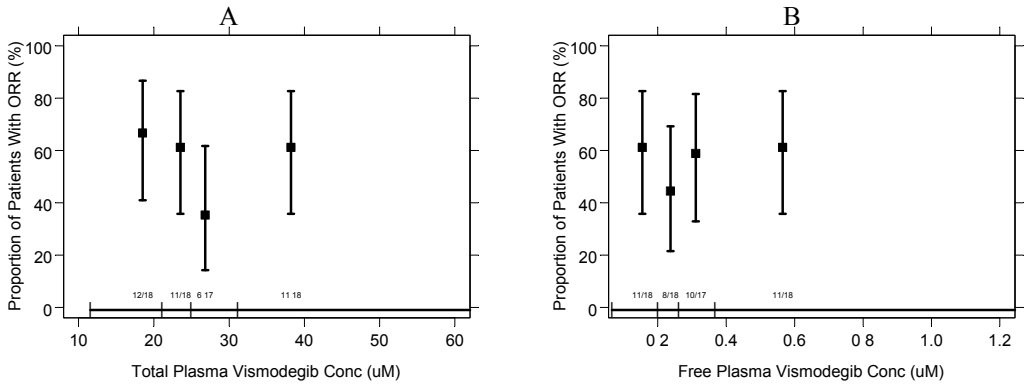
2.2.4.1 ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?***

(If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.)

In clinical trials, no significant E-R relationship was observed for biomarker *GLI1* expression in skin-punch biopsies from advanced BCC patients.

Exposure-response relationships were not identified for vismodegib efficacy based on the available data. Steady state plasma concentrations of total and free vismodegib along with efficacy data were available from 71 patients with mBCC or with laBCC who participated in the registrational trial (study SHH4476G). Exposure-response analyses were performed to determine whether total or free (unbound) vismodegib plasma concentrations correlate with the primary efficacy endpoint, ORR following vismodegib doses of 150 mg once daily. **Figure 2** below shows that increasing total or free vismodegib concentrations does not correlate with the proportions of patients with ORR.

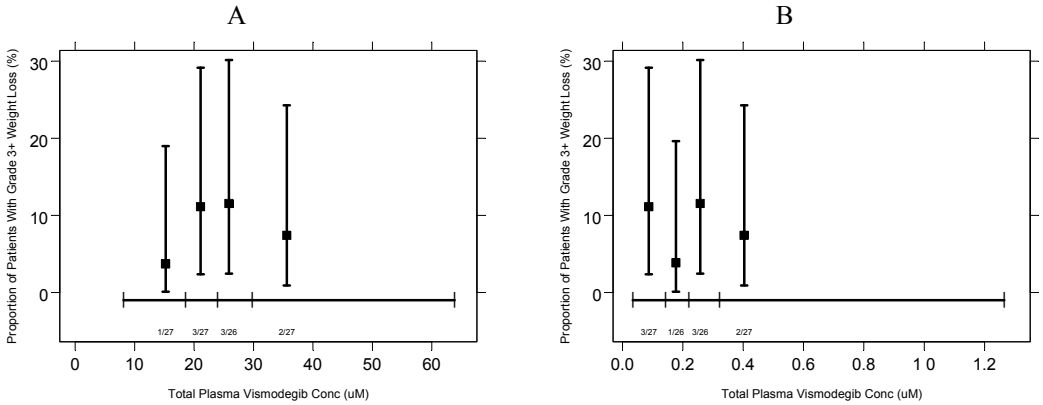
Figure 1. Proportion of objective response rate (ORR) is not influenced by increasing steady-state total (A) or free (B) plasma vismodegib concentrations.



2.2.4.2 ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*** **If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.**

Exposure-response relationships were not identified for vismodegib safety based on the available data. Safety data for vismodegib were available from 138 patients with advanced BCC who participated in the phase 1 and phase 2 trials. The most frequent Grade 3 or more adverse events (Grade 3+) were weight loss (n=10, 7.2 %) and fatigue (n=9, 5.1 %). Out of the 138 patients with BCC in the safety database, steady state PK samples were collected from 106 patients. As shown in Figure 2 below, the proportion of patients with Grade 3 or more weight lose (Grade 3+) does not increase with increasing total of free vismodegib concentrations. A similar trend was observed for Grade 3+ fatigue.

Figure 2. Proportion of patients with Grade 3+ weight loss does not increase with increasing total (A) or free (B) vismodegib plasma concentrations).



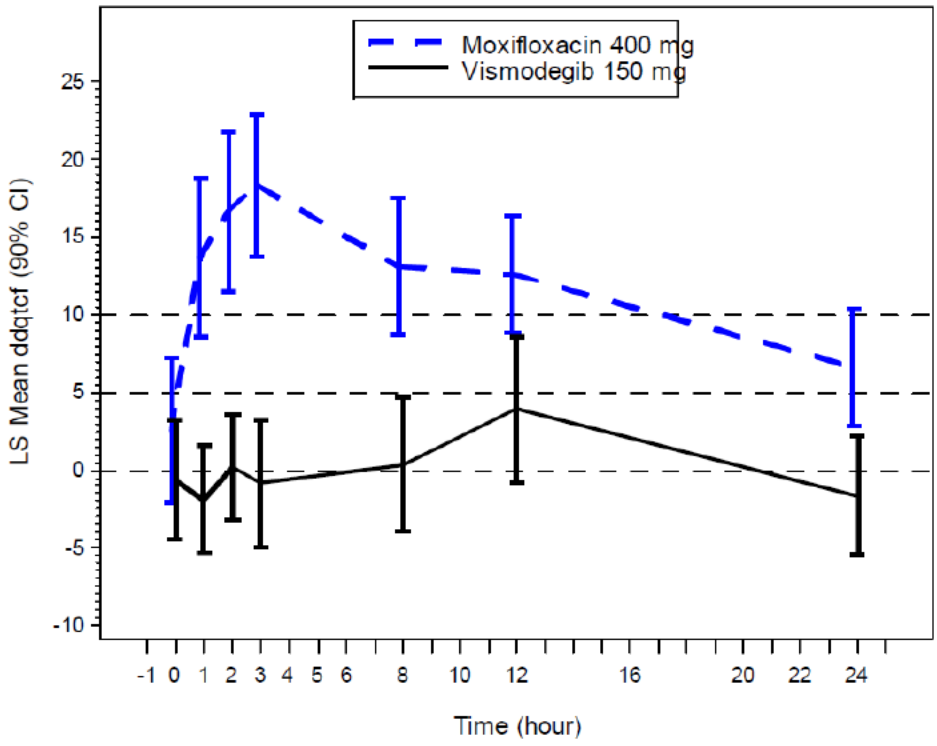
2.2.4.3 ***Does this drug prolong the QT or QTc interval?*** **(You must answer this question, unless this is addressed in the question above.)**

The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the results of the thorough QTc (TQT) study and concluded that no significant QTc prolongation effect of Vismodegib was detected (See IRT review by Dr. Qianyu Dang dated 11/30/2011 in DARRTS). In this randomized, blinded, mixture of parallel and crossover study, 60 healthy females received vismodegib 150 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 3. The largest upper bound of the 2-sided 90% CI for the mean difference (ΔΔQTcF) between vismodegib 150 mg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated (Figure 3), indicating that assay sensitivity was established. Please refer to Section 3 for the proposed labeling.

Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Vismodegib 150 mg and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Vismodegib 150 mg	12	3.9	(-0.8, 8.6)
Moxifloxacin 400 mg*	3	18.3	(13.7, 22.9)

Figure 3: Mean and 90% CI ΔΔQTcF Timecourse



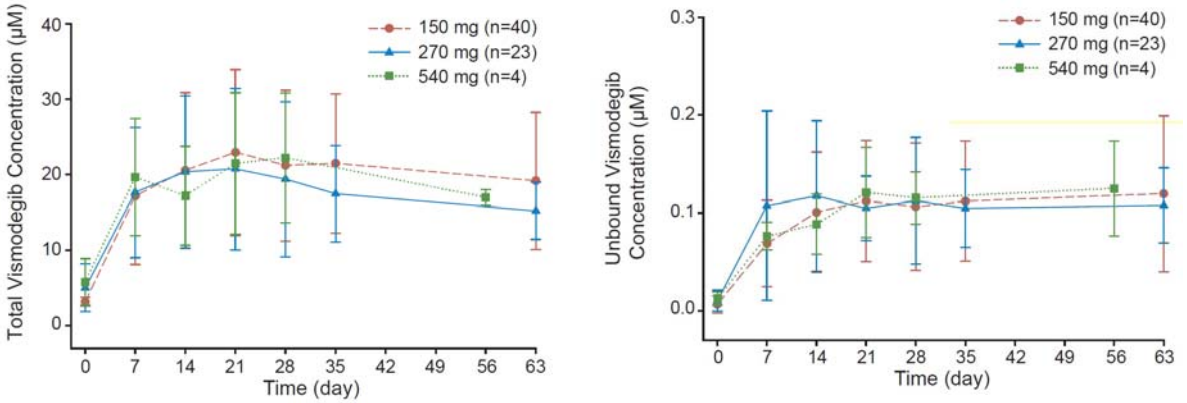
2.2.4.4 *Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

The proposed 150 mg QD dosing regimen is supported by two clinical dose-scheduling trials as summarized below.

Dose Level

In a Phase I dose-escalation study (SHH3925g), vismodegib was administered daily at a 150-, 270-, or 540-mg dose level. Increasing the daily dose from 150 mg to 270 or 540 mg did not result in higher steady-state plasma vismodegib concentrations (Figure 4). Doses higher than 150 mg were therefore not evaluated in subsequent clinical trials.

Figure 4: Plasma Concentrations of Total and Unbound Vismodegib versus Time after Daily Oral Dosing with 150 mg, 270 mg, or 540 mg (Study SHH3925g)



Because no dose-limiting toxicities or other serious toxicities were observed at the 150 mg/day Phase I starting dose, administration of a lower dose was not expected to provide better benefit to patients. Doses lower than 150 mg were therefore not evaluated in the initial Phase I study.

Dose Frequency

Less frequent dosing resulted in markedly lower unbound plasma concentrations. Different dosing frequencies (TIW, QW, or QD) of 150 mg vismodegib were studied to compare total and unbound vismodegib plasma concentrations at steady state (Study SHH4610g). Patients in each group were given 150 mg QD for 11 days for fast reaching state-state. During the 6-week multiple-dose period following the initial phase, total vismodegib plasma concentrations declined in a dosing frequency-related fashion, with the greatest decline observed in the QW group (see Figure 5, left panel; and Table 4). A similar pattern was observed for unbound vismodegib as for total vismodegib plasma concentrations; although the magnitude of the decrease in the TIW and QW groups was more pronounced for unbound than for total vismodegib concentrations (see Figure 5, right panel). A new steady-state for total and unbound vismodegib plasma concentrations appears to have been achieved on Days 29 and 36 for the TIW and QW groups, respectively.

Figure 5: Plasma Concentration-Time Profiles of Total and Unbound Vismodegib for Different Dosing Schedules (150 mg QD, TIW, or QW) in Study SHH4610g (Mean ± SD)

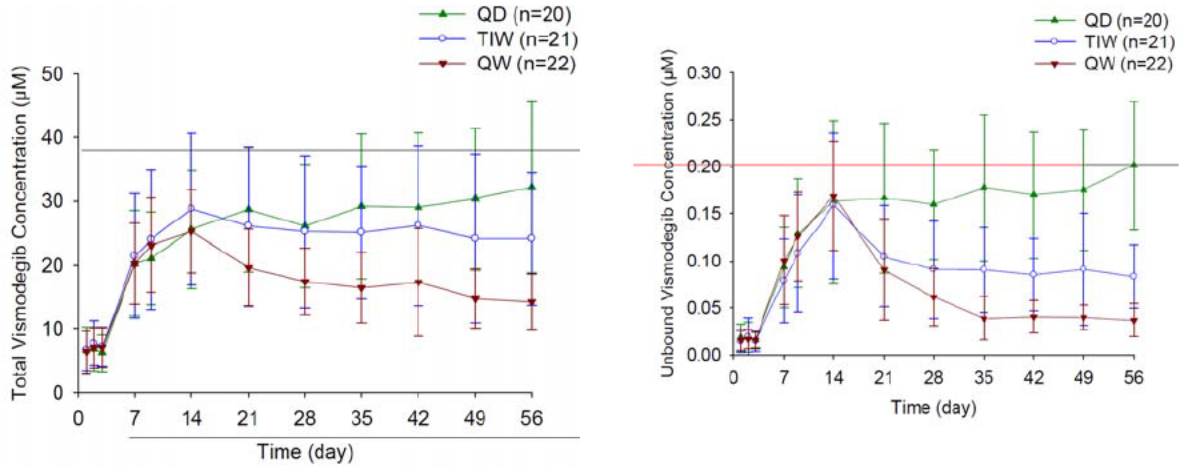


Table 4: Decline of steady-state vismodegib plasma concentration from Day 15 to Day 57

	Total Vismodegib	Unbound Vismodegib
150 mg TIW	24%	50%
150 mg QW	46%	80%

Table 5: PK Parameters (Unbound and Total) in Patients after Receiving Multiple-Dose Vismodegib

Dose Regimen	N	Total Vismodegib Css (μM, Mean ± SD,)	Unbound Vismodegib Css (μM, Mean ± SD)
150 mg QD x 42 days*	15	28 ± 11.4	0.163 ± 0.056
150 mg QD**	78	27.0 ± 9.68	ND
150 mg TIW x 42 days*	18	26.1 ± 11.8	0.088± 0.0408
150 mg QW x 42 days*	18	16.9 ± 5.89	0.0489± 0.0259

* Patients in each group were given 150 mg QD x 11 days prior to receiving their assigned dosing schedule in study SHH4610g.
** in study SHH4476g

Safety: Vismodegib administered at 150 mg QD regimen showed a favorable safety profile in more than 450 patients in five Phase I and three Phase II clinical trials. The most frequently

reported adverse events (AEs) that seem to be associated with vismodegib appear to be on-target toxicities. These include dysgeusia, alopecia, muscle spasms, fatigue, and nausea. In general, unwanted drug effects (e.g., toxicities) may be ameliorated by decreasing the drug exposure. However, decreasing vismodegib exposure to avoid AEs by lowering the dose or less frequent dosing may have a negative impact on efficacy because the AEs and efficacy associated with vismodegib are likely a result of interaction with the same pathway..

In summary,

1. Increasing the daily dose from 150 mg to 270 or 540 mg did not result in higher steady-state plasma vismodegib concentrations.

2. Any reduction in vismodegib dose or frequency of dosing could put patients at risk of sub-optimal exposure of unbound drug. PK results of the dose-scheduling trial in cancer patients suggest that patients receiving less frequent dosing of vismodegib, either as a TIW or QW regimen or a lower QD dose, would be at risk of not achieving unbound drug concentrations that associated with efficacy in advanced BCC.

3. The 150-mg vismodegib QD schedule has been well tolerated to date and shown to be effective in patients with advanced BCC.

Taken together, these findings support the use of a 150 mg daily oral dose of vismodegib regimen.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Single-Dose PK
In healthy subjects after receiving a single oral dose of vismodegib, the PK profile was unique with sustained plasma levels and an estimated terminal half-life of 12 days. Parallel concentration−time profiles were observed in the terminal elimination phase following oral and intravenous (IV) dosing, indicative of elimination rate-limited PK.

In patients after receiving a single oral dose of 150 mg, 270 mg, or 540 mg vismodegob, maximum total or unbound plasma concentrations (Cmax) were achieved by Day 2 with little decline in concentrations over the 6-day washout period. Mean Cmax increased with dose escalation from 150 mg to 270 mg. At 540 mg, the mean total and unbound plasma Cmax values were similar to those observed at 270 mg (6.3 μM versus 6.8 μM for the total drug; 0.032 μM versus 0.029 μM for the unbound drug).

Figure 6: Vismodegib Plasma Concentrations versus Time (Total [left] and Unbound [right]) after a Single Oral Dose of 150, 270, or 540 mg (Mean ± SD, Study SHH3925g)

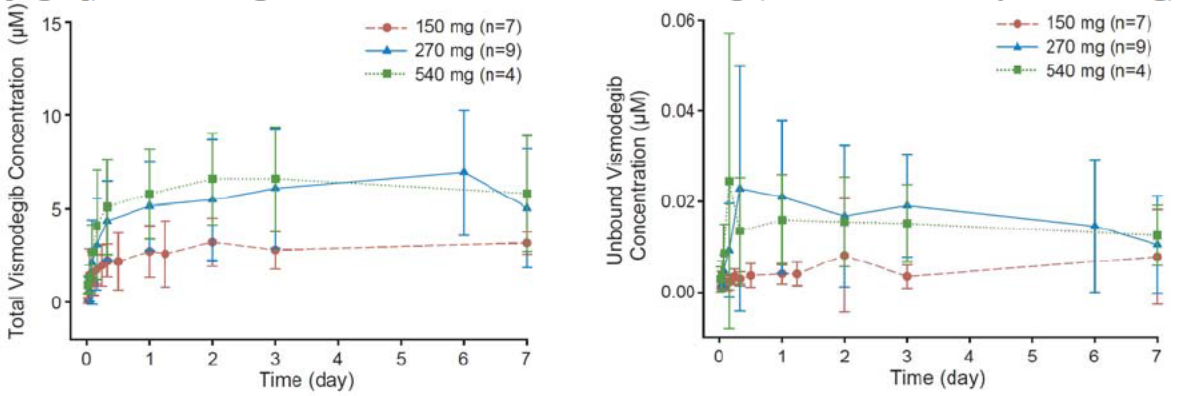


Table 6: Single-Dose Vismodegib PK Parameters (Unbound and Total) from Patients (Study SHH3925g)

	Total Vismodegib (Mean ± SD)			Unbound Vismodegib (Mean ± SD)		
	t_{max} (Day)	C_{max} (µM)	AUC_{last} (µM*hr)	t_{max} (Day)	C_{max} (µM)	AUC_{last} (µM*hr)
150 mg	2.00 (0.042–7.00)	3.58 ± 1.34	322 ± 185	2.00 (0.0417–7.00)	0.0093 ± 0.0121	0.577 ± 0.769
270 mg	2.00 (1.00–3.00)	6.34 ± 3.40	839 ± 458	1.00 (0.167–3.00)	0.0324 ± 0.0247	2.41 ± 1.37
540 mg	2.50 (0.167–3.00)	6.81 ± 2.69	1010 ± 446	0.583 (0.167–2.00)	0.0292 ± 0.0289	2.43 ± 1.45

The elimination half life of single-dose vismodegib could not be adequately characterized in patients. A decline in vismodegib plasma concentrations was observed during the limited 7-day washout period, which was not sufficient to reliably estimate the half-life. In the Phase II trial in patients with BCC, only one trough sample at steady-state was collected.

PK data in healthy subjects were used to understand the single-dose half-life of vismodegib, and the finding from a population PK analysis, performed with integrated data from five studies, indicated no difference with regard to vismodegib distribution and elimination between healthy subjects and patients. Thus, the reported single-dose half-life from healthy subjects is likely representative of the half-life in patients with advanced BCC.

Multiple-Dose PK

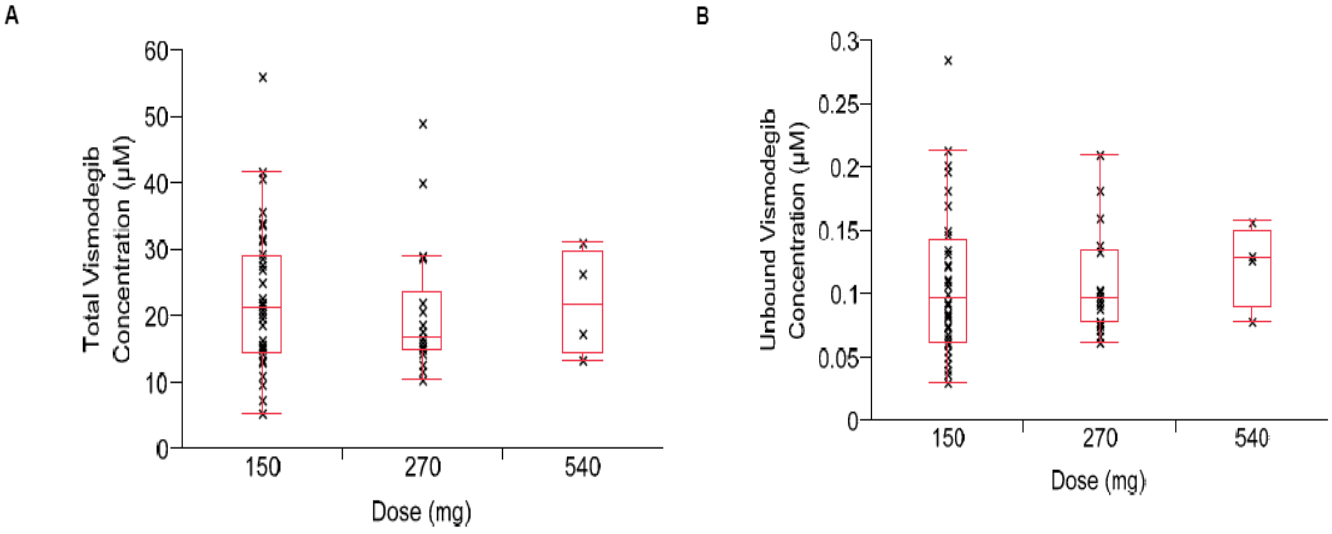
After continuous once-daily dosing, the PK of vismodegib appear to be nonlinear. Considering the 12-day half-life in healthy subjects after a single dose, steady-state plasma concentrations in patients were achieved faster than expected (typically within approximately 7 days of continuous daily dosing), with lower than expected accumulation. Increasing the daily dose from 150 mg to

270 or 540 mg did not result in higher steady-state plasma concentrations. The apparent half-life of vismodegib at steady-state is estimated to be 4 days with continuous daily dosing.

Because of the nonlinear PK of vismodegib, the half-life is different at steady-state from that after a single dose. The saturable binding of vismodegib to alpha-1-acid glycoprotein (AAG) led to concentration-dependent changes in the PK of vismodegib. The fraction unbound of vismodegib increased markedly with QD dosing in almost all patients, with a 3-fold higher of average fraction unbound at steady-state (0.0065) than after a single dose (0.0025), which led to a shorter apparent half-life at steady-state, relative to a single dose.

Total and unbound plasma vismodegib concentrations in patients in Stage 1 (single dose of vismodegib followed by continuous daily dosing beginning a week later) and Stage 2 (continuous daily dosing) are shown in Figure 5. The observed time to reach steady-state plasma concentrations ranged from 7 to 14 days. As shown in Figure 7, similar steady-state vismodegib levels (total and unbound) were observed across all dosing cohorts, indicating non-linearity in PK with regard to dose. The average unbound steady-state vismodegib concentrations were <1% of total vismodegib concentrations, regardless of dose or total plasma concentration (ranging from 5.5 to 56.0 µM). Additionally, unbound plasma vismodegib concentrations paralleled total plasma concentrations over time.

Figure 7: Average Steady-State Plasma Concentrations of Vismodegib (Total [A] and Unbound [B]) at all Dose Levels in Study SHH3925g



2.2.5.2 *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

The PK parameters based on the total vismodegib plasma concentrations in healthy subjects are summarized in Table 7. The unbound vismodegib plasma concentrations were not measured in healthy subjects. The population PK analysis, performed with integrated data from five trials, indicated no difference with regard to vismodegib distribution and elimination between healthy subjects and patients. Thus, the reported single-dose half-life from healthy subjects likely represents the half-life in patients with advanced BCC.

Table 7: Vismodegib Pharmacokinetic Parameters base on Total Vismodegib Concentrations in Healthy Subjects

	Dosage form	N	T_{max} (hr)	C_{max} (μM)	AUC_{inf} (μM * hr)	$t_{1/2}$ (hr)	CL/F(L/hr)	V/F(L)
150 mg SD	25, 125 mg capsule	3	2.00 (1.00-48.0)	4.71±1.37	2000 ±644	286±42.6	0.192 ±0.0652	76.4±14.2
150 mg SD	150 mg capsule	6	24.0 (1.00-48.0)	5.95±0.992	2850±1000	271±55.2	0.140 ±0.053	51.7±11.6
150 mg SD	5 mg/mL suspension	6	ND	7.67±1.12	2790±1250	224±79.2	ND	ND
150 mg QD X 7 days	150 mg capsule	6	4.00 (1.00-10.0)	16.4±3.40	356±75.7	238±58.4	ND	ND
150 mg SD*	5 mg/mL suspension	6	24.0 (4.00-24.0)	18.3±3.32	409±74.3	273±40.3	ND	ND

* Dose was given on Day 7 after 150 mg capsule QD x 6 days

2.2.5.3 *What are the characteristics of drug absorption?*

Vismodegib is a highly permeable compound with low aqueous solubility (Biopharmaceutics Classification System [BCS] Class 2). The single dose absolute bioavailability of vismodegib is 31.8%. Absorption is saturable as evidenced by the lack of dose-proportional increase in exposure after a higher dose of 270 mg or 540 mg (Figure 4), and the plasma vismodegib concentration at steady state was similar between 150 mg daily dose and 270 mg or 540 mg daily dose. Under clinically relevant conditions (steady-state), the PK of vismodegib is not affected by food (Figure 6).

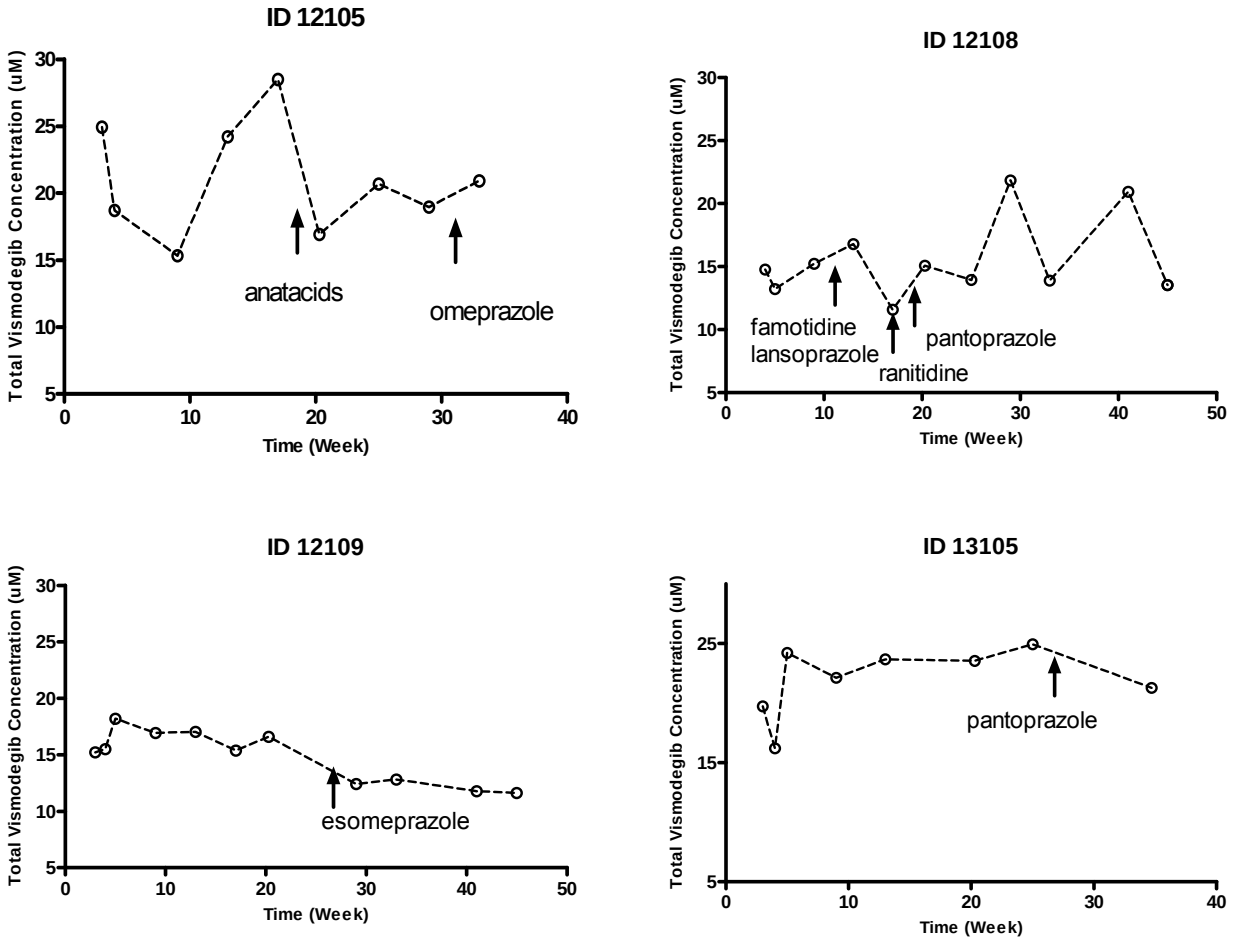
The solubility of vismodegib is pH dependent; the solubility (b) (4) at pH 7 is 0.1 μg/mL and is 0.99 mg/mL at pH 1. The pH effect on vismodegib absorption has not been studied in humans.

Reviewer's analysis: the reviewer analyzed the PK and efficacy data to assess the potential effects of pH elevating agents on vidmodegib. The gastric pH elevating agents include proton-pump inhibitors (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, esoprazole), an H2-receptor antagonists (e.g. ranitidine, famotidine), and/or antacids (e.g. calcium carbonate). The analyses for PK, efficacy and safety are summarized below.

Effect on PK

The reviewer conducted an exploratory analysis of the effect of concomitant administration of pH elevating agents on the systemic exposure of vismodegib. Only patients who took a pH elevating agent and with a relevant PK sample (i.e., a sample collected during concomitant administration with vismodegib at steady state) were considered for the PK analysis. There were also data available to make an intra-subject comparison for 4 patients as shown in Figure 8 (i.e., plasma concentrations of vismodegib were compared pre- and post-administration of a pH elevating agent within the same patient. There were four patients that had taken vismodegib prior to taking a pH elevating agent, with vismodegib PK samples collected before and after administration of the pH elevating agent. There was a trend of a decrease in steady state concentration of total vismodegib after receiving the pH elevating agents. Although the limited patient numbers preclude a conclusion from the analysis, results of this analysis suggests that when vismodegib is concomitantly administered with a pH elevating agent, the steady state concentration of vismodegib (total or unbound) could be affected.

Figure 8: Intra-Patient Steady State Concentrations of Vismodegib for Patients Taking a pH Elevating Agent Concomitantly with Vismodegib



The potential effect of pH elevating agents on vismodegib absorption is suggested by a PopPK analysis. The ka is 9.025 and 17.65 day^{-1} in cancer patients and healthy subjects, respectively. It showed that cancer patients had slower drug absorption (lower ka) than healthy subjects, with at most 5% impact on unbound vismodegib concentrations at steady-state, and less on total concentrations. The vismodegib disposition parameters (CLu, Vc, and KdAAG) did not differ among different subject populations (healthy versus patients, BCC versus non-BCC, locally advanced versus metastatic BCC). The slower absorption in patients may be due to multiple factors such as slower gastrointestinal (GI) transit, higher GI pH, and co-medications affecting GI conditions, which in turn may affect vismodegib solubility and absorption *in vivo*.

Efficacy

Table 8 contains the FDA analysis for the primary efficacy endpoint for registration trail SHH4476g. A trend towards lower objective response exists among patients with locally advanced disease BCC who have been systemically exposed to a pH elevating agent while on vismodegib treatment, and a similar trend exists for patients with metastatic BCC (Table 8).

Table 8: Objective Response by Exposure to pH Elevating Agents: Efficacy Evaluable patients in SHH4476g

Systemic Exposure to pH elevating agents	Metastatic BCC		Locally Advanced BCC		All Patients	
	n	Responders (%)	n	Responders (%)	n	Responders (%)
Yes	11	3 (27.2%)	16	4 (25.0%)	27	7 (25.9%)
No	22	7 (31.8%)	47	23 (48.9%)	69	30 (43.5%)
All Patients	33	10 (30.3%)	63	27 (42.9%)	96	37 (38.5%)

Safety

The safety data have not been analyzed. If there were an effect of pH elevating agent on vismodegib exposure, an decrease of vismodegib bioavailability would be expected for vidmodegib administrated concomitantly relative to vismodeib given alone. The safety is not of concern.

2.2.5.4 *What are the characteristics of drug distribution?*

Protein Binding

The steady-state volume of distribution (Vss) for vismodegib is 16.4 L which is 62% higher than that after single dose. *In vitro* binding of vismodegib to human plasma proteins is 97% and is independent of concentration up to 100 µM. Vismodegib binds to both human serum albumin (HSA) and AAG. *In vitro* binding to AAG is high affinity and saturable at concentrations >25 µM, which is within the clinically and physiologically relevant concentration range for vismodegib and AAG, respectively. *Ex vivo* plasma protein binding in humans is >99%. Vismodegib concentrations are strongly correlated with AAG levels, evidenced by parallel

fluctuations of AAG and total drug concentrations over time with consistently low unbound drug levels.

Blood-Plasma Partitioning

Vismodegib did not appear to distribute preferentially to red blood cells, with mean blood-plasma partition ratios ranging from 0.608 to 0.881 in all examined species including mouse, rat, dog, cynomolgus monkey, and pooled whole blood from humans (Study 06-0599). Blood-plasma partition ratios did not appear to exhibit substantial concentration dependence over the vismodegib concentration range from 1 to 100 μM. In human blood, the partition ratio ranged from 0.608 to 0.818.

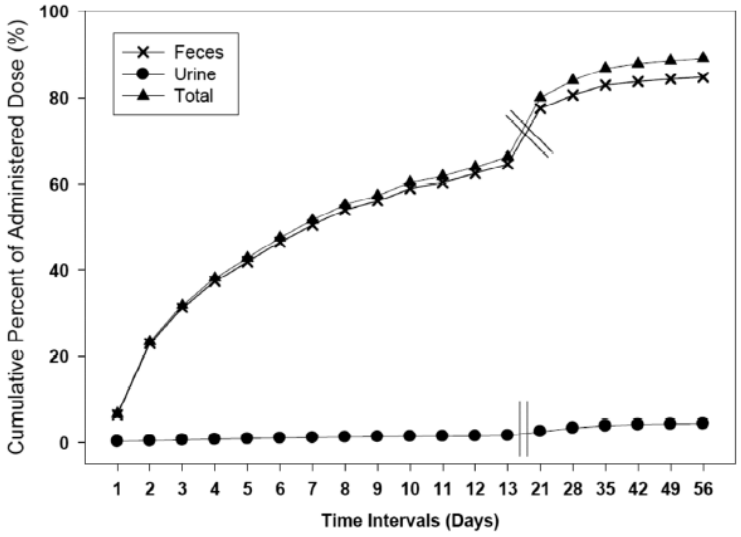
2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

Hepatic pathway is the major route of vidmodegib elimination. An ADME study (SHH4683g) was conducted in 6 healthy female subjects of non-childbearing potential to determine the routes of excretion and extent of vismodegib metabolism following administration of 30 mL of an oral suspension containing 150 mg vismodegib with 6.5 μg of ^{14}C-vismodegib to give a radioactivity of approximately 37 kBq (1000 nCi). Over a 56-day collection period, 86.6% of the administered dose was recovered, on average with 82.2% and 4.4% recovered in feces and urine, respectively (Figure 9).

Reviewer's comments:

- *Urine and feces samples were not collected after the IV dose.*
- *Following administration of ^{14}C-vismodegib oral suspension (Part B), the total estimated excretion was 86.6% of the administered dose over a collection period of 56 days, with the majority of vismodegib-related radioactivity recovered in feces (>80%) and low recovery in urine (<5%). Notably, detectable drug remained in plasma in all patients on Day 56, suggesting more complete recovery with extended duration of urine and feces collections.*
- *A limitation of the Part C study design is that 150 mg vismodegib was only administered through Day 7 which likely resulted in an underestimation of the true steady state CL and V_{ss}. Time dependent changes in unbound fraction of vismodegib could be responsible for the changes in CL and V_{ss}.*

Figure 9: Mean Cumulative Recovery of Total Radioactivity in Feces and Urine after Administration of 150 mg Vismodegib and 6.5 µg ^{14}C-Vismodegib Oral Suspension



2.2.5.6 *What are the characteristics of drug metabolism?*

(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)

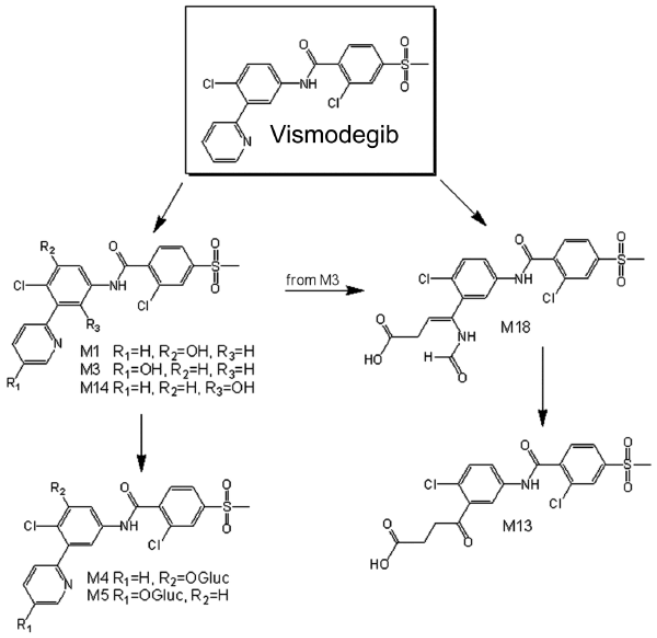
Vismodegib is slowly eliminated by a combination of minor metabolism and major excretion of parent drug. Vismodegib is the predominant species in plasma, with concentrations representing greater than 98% of the total circulating drug-related components. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and uncommon pyridine ring cleavage.

In vitro studies
Two oxidative metabolites (M1 and M3) were generated in rat, dog, and human microsomes. The major oxidative metabolite recovered in feces (M3) is produced by recombinant CYP 2C9 and, to a lesser extent, by CYP3A4/5, while another oxidative metabolite (M1) is formed primarily by recombinant CYP3A4/5. However, multiple isoenzymes are capable of forming both metabolites.

In vivo studies
Vismodegib and seven metabolites were detected from pooled plasma, urine, and feces, including oxidative metabolites (M1, M3, and M14), glucuronides (M4 and M5), and pyridine ring cleavage metabolites (M13 and M18) (see Figure 9). Vismodegib was the dominant species in all three matrices. In pooled plasma, vismodegib concentrations represented greater than 98% of the total circulating drug-related components. No metabolites unique to humans were identified in this study. Selected plasma and urine samples from patients in Study SHH3925g were profiled for metabolites using liquid chromatography/tandem mass spectrometry.

Metabolites M3, M4 and M5 were detected in plasma and metabolites M1, M3, M4 and M5 were detected in urine. All detected metabolites were minor based on mass-spectrometric response.

Figure 10: **Proposed Major Metabolic Pathways of Vismodegib in Human Subjects following an Oral Dose of 150-mg Vismodegib**



2.2.5.7 What are the characteristics of drug excretion?

Vismodegib is slowly eliminated by a combination of minor metabolism and major excretion of parent drug, the majority of which is recovered in the feces (82% of the administered dose), with 4.4% of the administered dose recovered in urine, suggesting limited renal excretion. These findings indicate that vismodegib and its metabolites are eliminated primarily by the hepatic route.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK of vismodegib are characterized by less than dose-proportional increasing in plasma concentration with increasing dose and lower than expected accumulation after continuous daily dosing. These observations are suggestive of nonlinear PK.

The nonlinear PK of vismodegib resulted from two separate, nonlinear processes (1) saturable absorption and (2) high-affinity, saturable protein binding. Nonlinear absorption is consistent with the poor solubility of vismodegib at physiologic pH resulting in a lack of dose-proportional increase in exposure after a single dose of 270 mg and 540 mg vismodegib relative to 150 mg single dose. Please see Section 2.2.5 for more details.

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

After multiple doses, the clinically relevant nonlinear process for vismodegib is saturable binding to AAG, which results in concentration dependent changes in the PK of vismodegib. Following an IV administration at steady-state, the mean vismodegib clearance (CL) and Vss increased >50%, suggestive of concentration-dependent changes in PK. The fraction unbound of vismodegib increased approximately 3-fold after continuous daily dosing relative to a single dose, which can account for the increase in vismodegib CL and Vss after repeated dosing.

Given the non-linear PK observed with daily dosing of vismodegib, the applicant conducted a clinical trial to determine whether less frequent dosing could result in steady-state levels of total and unbound vismodegib that are similar to daily dosing. With three times a week (TIW) or once a week (QW) dosing, total plasma vismodegib levels decreased in a less-than-dose-proportional fashion compared with QD dosing, consistent with nonlinear PK. The decrease in unbound plasma vismodegib concentrations with less frequent dosing is more pronounced than for total concentration and is proportional to the decrease in total dose amount over a 1-week period. The large decrease in unbound vismodegib concentrations after TIW and QW dosing is consistent with a decreased saturation of AAG binding.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Table 9 below summarizes the PK parameter estimates and associated inter- and intra-individual PK variability. The inter-individual variability of clearance (CL) and volume of distribution (Vc) was 49% and 46%, respectively. Residual or intra-individual variability for total and unbound concentrations was 27% and 42%, respectively. AAG level was determined to be the main source of inter-individual variability.

Table 9: Population PK Parameter Estimates of Vismodegib

Parameter	Parameter Description	Population Estimate	Bootstrap Final Model Median (2.5^{th}, 97.5^{th} Percentiles)
$\exp(\theta_1)$	Apparent clearance of unbound, $CL_{unbound}$ (L/day)	1326	1332 (1196, 1467)
θ_9	Influence of age on $CL_{unbound}$	-0.527	-0.526 (-0.842,-0.248)
$\exp(\theta_2)$	Apparent volume of distribution of central compartment, V_c (L)	58.0	58.4 (53.2, 63.4)
θ_{10}	Influence of body weight on V_c	0.660	0.65 (0.31, 0.96)
$\exp(\theta_3)$	Dissociation constant, KD_{AAG} (μM)	0.056	0.056 (0.053, 0.058)
$\exp(\theta_6)$	Relative bioavailability for Phase I formulation in patients (Phase II formulation as reference), F	0.346	0.347 (0.293, 0.403)
θ_7	Influence of population on F	0.881	0.880 (0.566, 1.33)
$\exp(\theta_4)$	Absorption rate constant, k_a (day^{-1})	9.025	9.065 (6.870, 11.865)
θ_5	Influence of population on k_a	0.671	0.621 (0.215, 0.991)
θ_8	Influence of formulation on k_a	-0.602	-0.594 (-1.07, -0.11)
Inter-subject variability (%)	$CL_{unbound}$	48.7	47.4 (39.6, 57.5)
	V_c	45.5	44.8 (39.7, 50.8)
	KD_{AAG}	19.7	19.5 (15.0, 23.2)
Residual variability (%)	Total vismodegib plasma concentration	26.7	26.5 (24.7, 28.6)
	Unbound vismodegib plasma concentration	42.4	42.3 (39.5, 44.9)

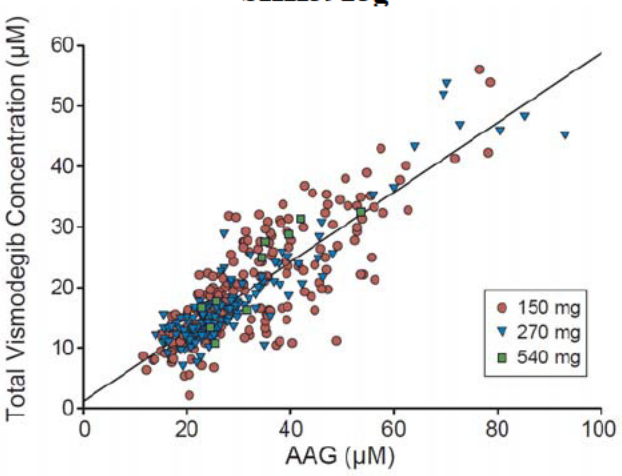
2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Vismodegib PK was, to some extent, dependent on systemic levels of AAG. A linear mixed model with subjects as a random effect was used to explore the relationship between total vismodegib plasma concentration and AAG concentration. All vismodegib and AAG plasma samples collected after Day 21 from each patient were included; data were pooled across cohorts and dose groups for the analysis. A strong relationship was observed (R^2 =0.73; see Figure 10) between total vismodegib plasma concentration and AAG concentration. However, there was no significant correlation between unbound vismodegib plasma concentration and AAG or between total vismodegib plasma concentration and HSA levels.

Population PK analysis showed that AAG concentration was the most important factor influencing steady-state plasma vismodegib concentrations. Variability of total vismodegib concentration at steady-state was predominantly explained by the variation of AAG level in patients (range: 47-101%). AAG was also the most influential factor for the steady-state concentration of unbound vismodegib, but the impact was not clinically significant (±21%), indicating that no dose adjustment would be necessary for AAG level in patients. In addition, with lack of dose-proportional increase of vismodegib total and unbound concentration at higher doses, and the lack of exposure-response relationship for efficacy and safety of vismodegib, additional clinical benefit would not be expected with dose adjustment for vismodegib.

Figure 11: Total Vismodegib Concentration versus Plasma AAG Concentration in Study SHH3925g



2.3.2 ***Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?***

(If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.)

Dosage regimen adjustments for vismodegib are not recommended to any specific population.

2.3.2.1 **Elderly (see Study of Drugs Likely to be used in the Elderly, (http://www.fda.gov/cder/guidance/old040fn.pdf)**

A population PK analysis included subjects with age ranging from 26 to 89 years old and showed that age does not influence the disposition of vismodegib.

2.3.2.2 **Pediatric patients.** ***Also, what is the status of pediatric studies and/or any pediatric plan for study?***

The applicant has not conducted clinical studies with vismodegib in pediatric patients. The only data comes from a single child who received vismodegib for medulloblastoma. Data from studies in animals showed that the use of vismodegib resulted in irreversible alteration/loss of incisors (erupting teeth) and closure of the femoral epiphysis (growth plate) in rats (Study 07-1224). (b) (4) 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.

2.3.2.3 Gender

Population PK analysis showed that gender has no influence on the PK of vismodegib.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

Because most patients who were included in the population PK analyses were Caucasians, with non-Caucasian comprising < 3% (6 black) of the total population, race was not included as a covariate in the population PK analysis.

2.3.2.5 Renal impairment

Renal elimination accounts for approximately 4% of the total vismodegib dose; however, there have been examples where renal impairment has a substantial impact on PK even when the drugs are minimally eliminated by the kidney.

Pharmacokinetic results from a dedicated renal impairment study are not available at the time of the NDA submission and a renal trial (Protocol GP27839) will be conducted in patients with normal hepatic function and severe renal impairment under a PMR. The population PK analysis suggests that creatinine clearance (CrCL range: 30 to 80 mL/min) does not influence the PK of vismodegib.

2.3.2.6 Hepatic impairment

Vismodegib and its metabolites are eliminated primarily by the hepatic route. There is insufficient data available in patients with hepatic impairment in the clinical trials. A trial (Protocol GP27839) in patients with normal hepatic function and patients with varying degrees of hepatic impairment (i.e., mild, moderate, and severe) to assess the effect of hepatic dysfunction on the PK of vismodegib will be conducted under a PMR.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

None.

2.3.2.8 What pregnancy and lactation use information is there in the application?

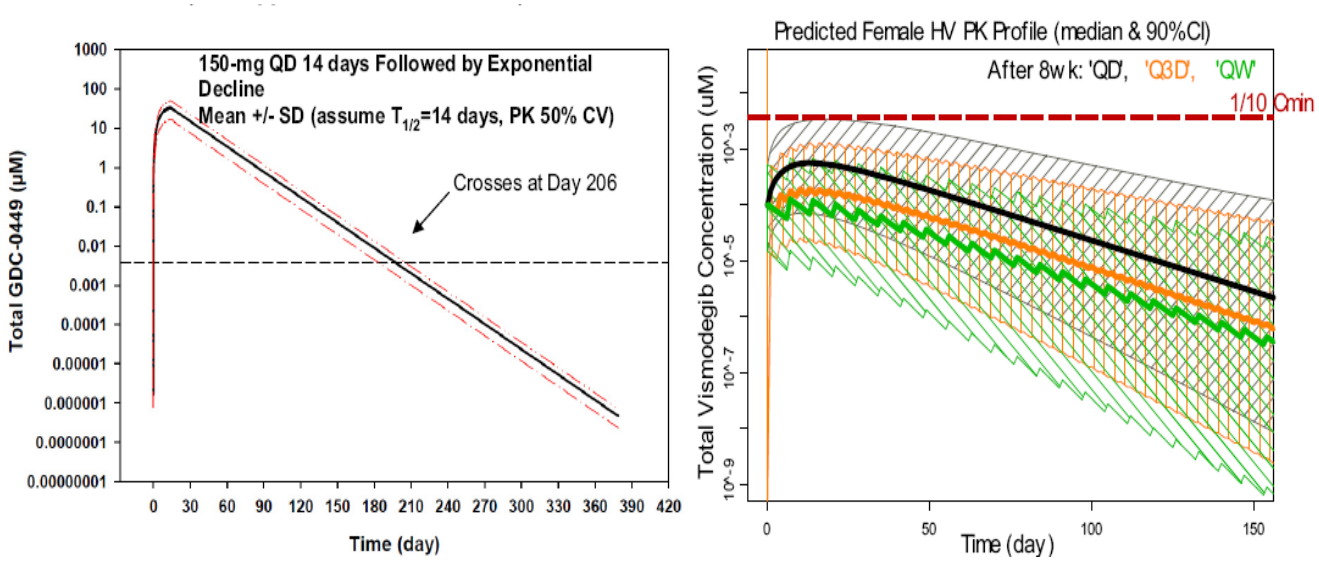
Vismodegib may cause fetal harm when administered during pregnancy. Vismodegib was teratogenic and embryolethal in rats. Malformations included craniofacial abnormalities, open perineum, and missing or fused digits. There are no data on the use of vismodegib in pregnant women. No data regarding the excretion of vismodegib in the milk of humans or animals was provided.

As stated in the Vismodegib labeling, Vismodegib is contraindicated in women who are or may become pregnant. If the patient becomes pregnant while taking this drug, treatment should be stopped and the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with vismodegib, and prior to each treatment cycle, by a medically supervised pregnancy test.

Based on the simulation shown in Figure 12, pregnancy must be prevented during treatment and for seven months after last dose by the use of two acceptable methods of contraception, including one acceptable barrier method with spermicide. Male patients must use condoms with

spermicide at all times, even after a vasectomy, during sexual intercourse with female partners of reproductive potential while being treated with vismodegib and for 2 months after last dose.

Figure 12: Sponsor's Simulations for Pregnancy Prevention in Female Patients and Condom Use in Male Patients



Left panel: Pregnancy Prevention in Female Patients (7 months after last dose): Solid black line represents a typical patient concentration-time profile, red lines ± 50% CV.

Right panel: Condom use in Male Patients (2 months after last dose); assumes once daily intercourse; horizontal dashed line represents 1/10th of C_{min} observed in rat EFD study at 10 mg/kg/day.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety?

Locally advanced BCC vs. metastatic BCC

In the efficacy trial (SHH4476g), the steady-state vismodegib plasma concentrations were comparable in patients with laBCC (26.3 ± 9.6 μM; n = 56) and mBCC (29.0 ± 9.8 μM, n = 22), with an overall steady-state concentration of 27.0 ± 9.7 μM. The mean and range of vismodegib plasma concentrations following 150-mg daily dosing in patients from both cohorts were consistent with the results from phase 1 trials.

The population PK analysis also suggested that disease status (healthy vs. cancer patient) and cancer type do not influence the PK of vismodegib.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet, smoking or alcohol use on the PK of vismodegib.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Vismodegib has a potential for inhibiting CYP2C8 and CYP2C9 and to a lesser extent, a potential for inhibiting CYP2C19, based on the *in vitro* studies with human liver microsomes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

It has been demonstrated that vismodegib can be metabolized by multiple CYP enzymes. In the human mass balance study, the major metabolite recovered in the feces was oxidative metabolite M3. This metabolite was observed in the *in vitro* human liver microsomal incubations. Recombinant CYP2C9 and to a lesser extent CYP3A4/5, CYP2C18, CYP2C19, and CYP2D6 are responsible for the formation of M3. In addition to M3, another oxidative metabolite of vismodegib, M1 was identified in this study, which was recovered in the urine and feces. M1 was formed primarily by recombinant CYP3A4/5; however multiple other CYP enzymes were capable of forming M1 (Figure 10). *In vitro* metabolic stability of vsimodegib was high, with 96% of the parent drug remaining after a 3-hour incubation with human hepatocytes.

The effects of genetic polymorphisms of CYP enzymes on vismodegib have not been studied. The potential influence is expected to be low considering the slow clearance of vismodegib, minor CYP metabolism by multiple CYP enzymes, and major elimination of unchanged drug.

Two oxidative metabolites (M1 and M3) were generated in rat, dog, and human microsomes. Recombinant human CYP isoforms (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, and 3A5), were incubated with 50 uM vismodegib to identify the CYP enzymes capable of forming the oxidative metabolites, M1 and M3. The greatest quantity of M1 was produced by CYP3A4 followed by CYP3A5. CYP2C9 appeared to produce the greatest quantity of M3. Both metabolites were produced by several other CYP enzymes but to a lesser extent.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

<u>CYP Enzyme Inhibition</u>

Vismodegib has a potential for inhibiting CYP2C8 and CYP2C9 and to a lesser extent, CYP2C19, based on *in vitro* studies with human liver microsomes. The [I]/Ki ratios for CYP 2C8, 2C9, and 2C19 are presented in Table 10. $[I]/K_i$ ratios were similar for CYP2C8 and 2C9, which were calculated using the mean steady-state concentration of vismodegib (22.3 μM) in patients.

Table 10: Inhibition Constants (K_i) and [I]/K_i Ratio for CYP2C8, CYP2C9, and CYP2C19 in Human Liver Microsomes

CYP Isoforms	Ki (Probe Substrate)	[I]/Ki
2C8	6.0 ± 0.2 µM (paclitaxel)	3.7
2C9	5.4 ± 0.4 µM (diclofenac)	4.1
2C19	24 ± 1 µM (mephenytoin)	0.9

CYP Enzyme Induction

The induction potential of vismodegib was investigated using cryopreserved hepatocytes from three human donors (Study 08-1985). Vismodegib was incubated at concentrations ranging from 0.1 to 100 µM for 48 hours. Omeprazole, phenobarbital, and rifampicin were used as positive controls for CYP1A2, CYP2B6, and CYP3A4/5 induction, respectively. The activities of these CYP enzymes did not increase in cells exposed to up to 10 µM vismodegib when compared with vehicle and positive controls. Results were inconclusive at vismodegib concentrations above 10 µM because of a decrease in enzyme activity without direct evidence of cytotoxicity.

An *in vitro* PXR competitive binding TR-FRET assay (Study 09-0054) was performed as an additional assessment of vismodegib induction potential for drug metabolism enzymes regulated by PXR. Vismodegib does not appear to be a potent binder of PXR, with an IC_{50} of 83.3 µM.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Vismodegib appears to be a P-glycoprotein (P-gp) substrate. Vismodegib was assessed as a P-gp substrate and inhibitor in a MDR1-MDCK cell system at a single concentration of 15 μM based upon solubility studies in the assay buffer. In the absence and presence of cyclosporine A (10 μM), a known P-gp inhibitor, vismodegib had an efflux ratio of 8.6 and 1.0, respectively, suggesting that it is a P-gp substrate.

Vismodegib does not appear to be a P-gp inhibitor, as the permeability of digoxin (10 μM), a P-gp substrate, was not affected by the addition of vismodegib to the assay buffer.

Exploratory Analysis

P-gp inhibitors could potentially affect vismodegib exposure because vismodegib is a P-gp substrate *in vitro* with net flux ratio of 8.6 (≥ 2), has minor CYP metabolism (see highlights above) and is BCS Class 2 drug with low bioavailability (31.8%). P-gp may play a more important role in vismodegib PK than CYP enzymes. The purpose of this exploratory analysis is to evaluate the effect of P-gp inhibitors on systemic exposure, efficacy and safety, which considered patients who concomitantly received any of the P-gp inhibitors listed in the FDA drug-drug interaction guidance: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, or verapamil. Patients who stopped taking a P-gp inhibitor prior to taking vismodegib or who stopped taking vismodegib prior to taking a P-gp inhibitor were excluded from the analysis.

Results of this analysis show that when vismodegib is concomitantly administered with P-gp inhibitors, the steady state concentration of vismodegib (total or unbound) was not affected. For the exploratory PK analysis, steady state plasma concentrations (Css) of total and unbound vismodegib were from three studies in patients with cancer (SHH3925g, SHH4476g, SHH4610g). Only patients who took a P-gp inhibitor and having a relevant PK sample (i.e., a sample collected during concomitant administration with vismodegib at steady state) were considered for the PK analysis. The majority of the data allowed for an inter-subject comparison (i.e., patients taking vismodegib alone were compared with patients taking vismodegib with a P-gp inhibitor) (Figure 13), and there were also data available to make an intra-subject comparison for 5 patients (i.e., plasma concentrations of vismodegib were compared pre- and post-administration of a P-gp inhibitor within the same patient) (Figure 14).

If there was an effect of P-gp inhibitors on the systemic exposure of vismodegib, an increase in steady state plasma concentration would be expected for vismodegib administered concomitantly with P-gp inhibitors relative to vismodegib given alone. As shown in Figure 12, the steady state concentrations of total and unbound vismodegib for patients taking a P-gp inhibitor concomitantly with vismodegib were within the range of concentrations of patients taking vismodegib alone.

Five patients who had taken vismodegib prior to a P-gp inhibitor administration had vismodegib PK samples collected before and after administration of the P-gp inhibitor. There was no obvious

trend of a change in steady state concentration of total or unbound vismodegib with or without a P-gp inhibitor. In one patient (ID 13005), the total and unbound steady state concentration of vismodegib was increased by approximately 1.6 fold with the P-gp inhibitor (Figure 13).

Figure 13: Inter-Patient Steady State Concentrations of Total (A) and Unbound (B) Vismodegib for Patients Taking Vismodegib Concomitantly with a P-gp Inhibitor

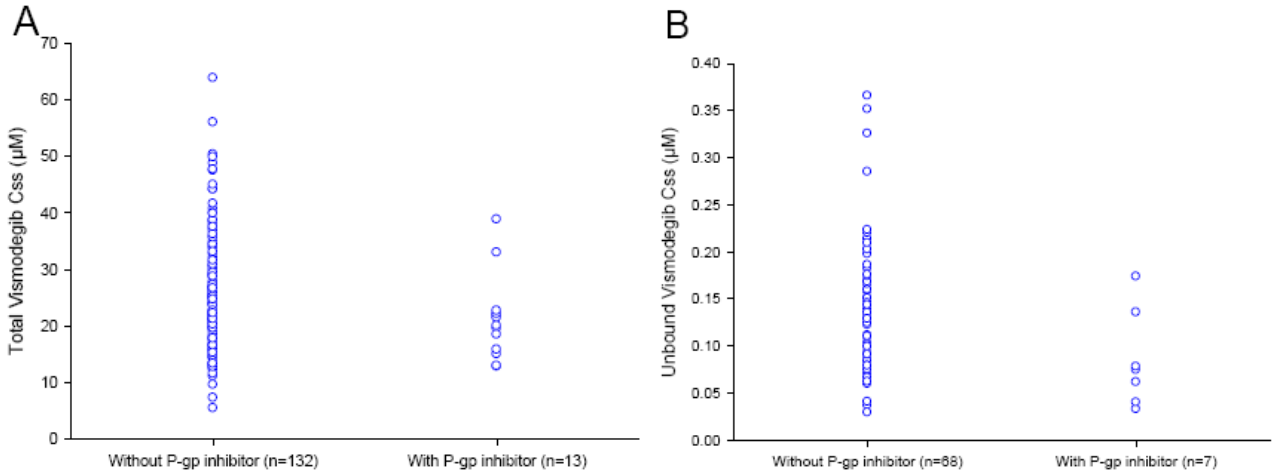
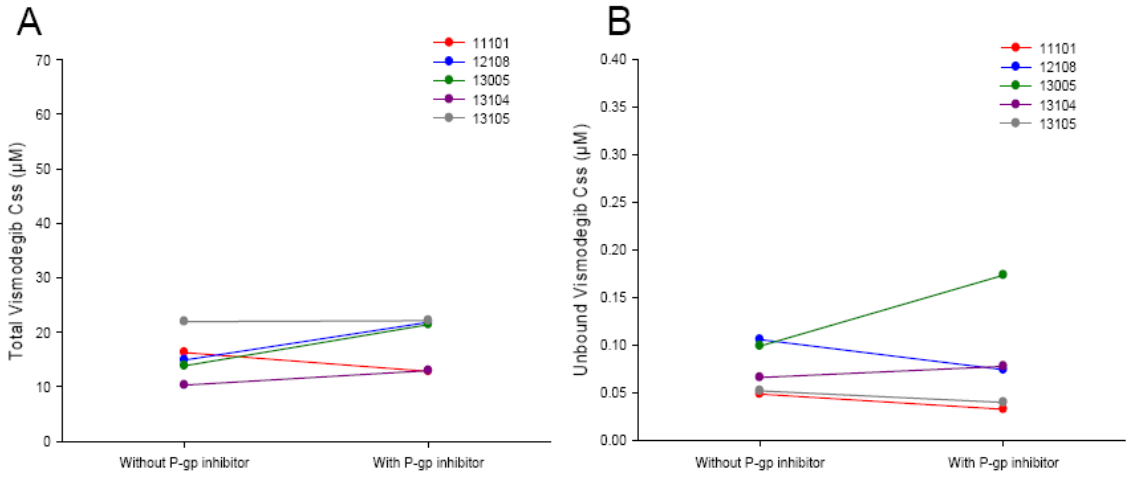


Figure 14: Intra-Patient Steady State Concentrations of Total (A) and Unbound (B) Vismodegib for Patients Taking a P-gp Inhibitor Concomitantly with Vismodegib



Safety: Grade ≥ 3 adverse events were observed in 65% (17 of 26) of patients who were exposed to a P-gp inhibitor and 39% (44 of 112) of those who were not (Table 12). There was also a higher incidence of SAEs leading to discontinuation observed in patients who were exposed to a P-gp inhibitor compared to those who were not. However, the causal

relationship between vismodegib exposure and the safety profile is uncertain, given the data are only available from the single-arm trial.

Efficacy: A trend towards higher objective response exists among patients with metastatic BCC who have been systemically exposed to a P-gp inhibitor while on vismodegib treatment, and a trend in the opposite direction exists for patients with locally advanced disease (Table 11).

Table 11: Objective Response by Systemic Exposure to P−gp Inhibitors: Efficacy Evaluable patients in SHH4476g

Systemic Exposure to P−gp Inhibitors	Metastatic BCC		Locally Advanced BCC		All Patients	
	n	Responders (%)	n	Responders (%)	n	Responders (%)
Yes	5	2 (40.0%)	12	7 (58.3%)	17	9 (52.9%)
No	28	8 (28.6%)	51	20 (39.2%)	79	28 (35.4%)
All Patients	33	10 (30.3%)	63	27 (42.9%)	96	37 (38.5%)

FDA Recommendations: Considering the rare population of the proposed indication with estimated 2300 cases per year, a post-marketing study on P-gp inhibition appears to be not well justified. However, the reviewer recommends that during the future development of vismodegib for other indications the applicant should conduct a clinical study to assess the interaction potential of vidmodegib when co-administered with drugs known to be strong inhibitors of P-gp (See section 1.4).

Table 12: Treatment−Emergent Adverse Events (Grade >= 3) by Systemic Exposure to P−gp Inhibitors

	Yes (n=26)	No (n=112)
All Grade >= 3 AEs	17/ 26 (65.4%)	44/112 (39.3%)
Grade 5	1 (3.8%)	7 (6.3%)
Grade 4	5 (19.2%)	7 (6.3%)
Grade 3	11 (42.3%)	30 (26.8%)
Grade 2	9 (34.6%)	50 (44.6)
Grade 1	(0.0%)	17 (15.2%)
Discontinuation	6/26 (23.1%)	9/112 (8.0%)
Dyspnoea	3/26 (11.5%)	0/112 (0%)
Infections/ infestations	5/ 26 (19.2%)	6/112 (5.4%)
Adenocarcinoma Pancreas	2/26 (7.7%)	0/112 (0%)

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

BCRP

Vismodegib is not a BCRP substrate. The efflux ratio for vismodegib was 0.79 and 0.72 in Caco-2 and CPT B1 (BCRP knockdown cell line) cell monolayers, respectively.

Vismodegib is a BCRP inhibitor *in vitro*. It inhibited the efflux ratio of prazosin (a BCRP substrate) from 8.5 to approximately 1.6 in MDCKII BCRP cell monolayers with an IC_{50} of 2.4 μM. Based on steady-state total vismodegib concentrations of 22.3 μM with a daily dose of 150 mg, the $[I_1]$ /IC_{50} is 9.3 and $[I_2]/IC_{50}$ is 593. Although no clinically meaningful effects of vismodegib on the exposure of irinotecan, a BCRP substrate was observed in the clinical trials, irinotecan is not a sensitive BCRP substrate. The results could not preclude the possible interaction between vismodegib (as a BCRP inhibitor) with other BCRP substrates, such as methotrexate, mitoxantrone, imatinib, lapatinib, rosuvastatin, sulfasalazine, and topotecan.

FDA Recommendations: The reviewer recommends that during the future development of vismodegib for other indications, the applicant should conduct a clinical study to assess the interaction potential of vidmodegib when co-administered with drugs known to be sensitive substrates of BCRP (See section 1.4).

OATP

Studies have not been conducted to determine whether vismodegib is a substrate or inhibitor of OATP1B1 and OATP1B3.

FDA Recommendations: Since hepatic route is the major elimination pathway (>25% of total clearance) for vismodegib and its metabolites, the reviewer recommends that the applicant conduct *in vitro* studies first to determine whether vidmodegib is a substrate and/or an inhibitor of OATP1B1 and OATP1B3 (See section 1.4) and the results will determine the need for further clinical investigations(See section 1.4).

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Yes. Females of reproductive potential are required to use two forms of acceptable contraception (including one barrier method) during therapy and for 7 months after discontinuing treatment. Acceptable forms of additional contraception include the following: combination hormonal contraceptives, hormonal patch, hormonal intramuscular contraceptives, (subcutaneous hormonal implant, medroxyprogesterone acetate depot), non-progestin IUD, tubal sterilization and vasectomy.

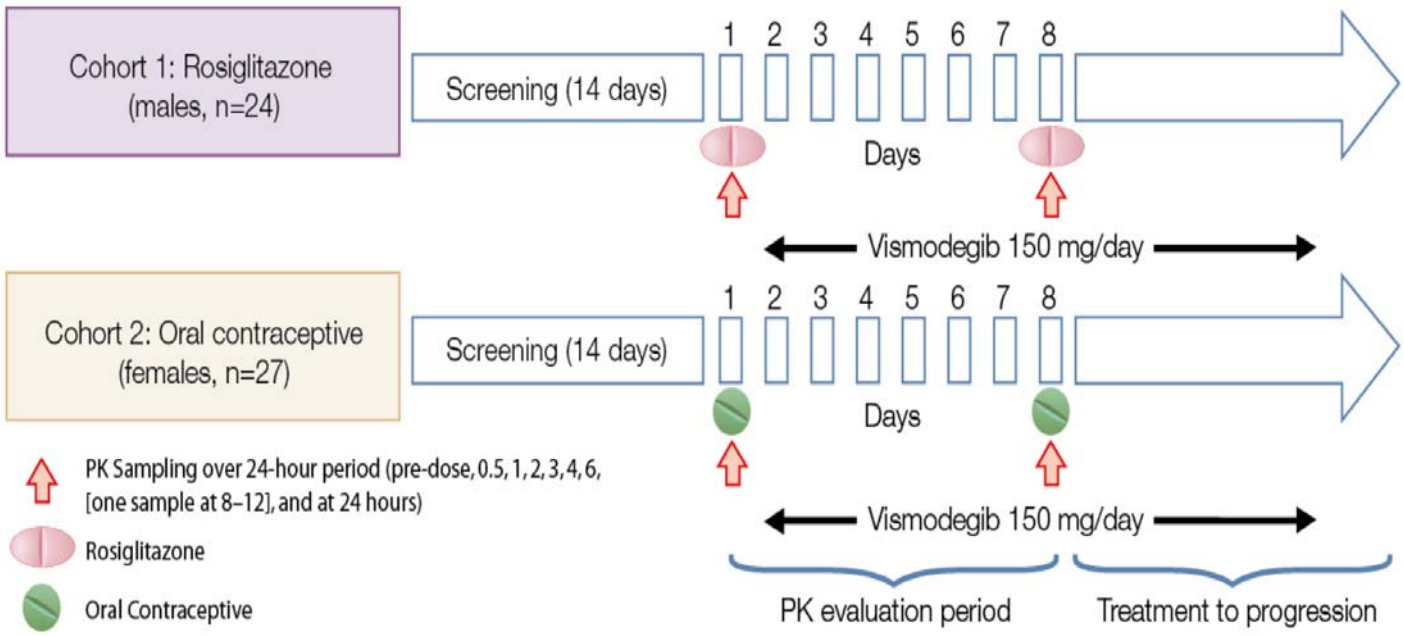
2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

CYP-mediated Drug-Drug Interactions (DDI)

Vismodegib as a Perpetrator of Metabolism-Based Interaction

1. Vismodegib with rosiglitazone or oral contraceptives

An *in vivo* DDI study (SHH4593g) with rosiglitazone (vismodegib as a perpetrator of sensitive CYP2C8 substrate inhibition) and oral contraceptives (vismodegib as a perpetrator of CYP3A induction) is ongoing in cancer patients to evaluate their DDI potential. The sponsor submitted an interim synoptic report. The study design is shown below:



When administered with vismodegib, Cmax and AUC for rosiglitazone and ethinyl estradiol were unchanged (≤ 8% difference based on GMR) relative to without vismodegib (Table 13, Table 14). Cmax and AUC increased 12% and 23% (based on GMR), respectively, for norethindrone when administered with vismodegib (Table 15). The observed increase in systemic exposure of norethindrone is the opposite of an enzyme induction-mediated effect. Although norethindrone is a substrate of CYP3A, vismodegib does not inhibit CYP3A4/5 *in vitro*. Nevertheless, the *in vivo* study results indicate that the efficacy of oral contraceptives would not be compromised by co-administration of vismodegib.

Vismodegib has the strongest inhibition potential on CYP2C8 among other CYP enzymes based on the *in vitro* studies. The lack of effect of vismodegib on CYP2C8 in the dedicated DDI study suggests that further DDI studies with CYP isozymes are not necessary according to the FDA drug-drug interaction guidance.

The mean steady-state concentration of vismodegib (20.6 μM) observed in this study was consistent with clinical relevant concentrations observed in Phase 1 and 2 trials, where the average steady-state concentration of vismodegib in patients with cancer was 22.3 μM.

Overall, the results from this study indicate that there was no clinically meaningful difference in the PK of rosiglitazone (a CYP2C8 substrate), ethinyl estradiol, or norethindrone (a CYP3A substrate) when co-administered with vismodegib. Results indicated that vismodegib can be co-administered with CYP substrates and with combined oral contraceptives without the risk of clinically relevant drug-drug interactions.

Table 13: Rosiglitazone $AUC_{0\text{-}inf}$ and C_{max} without (Day 1) and with (Day 8) Vismodegib Co-Administration (n = 24)

	Day 1	Day 8	GMR (90% CI)
$AUC_{0\text{-}inf}$ (ng/mL*hr)	1300 (±560)	1190 (±487)	92.0 (87.4–96.8)
C_{max} (ng/mL)	209 (±66.4)	197 (±73.3)	93.1 (85.0–102)
T_{max} (hr)	1.00 (0.500–6.00)	1.42 (0.0800–3.28)	NA
$t_{1/2}$ (hr)	4.23 (±1.32)	4.02 (±1.07)	NA

Table 14: Ethinyl Estradiol $AUC_{0\text{-}inf}$ and C_{max} without (Day 1) and with (Day 8) Vismodegib Co-Administration (n = 27)

	Day 1	Day 8	GMR (90% CI)
$AUC_{0\text{-}inf}$ (ng/mL*hr)	0.851 (±0.302)	0.850 (±0.319)	99.6 (92.9–107)
C_{max} (ng/mL)	0.0873 (±0.0434)	0.0920 (±0.0428)	105 (94.4–116)
T_{max} (hr)	1.00 (0.500–5.00)	1.42 (0.0800–4.47)	NA
$t_{1/2}$ (hr)	15.4 (±7.28)	14.4 (±10.3)	NA

Table 15: Norethindrone $AUC_{0\text{-}inf}$ and C_{max} without (Day 1) and with (Day 8) Vismodegib Co-Administration (n = 27)

	Day 1	Day 8	GMR (90% CI)
$AUC_{0\text{-}inf}$ (ng/mL*hr)	64.4 (±34.4)	77.0 (±36.5)	123 (115–131)
C_{max} (ng/mL)	8.44 (±3.97)	9.43 (±4.38)	112 (101–124)
T_{max} (hr)	1.00 (0.500–4.00)	1.48 (0.330–4.47)	NA
$t_{1/2}$ (hr)	11.9 (±4.95)	10.9 (±3.64)	NA

2. Vismodegib in combination with FOLFOX or FOLFIRI + bevacizumab

The DDI potential of vismodegib was assessed based on results from the Phase II trial of vismodegib in combination with FOLFOX (oxaliplatin, leucovorin, and infusional 5-fluorouracil [5-FU]) and bevacizumab or FOLFIRI (irinotecan, leucovorin, and infusional 5-FU) and bevacizumab. Study SHH4429g was a randomized, placebo-controlled, double-blind trial of

vismodegib added to standard-of-care regimens for metastatic colorectal cancer (CRC). Patients were randomized in a 1:1 ratio to receive either vismodegib or placebo in combination with bevacizumab and either FOLFOX or FOLFIRI chemotherapy. There were no clinically meaningful differences in 5-FU, oxaliplatin, irinotecan, SN-38, and SN-38G levels with or without vismodegib.

- 5-FU concentrations at 6 hours after dosing (n ≤10) were 22% lower in combination with vismodegib.
- AUC_{last} and C_{max} values (n = 5) of mean irinotecan, SN-38, and SN-38G were similar in the presence and absence of vismodegib.
- AUC_{last} and C_{max} values (n = 4) of total oxaliplatin were 27% and 21% higher, respectively, with vismodegib co-administration. Similarly, AUC_{last} and C_{max} values (n = 4) of mean free oxaliplatin were 29% and 40% higher, respectively, with vismodegib co-administration.
- On average, the pre-dose serum concentration of bevacizumab (n ≤ 9) was 58% higher with vismodegib than without vismodegib. However, only trough bevacizumab levels were measured from a limited number of patients, the results are inconclusive regarding the effects of vismodegib on bevacizumab exposure.

Table 16: Comparison of Mean 5-FU Concentration 6 Hours Post-Dose in the Absence (Day 1) and Presence (Day 28) of Vismodegib

	5-FU Concentration (ng/mL)		
	Mean	SD	n
Without vismodegib	540	245	10
With vismodegib	419	141	8

Table 17: Irinotecan, SN-38, and SN-38G PK Parameters

	Irinotecan			SN-38			SN-38G		
	AUC_{last} (ng*hr/mL)	Cmax (ng/mL)	n	AUC_{last} (ng*hr/mL)	Cmax (ng/mL)	n	AUC_{last} (ng*hr/mL)	Cmax (ng/mL)	n
Without vismodegib	14100 ± 5000	2460 ± 902	5	236 ± 48.9	27.8 ± 6.52	5	2110 ± 1290	168 ± 60.8	5
With vismodegib	13900 ± 3960	2110 ± 541	5	273 ± 102	26.3 ± 10.6	5	1960 ± 565	156 ± 42.2	5

Table 18: Total and Free Oxaliplatin PK Parameters

	Total Oxaliplatin			Free Oxaliplatin		
	AUC_{last} (ng*hr/mL)	Cmax (ng/mL)	n	AUC_{last} (ng*hr/mL)	Cmax (ng/mL)	n
Without vismodegib	54300 ± 8110	4360 ± 817	4	4550 ± 828	779 ± 90	4
With vismodegib	69100 ± 7170	5260 ± 1120	4	5850 ± 687	1090 ± 293	4

Table 19: Bevacizumab Serum Concentrations

	Bevacizumab Concentration (µg/mL)		
	Mean	SD	n
Without vismodegib	97.4	28	9
With vismodegib	154	32	6

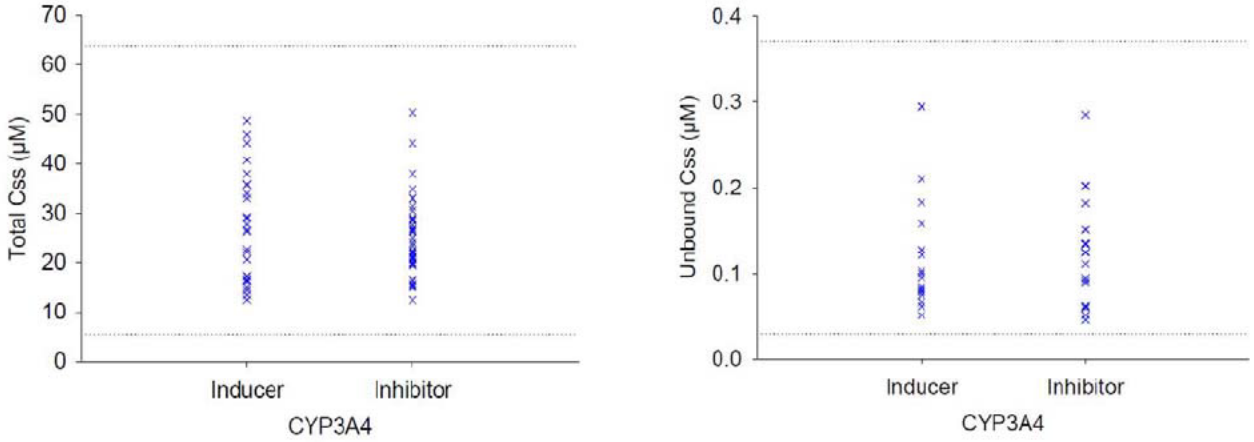
Reviewer Comments: Irinotecan is not a sensitive BCRP substrate. The results could not preclude the possible interaction between vismodegib (as a BCRP inhibitor) with other BCRP substrates.

Vismodegib as a Victim of Metabolism-Based Interaction

The risk of DDIs with vismodegib as a victim of CYP3A4/5 and CYP2C9 inhibitors/inducers appears low. CYP inhibition is unlikely to alter vismodegib metabolism because of the slow elimination of vismodegib via multiple pathways, including minor metabolism by several CYPs and major excretion of the unchanged drug.

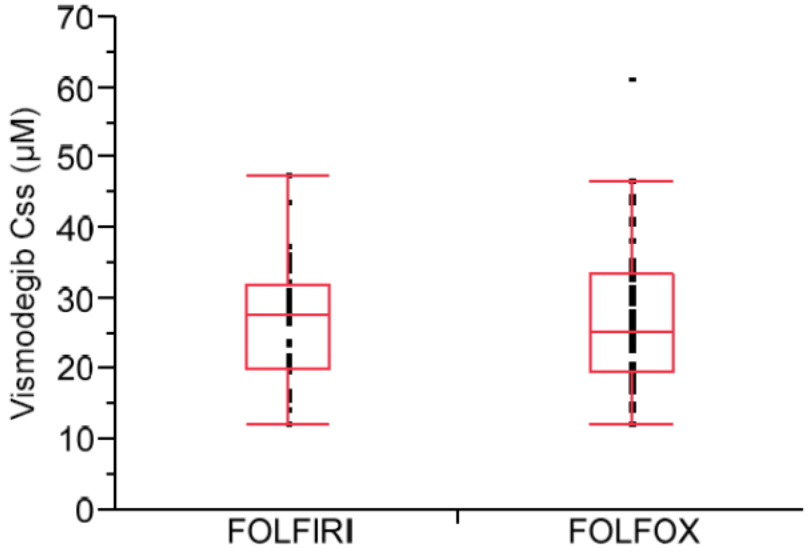
Clinical data shows the lack of an effect of CYP inhibitors and inducers on vismodegib PK. Total and unbound vismodegib plasma concentrations were obtained from patients taking known CYP3A4 inducers or inhibitors with vismodegib in three clinical trials (SHH3925g, SHH4610g, and SHH4476g). The concomitant medications included strong CYP3A4 inhibitors (erythromycin and fluconazole) as well as strong CYP3A4 inducers (carbamazepine, modafinil, and Phenobarbital). As shown in Figure 14, the total and unbound vismodegib steady-state concentrations was similar whether patients were taking CYP3A4 inhibitors or inducers. Furthermore, total and unbound plasma vismodegib concentrations were within the range observed from patients not taking concomitant CYP3A4 inhibitors or inducers (range is represented by horizontal dashed lines).

Figure 15: Steady-State Plasma Concentrations of Vismodegib in Patients Taking Concomitant CYP3A4 Inducers or Inhibitors



The results from the Phase II trial of vismodegib in combination with FOLFOX and bevacizumab or FOLFIRI and bevacizumab (Study SHH4429g) provide supportive evidence that vismodegib is not likely to be a victim of a CYP mediated DDI. In this study, the mean ± SD steady-state plasma concentrations of vismodegib were similar for patients receiving FOLFIRI-bevacizumab (26.5 ± 8.56 µM, N=33) or FOLFOX-bevacizumab (27.1 ± 9.75 µM, N=52). Vismodegib steady-state concentrations were also similar to those observed in patients with advanced BCC receiving vismodegib as a monotherapy (27.0 ± 9.68 µM).

Figure 16: Vismodegib Concentrations at Steady-State in Patients Receiving Concomitant FOLFOX-bevacizumab or FOLFIRI-bevacizumab



FOLFIRI = irinotecan, leucovorin, and bolus + infusional 5-fluorouracil;
FOLFOX = oxaliplatin, leucovorin, and bolus + infusional 5-fluorouracil.

Lack of an effect of chemotherapy on vismodegib steady-state levels is a supportive evidence that vismodegib is not likely to be a victim of a CYP mediated DDI, especially considering the complex elimination pathway of irinotecan and the potential for it to interact with CYP3A4/5

and UGT1A1 substrates. These results suggest that neither chemotherapy regimen is likely to have a clinically meaningful impact on vismodegib steady-state plasma concentration.

Transporter Based Interaction

Vismodegib as a Perpetrator of Transporter-Based Interactions
Vismodegib did not inhibit P-gp in a MDR1-MDRCK cell system. Vismodegib was shown to have an inhibition potential on BCRP in MDCKII-BCRP cell monolayers.

The applicant states that this finding is unlikely to be of clinical relevance due to the high degree of plasma protein binding of vismodegib and the low confirmed clinical occurrence of BCRP based drug-drug interactions.

Vismodegib as a Victim of Transporter-Based Interactions
In vitro study showed that vismodegib appeared to be a P-glycoprotein (P-gp) substrate. *In vivo* study has not been conducted for vismodegib concomitant administration with a strong P-gp inhibitor.

Potential for Drug-Displacement Interactions
Given that vismodegib is highly bound to plasma proteins, the potential to cause clinically relevant drug displacement interactions when vismodegib is concomitantly administered with other drugs was explored. While it has been hypothesized that increases in unbound drug concentrations may lead to increases in drug effect, there are very limited cases when protein binding changes may be clinically important (Benet and Hoener 2002). Depending on PK parameters and the intrinsic clearance of the drug, certain PK parameters will change with protein binding but others will not. For drugs with a low-hepatic-extraction ratio, regardless of route of administration, unbound exposure is independent of protein binding and no dosage adjustments will need to be made for real or anticipated changes in fraction unbound. Only high-extraction ratio drugs given IV and oral drugs eliminated by non-hepatic, high-extraction routes will exhibit changes in unbound drug exposure when protein binding changes.

Vismodegib as a Victim of Drug Displacement
Based on *in vitro* metabolism and clinical PK data, it appears that vismodegib exhibits low hepatic extraction and thus falls into the category where unbound exposure would not change upon displacement of vismodegib from plasma binding protein. Furthermore, vismodegib does not appear to be a narrow therapeutic index drug given that the MTD or DLT was not identified in clinical trials. Therefore, even if unbound fraction increased, it is unlikely that this would be clinically important. Finally, in addition to AAG binding, vismodegib also binds with relatively high affinity to HSA, thus in the event of displacement from AAG, unbound drug would be expected to bind instantaneously to HSA, which is present in a large amount in plasma.

Vismodegib as a Perpetrator of Drug Displacement
Benet and Hoener (2002) examined a list of 456 drugs to identify drugs that fulfilled the following criteria: 1) non-oral delivery; 2) high degree of protein binding; and 3) high-extraction-ratio. Twenty-five of these 456 drugs met these criteria; however, therapeutic index was not considered. Therapeutic index may be an important consideration in the risk assessment

of vismodegib as a perpetrator of drug displacement because, if a drug has a wide therapeutic index, changes in unbound drug concentrations may not be clinically apparent. Because most of the 25 identified drugs either have wide therapeutic indices or are rarely used clinically, there is low risk of a clinically meaningful drug displacement interaction when administered concomitantly with vismodegib.

The reviewer agrees with the applicant's view for that the DDI potential for vismodegib mediated by drug displacement is low.

2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Since no pharmacodynamic (PD) markers were identified and measured during vismodegib development, the potential for PD drug-drug interactions are unknown.

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Insert the potential of DDI with antiacid.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Vismodegib is identified as a Biopharmaceutics Classification System (BCS) Class 2 compound with low solubility and high permeability.

In vitro dissolution correlated with plasma vismodegib concentrations following single-dose administration in the clinic. However, no differences in steady-state exposure have been observed following multiple-dose administration of capsule formulations with different *in vitro* dissolution profiles.

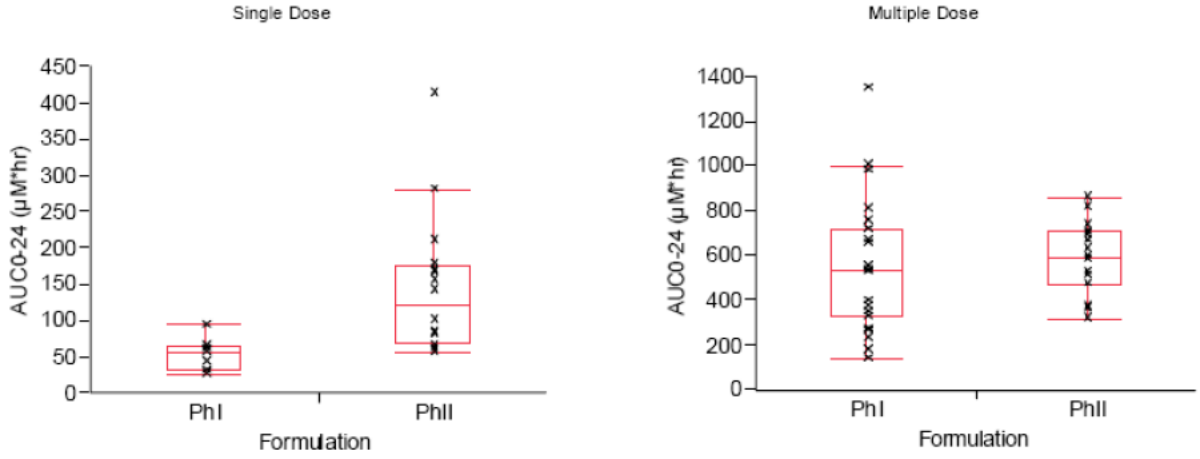
2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The initial vismodegib clinical studies utilized multiple strengths (25, 125, and 270 mg) of a capsule formulation referred to as Phase I (b) (4) However, the majority of the clinical studies in the present NDA were conducted using a 150-mg capsule formulation referred to as Phase II (b) (4) and Phase II pivotal (b) (4) both of which are virtually identical to the proposed commercial capsule product.

The PK of the Phase I (b) (4) and Phase II (b) (4) (b) (4) were evaluated in two separate groups of solid tumor patients in the Phase I dose-escalation trial (SHH3925g). Following a single 150-mg dose of the Phase I and Phase II

Drug Product, vismodegib PK were studied in 7 and 16 subjects, respectively. After multiple daily 150-mg doses, vismodegib PK were studied in 23 and 15 subjects receiving the Phase I and Phase II Drug Product, respectively. As shown in Figure 17, while average $AUC_{0\text{-}24h}$ was approximately 3-fold greater for the Phase II than the Phase I Drug Product after a single dose, no such difference was observed after once-daily multiple dosing (21 days), as steady-state $AUC_{0\text{-}24h}$ values were similar. The mean (± SD) steady-state concentrations, which were computed by averaging the vismodegib concentrations in each subject after 21 days of dosing, for Phase I and Phase II formulations were 22.2 ± 12.5 µM (n = 23) and 24.4 ± 6.86 µM (n = 15), respectively. Phase II Drug Product does not pose an increased risk of under- or over-exposure in patients after repeated dosing.

Figure 17: Plasma Vismodegib Exposure after a Single Dose (left panel) or Multiple Once-Daily Dosing (right panel) of Phase I or Phase II 150-mg Vismodegib Capsules



2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

A PK analysis in 29 patients suggested that food affected the single dose PK of vismodegib (up to a 38% increase in Cmax and AUC with a high-fat meal), but no appreciable change in drug exposure at steady-state when vismodegib was taken with food (Table 20, Table 21). These findings suggest that vismodegib may be taken without regard to meals.

Table 20: Vismodegib Pharmacokinetic Parameters after a Single 150-mg Vismodegib Dose with or without Food

Group	Cmax (µM)	$AUC_{0\text{-}168}$ (µM*hr)
Fasted (n = 13)	10.0 ± 5.73	1270 ± 749
Low-fat (n = 3)	11.3 ± 3.32	1410 ± 368
High-fat (n = 13)	13.8 ± 6.35	1680 ± 1100

Table 21: Vismodegib Pharmacokinetic Parameters on Day 14 following 150 mg Vismodegib Once Daily with or without Food

Group	Cmax (µM)	AUC_{0-24} (µM*hour)
Fasted (n = 13)	29.2 ± 11.0	698 ± 274
Fed (n= 13)	30.9 ± 11.2	727 ± 280

The geometric mean ratios and corresponding 90% confidence intervals (CIs) for the comparison of steady-state vismodegib Cmax and AUC_{0-24h} (fed:fasted) were 107% (90% CI: 82%, 139%) and 105% (90% CI: 80%, 137%), respectively(Table 22).

Table 22: Statistical Analysis of Steady-State Vismodegib Cmax and AUC_{0-24h} for Fed (n=13) versus Fasted (n=13) Groups

PK Parameter	Treatment Ratio	GMR	Lower End of 90% CI	Upper End of 90% CI
Cmax	Fed/fasted	106.6%	81.9%	138.8%
AUC_{0-24h}	Fed/fasted	104.7%	80.0%	137.2%

In the efficacy trial, information on prandial state was not collected from investigators or patients. In the Phase II studies (SHH4476g, SHH4429g, SHH4489g), patients were instructed to take vismodegib with or without food, at the same time each day.

Reviewer's comment:

- *The formulation used in the food-effect study is the same as the to-be-marketed formulation.*
- *It has been previously shown that there is a strong correlation between vismodegib steady-state plasma concentration and level of alpha-1-acid glycoprotein (AAG), and that AAG levels explain > 70% of the observed PK variability. Under single-dose conditions, vismodegib concentrations are not sufficient to saturate AAG binding allowing for an effect of food on the extent of absorption. In contrast, AAG binding is saturated with continuous daily dosing (at steady-state) under which conditions food would not be expected to have an impact on vismodegib exposure.*
- *In the pivotal phase 2 trials, information on prandial state was not collected from investigators or patients. In the Phase II studies (SHH4476g, SHH4429g, SHH4489g), patients were instructed to take vismodegib with or without food, at the same time each day.*

- *For the food-effect study, SHH4893s (NCI 8395), the applicant states that the PK results provided in the synoptic report are considered to be final. The applicant states that although the study is ongoing, the primary endpoints have been met.*

- *Overall the applicant's conclusions appear reasonable from a clinical pharmacology perspective.*

2.5.4 When would a fed BE study be appropriate and was one conducted?

See 2.5.3.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

A faster *in vitro* dissolution rate was observed for the Phase II (b) (4) than the Phase I (b) (4)) Drug Product as shown in Figure 18. (b) (4) Plasma vismodegib exposure following a single 150-mg dose of the Phase II Drug Product was approximately (b) (4) than that with the Phase I Drug Product, which is consistent with the observed difference in *in vitro* dissolution rate. In contrast to single-dose results, no difference in steady-state plasma concentration between the Phase I and Phase II Drug Product was observed with continuous daily dosing. These results demonstrate that changes in *in vitro* dissolution rate affect single-dose but not steady-state vismodegib exposure in patients.

Figure 18: *In Vitro* Dissolution: Comparison of Phase I and Phase II Vismodegib Drug

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

There is only one dose strength as a 150 mg capsule proposed for Vismodegib.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Total and unbound vismodegib were analyzed by validated methods in plasma samples collected from several clinical trials. The ADME study (SHH4683g) utilized accelerator mass spectrometry (AMS) to measure [^{14}C]-vismodegib and total ^{14}C content in plasma, whole blood, urine, and freeze-dried feces samples.

2.6.2 Which metabolites have been selected for analysis?

Plasma, urine, and homogenized feces collected in the ADME study (SHH4683g) were pooled across subjects at selected time points and analyzed by HPLC-AMS to obtain metabolite profiles. Vismodegib and seven metabolites were detected from pooled plasma, urine, and feces samples, including oxidative metabolites (M1, M3, and M14), glucuronides (M4 and M5), and pyridine ring cleavage metabolites (M13 and M18) (see Figure 10). Vismodegib was the dominant species in all three matrices. In pooled plasma, vismodegib concentrations represented greater than 98% of the total circulating drug-related components. No metabolites unique to human were identified in this study.

Selected plasma and urine samples from patients in Study SHH3925g were profiled for metabolites using liquid chromatography/tandem mass spectrometry. Metabolites M3, M4 and M5 were detected in human plasma and metabolites M1, M3, M4 and M5 were detected in human urine. All detected metabolites were minor based on mass-spectrometric response.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Both total and unbound vismodegib were measured in human plasma samples. Vismodegib protein binding is characterized as high-affinity and saturable.

2.6.4 What bioanalytical methods are used to assess concentrations?

The performance of the assay method for total vismodegib in plasma during analysis of plasma samples from the clinical studies is summarized in Table 23

Table 23: Summary of Intra-Assay Performance of Total Vismodegib in Human Plasma

		Range of Values			
Clinical Study No.	Calibration Range (ng/mL)	Calibration Standards Accuracy (%RE)	Calibration Standards Precision (%CV)	QC Accuracy (%RE)	QC Precision (%CV)
SHH3925g (high range)	5–5000	- 0.5% to 1.0%	2.5% to 4.5%	- 8.0% to 0.0%	4.1% to 6.0%
SHH3925g (low range)	0.100–100	- 3.1% to 3.0%	NR	0.0% to 7.5%	NR
SHH4429g	5–5000	- 1.0 % to 0.8 %	2.3 % to 4.2%	- 3.0% to 1.3%	2.6% to 4.3%
SHH4683g	5–5000	- 2.9% to 3.8%	2.7% to 4.1%	- 5.5% to - 0.7%	3.3% to 4.4%
SHH4610g	5–5000	- 1.8% to 2.0%	2.7% to 4.0%	- 4.0% to - 1.3	2.6% to 5.5%
SHH4433g	5–5000	- 1.0% to 1.3%	1.3% to 6.0%	- 13 % to - 6.0%	1.6% to 2.0%
SHH4318g	5–5000	- 4.0% to 3.0%	1.2% to 3.1%	- 6.0% to - 11.0%	3.6% to 3.8%
SHH4476g	5–5000	- 2.8% to 4.2%	2.3% to 6.1%	- 3.8% to - 2.0%	2.6% to 4.7%
SHH4871g	5–5000	- 5.2% to 7.3%	1.8% to 4.1%	- 2.5% to - 0.7%	2.2% to 6.8%

CV = coefficient of variation; NR = not reported (because of insufficient data); QC = quality control; RE = relative error.

The performance of the assay method for unbound vismodegib in plasma:PBS during analysis of samples from the clinical trials is summarized in Table 24

Table 24: Summary of Intra-Assay Performance of Unbound Vismodegib in Human Plasma: PBS

Clinical Study No.	Calibration Range	Range of Values: Calibration Standards Accuracy (%RE)	Calibration Standards Precision (%CV)	QC Accuracy (%RE)	QC Precision (%CV)
SHH3925g	0.100–100 ng/mL	- 1.6% to 2.0%	1.4% to 5.2%	- 4.0% to 0.7%	2.0% to 7.8%
SHH4610g	0.100–100 ng/mL	- 1.5% to 1.0%	1.5% to 7.0%	- 3.3% to - 0.7%	2.1% to 7.5%
SHH4433g	0.100–100 ng/mL	- 6.2% to 4.5%	1.2% to 4.7%	- 7.3% to 1.3%	2.4% to 4.5%

CV = coefficient of variation; QC = quality control; RE = relative error.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve for total vismodegib concentrations is 5-5000 ng/mL for high range and 0.1-100 ng/mL for low range measurement. The range of the standard curve for unbound vismodegib concentrations is 0.1-100 ng/mL. These ranges are adequate for PK measurements in clinical trials. Refer to Question 2.6.4 for details.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

As for total vismodegib in plasma samples, the LLOQ is 5 and 0.1 ng/mL for high range and low range methods, respectively. The ULOQ is 5000 and 100 ng/mL for high range and low range methods, respectively.

As for unbound vismodegib, the LLOQ is 0.1 ng/mL and the ULOQ is 100 ng/mL. Refer to Question 2.6.4 for details.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

The accuracy, precision, and selectivity at these limits are summarized in Table 23 and Table 24. Refer to Question 2.6.4 for details.

3 DETAILED LABELING RECOMMENDATIONS

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 Individual Study Reviews

Study SHH3925g

Title of Study:
A Phase Ib, Open-Label, Dose-Scheduling Study of Hedgehog Pathway Inhibitor GDC-0449 in Patients with Locally Advanced or Metastatic Solid Tumors That Are Refractory to Standard Therapy or for Whom No Standard Therapy Exists

Objectives
Primary:

- To evaluate the relative effect of dosing schedules on steady-state trough plasma concentration (Css,trough) of total and unbound GDC-0449 administered as a daily (QD), three times per week (TIW), or once weekly (QW) maintenance dose following an 11-day loading dose in patients with advanced solid tumors that were refractory to treatment or for whom no standard therapy existed

- To evaluate the safety and tolerability of QD, TIW, and QW dosing of GDC-0449 administered to patients with advanced solid tumors that were refractory to treatment or for whom no standard therapy existed

Secondary:

- To characterize the unbound plasma concentration of GDC-0449 for up to 72 hours after a single dose
- To characterize the total and unbound plasma concentrations of GDC-0449 administered TIW and QW from the initiation of treatment (i.e., starting on Day 1 without a loading phase)

The activity objective of this study was as follows:

- To make a preliminary assessment of tumor response in patients with advanced solid tumors that were refractory to treatment or for whom no standard therapy existed receiving GDC-0449 administered QD, TIW, or QW

Study design
Study SHH4610g was a two-part, randomized, open-label, Phase Ib study designed to evaluate whether less frequent dosing (TIW or QW) of 150 mg vismodegib following a loading dose (150 mg QD for 11 days) would result in similar safety, tolerability, and steady-state levels of total and unbound vismodegib as continuous QD dosing. Sixty-seven patients with advanced solid tumors were stratified by baseline plasma AAG levels and randomized to one of three vismodegib 150-mg regimens: QD (n = 23), TIW (n = 22), or QW (n = 22) for up to 42 days after an 11-day loading phase (150 mg QD). A vismodegib 150-mg capsule was taken at

approximately the same time each day on an empty stomach (nothing but water for 2 hours before and 1 hour after drug administration). In Part 1, all patients received a single dose of vismodegib on Day 1. No drug was taken on Days 2 or 3. Serial blood samples for the determination of total and unbound plasma vismodegib concentrations were collected through 72 hours after the single vismodegib dose on Day 1.

Test Product, Dose and Mode of Administration
During Part 1 of Stage 1 (Day 1 to Day 14; loading), patients were instructed to take one 150 mg capsule in the morning of Day 1 and then one 150 mg capsule every morning from Day 4 to Day 14. No study drug was administered on Day 2 or Day 3. During Part 2 of Stage 1 (Day 15 to Day 57; maintenance), patients were instructed to take one 150 mg capsule in the morning based on the schedule to which they had been randomized. During Stage 2, patients were to be instructed to take one 150 mg capsule in the morning based on the schedule to which they had been allocated.

Pharmacokinetic and Pharmacodynamic Outcome Measures:
The following outcome measures were to be derived from the GDC-0449 plasma concentration time profile, as considered appropriate:

- Time to achieve steady-state concentration
- Total and unbound trough (pre-dose) concentration after loading and maintenance phase in Stage 1 (Ctrough [Day 15] and Ctrough [Day 57], respectively)
- Trough concentration at steady state (Css,trough, total and Css,trough, unbound)
- Maximum plasma concentration (Cmax, total and Cmax, unbound)
- AUCtotal and AUCunbound achieved during a specified dosing interval
- Single-dose half-life (t1/2) unbound, if this parameter can be described within 72 hours
- Other parameters, such as maximum and minimum steady-state concentration (Css, max and Css,min), time to maximum plasma concentration (Tmax), and AUC from time 0 to the last measured concentration (AUC0−tlast), for total and unbound GDC-0449 may also be calculated as data allow.

Pharmacokinetic/Pharmacodynamic and Activity Conclusions:
- A sustained concentration-time profile was observed for both total and unbound GDC-0449 after a single dose.
- Steady state was attained within 11 days of continuous once daily dosing of GDC-0449.
- During the maintenance phase, both total and unbound plasma GDC-0449 concentrations decreased with TIW and QW relative to QD dosing schedules, reaching a new steady state after about 2 weeks; the observed decreases in the less frequently dosed groups were considerably greater for unbound than total GDC-0449.
- A strong correlation was observed between total plasma GDC-0449 and serum alpha-1-acid glycoprotein (AAG) concentrations for the QD and TIW groups, and, as expected, there was no relationship between unbound GDC-0449 and AAG.

Safety Conclusions:
- GDC-0449 was generally well tolerated in this study.

- Two patients in the QD dose group (14200 and 14206) died within 30 days of discontinuing study treatment. The cause of death for both patients was considered to be disease progression.
- All patients except one experienced at least one adverse event while on study. The most common adverse event was nausea (27 patients; 42.9%).
- No Grade 5 adverse event was reported on this study. A total of 24 patients (38.1%) experienced Grade 3−4 adverse events on study. One patient experienced a Grade 3 adverse event that was considered to be related to GDC-0449 (hyponatremia).
- Twenty-two patients (34.9%) experienced serious adverse events, the most common of which was intestinal obstruction (3 patients; 4.8%). No serious adverse event was considered to be related to GDC-0449.
- No pattern of clinically significant change was identified for any of the hematologic, chemistry, or urinalysis parameters measured.
- The overall rate and severity of adverse events did not appear to differ substantially across dose groups.

Overall Conclusions:
The PK profiles of GDC-0449 in patients after a single 150-mg dose of GDC-0449 and after once-daily dosing with 150 mg GDC-0449 were consistent with previous findings. Both total and unbound plasma GDC-0449 concentrations were sustained through 72 hours after a single dose of GDC-0449, and steady state was achieved within 11 days of continuous once-daily dosing. When the dosing schedule was altered to TIW or QW, total plasma GDC-0449 levels decreased compared with once-daily dosing. The magnitude of the observed change was less than dose proportional, consistent with nonlinear pharmacokinetics.

Unbound steady-state vismodegib concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group. Such decreases may be associated with loss of vismodegib activity based on findings from nonclinical models. Integrated PK/PD modeling of vismodegib in xenograft models has revealed a steep relationship between pathway modulation (Gli1 inhibition) and anti-tumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in vismodegib activity. Furthermore, the 150 mg QD regimen has shown activity in patients with advanced BCC. Integration of the nonclinical concentration-response relationship, human efficacy data, and PK results of this dose-scheduling study in cancer patients suggests that patients receiving 150 mg vismodegib on a TIW or QW regimen could be at risk of not achieving unbound drug concentrations associated with maximum clinical benefit.

It is important to note that serum AAG concentrations remained relatively constant in all dose groups during the course of the study, thus maintaining the even stratification of AAG levels among dose groups. As previously observed in Study SHH3925g, total GDC-0449 and AAG concentrations were strongly correlated after QD dosing. This strong correlation was maintained with the TIW dosing schedule. However, less of a correlation between total GDC-0449 and AAG levels was observed for the QW dosing schedule, which may be because of less saturated AAG binding compared with more frequent dosing. The large decreases in unbound GDC-0449 concentrations after TIW and QW dosing are also consistent with a decreased saturation of AAG binding. GDC-0449 was generally well-tolerated in this Phase I trial, with an acceptable safety

profile. One patient experienced a severe adverse event that was considered to be related to GDC-0449 (i.e., Grade 3 hyponatremia). No serious adverse event was considered to be related to GDC-0449. The small number of patients in this study precludes a meaningful comparison of safety profiles among the three dosing schedules; however, no differences were apparent. Of the 57 efficacy-evaluable patients in this study, 1 patient with BCC as their primary tumor had a PR as their best response.

In conclusion, the results of this study provided important insights on the nonlinear pharmacokinetics of GDC-0449. These findings support the use of a 150 mg once-daily regimen for future clinical trials.

Reviewer Comments:

- *The observed decline in unbound steady-state vismodegib plasma concentration from Day 15 to Day 57 was even more pronounced, with an average decrease of 50% and 80%, respectively, for the TIW and QW groups. These differences were in accordance with the change in dose (57% and 86% lower weekly dose for TIW and QW compared with QD).*

- *Integration of the concentration-response relationship, human efficacy and safety data, PK results of the dose-scheduling study in cancer patients suggests that patients receiving lower doses of vismodegib, either as a TIW or QW regimen or a lower QD dose, would be at risk of not achieving unbound drug concentrations associated with efficacy in advanced BCC. Therefore, reduction of dose level or decreasing dosing frequency is not recommended.*

- *Assay appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation."*

- *Age, sex, race and body weight are well balanced between each treatment group.*

- *Overall the applicant's conclusions appear reasonable from a clinical pharmacology perspective.*

Study SHH4429g

Title of Study:
A Randomized, Placebo-Controlled Phase II Study of GDC-0449 (Hedgehog Antagonist) with Concurrent Chemotherapy and Bevacizumab As First-Line Therapy for Metastatic Colorectal Cancer

Phase of Development: II

Study Period: 1 May 2008 to 10 December 2010

Objectives
Primary:
The primary objective of this study is to make an assessment of whether adding GDC-0449 to the standard of care (FOLFOX bevacizumab or FOLFIRI bevacizumab) increases anti-tumor efficacy as measured by PFS when compared with the standard of care (FOLFOX bevacizumab or FOLFIRI bevacizumab) alone in patients with previously untreated metastatic CRC.

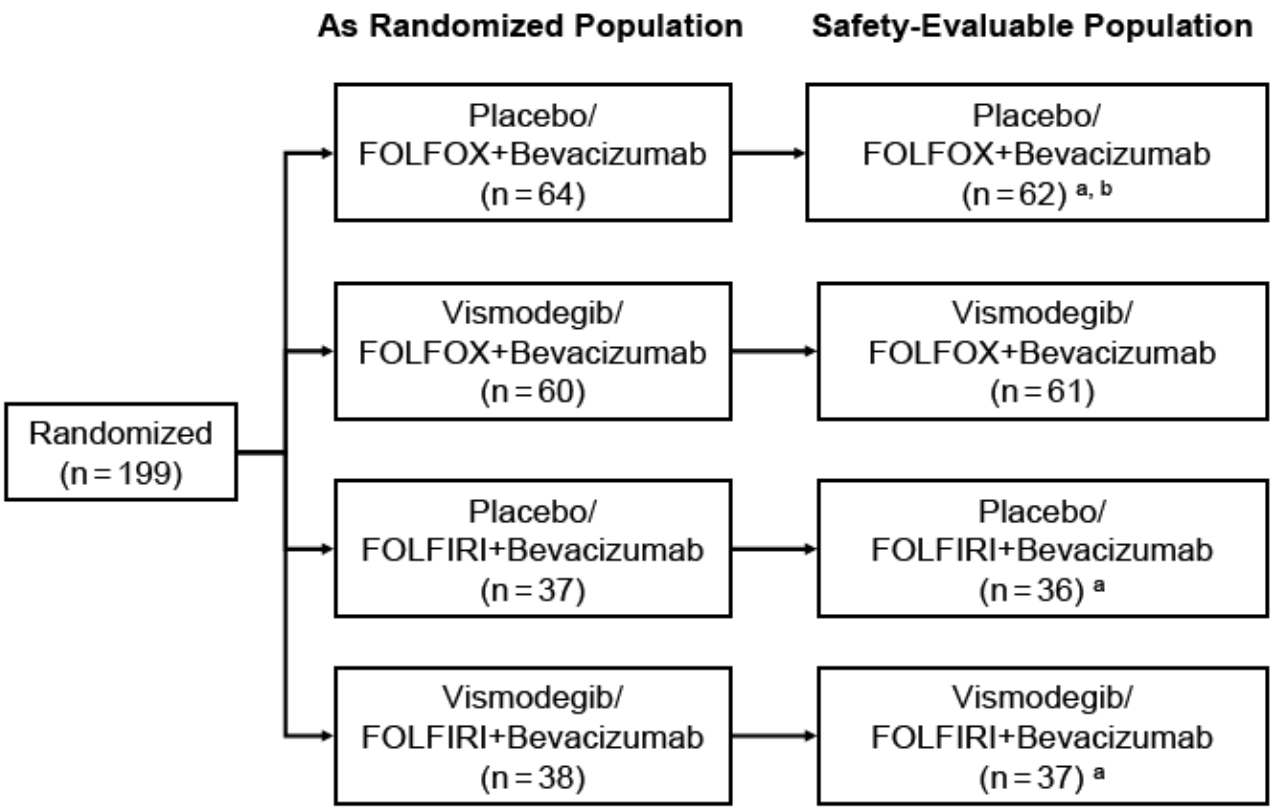
Secondary:
• To make a preliminary assessment of the safety and tolerability of GDC-0449 when added to the standard of care (FOLFOX + bevacizumab or FOLFIRI + bevacizumab) in patients with previously untreated metastatic CRC and to make a preliminary assessment of whether adding GDC-0449 to FOLFOX + bevacizumab or FOLFIRI + bevacizumab increases the risk of Grade 3 or 4 adverse events in patients with previously untreated metastatic CRC

• To evaluate the relationship between detectable Hh expression in archival tumor tissue and the clinical benefit of GDC-0449 with the standard of care (FOLFOX + bevacizumab or FOLFIRI + bevacizumab) in patients with previously untreated metastatic CRC as measured by PFS

• To evaluate the pharmacokinetics of GDC-0449 when given in conjunction with oxaliplatin or irinotecan, 5-FU, and bevacizumab and to evaluate the possible effect of GDC-0449 on the pharmacokinetics of oxaliplatin or irinotecan, 5-FU, and bevacizumab

Patient and Treatment
Of the 199 randomized patients, 124 received FOLFOX chemotherapy with bevacizumab. Within the FOLFOX-bevacizumab stratum, 64 were randomized to the placebo arm and 60 to the vismodegib arm. A total of 75 patients received FOLFIRI chemotherapy with bevacizumab. Within the FOLFIRI-bevacizumab stratum, 37 patients were randomized to placebo and 38 to vismodegib.

Study Design
Flowchart of Patient Disposition are below:



FOLFIRI = irinotecan, leucovorin, and bolus + infusional 5-fluorouracil;
FOLFOX = oxaliplatin, leucovorin, and bolus + infusional 5-fluorouracil.

[a] One patient received no study medication.

[b] One patient erroneously received vismodegib.

Pharmacokinetics

The main objective of the pharmacokinetic (PK) analyses was to evaluate the pharmacokinetics of vismodegib when given in conjunction with oxaliplatin or irinotecan, 5-FU/leucovorin and bevacizumab and to evaluate the effects of vismodegib on the pharmacokinetics of oxaliplatin or irinotecan, 5-FU, and bevacizumab.

DDI potential was assessed based upon results from the Phase II study of vismodegib in combination with FOLFOX (oxaliplatin, leucovorin, and infusional 5-fluorouracil [5-FU]) with bevacizumab or FOLFIRI (irinotecan, leucovorin, and infusional 5-FU) with bevacizumab. Study SHH4429g was a randomized, placebo-controlled, double-blind study of vismodegib added to standard-of-care regimens for metastatic colorectal cancer (CRC). Patients were randomized in a 1:1 ratio to receive either vismodegib or placebo in combination with bevacizumab and either FOLFOX or FOLFIRI chemotherapy.

- There were no clinically meaningful differences in 5-FU, oxaliplatin, irinotecan, SN-38, SN-38g, and bevacizumab levels with or without vismodegib.

- For 5-FU, concentrations at 6 hours after dosing (n ≤10) were 22% lower in combination with vismodegib.

- Mean irinotecan, SN-38, and SN-38g AUC_{last} and C_{max} values (n = 5) were similar in the presence and absence of vismodegib.

- Total oxaliplatin AUC_{last} and C_{max} values (n = 4) were 27% and 21% higher, respectively, with vismodegib co-administration. Similarly, mean free oxaliplatin AUC_{last} and C_{max} values (n = 4) were 29% and 40% higher, respectively, with vismodegib co-administration.

- On average, the bevacizumab pre-dose serum concentration (n ≤9) was 58% higher with vismodegib than without vismodegib.

Table 25: Comparison of Mean 5-FU Concentration 6 Hours Post-Dose in the Absence (Day 1) and Presence (Day 28) of Vismodegib

	5-FU Concentration (ng/mL)		
	Mean	SD	n
Without vismodegib	540	245	10
With vismodegib	419	141	8

Table 26: Irinotecan, SN-38, and SN-38G Pharmacokinetic Parameters

	Irinotecan			SN-38			SN-38G		
	AUClast (ng*hr/mL)	Cmax (ng/mL)	n	AUClast (ng*hr/mL)	Cmax (ng/mL)	n	AUClast (ng*hr/mL)	Cmax (ng/mL)	n
Without vismodegib	14100 ± 5000	2460 ± 902	5	236 ± 48.9	27.8 ± 6.52	5	2110 ± 1290	168 ± 60.8	5
With vismodegib	13900 ± 3960	2110 ± 541	5	273 ± 102	26.3 ± 10.6	5	1960 ± 565	156 ± 42.2	5

Table 27: Total and Free Oxaliplatin Pharmacokinetic Parameters

	Total Oxaliplatin			Free Oxaliplatin		
	AUClast (ng*hr/mL)	Cmax (ng/mL)	n	AUClast (ng*hr/mL)	Cmax (ng/mL)	n
Without vismodegib	54300 ± 8110	4360 ± 817	4	4550 ± 828	779 ± 90	4
With vismodegib	69100 ± 7170	5260 ± 1120	4	5850 ± 687	1090 ± 293	4

Table 28: Bevacizumab Serum Concentrations

	Bevacizumab Concentration (μg/mL)		
	Mean	SD	n
Without vismodegib	97.4	28	9

With vismodegib	154	32	6

Overall Summary and Conclusions

• Vismodegib in combination with standard-of-care treatment for first-line metastatic colorectal cancer did not confer incremental clinical benefit as measured by PFS. The median PFS estimates for the placebo and vismodegib treatment arms were 10.1 months and 9.3 months, (HR [90% CI]: 1.25 [0.89, 1.76]; p = 0.279). for all randomized patients.

• There was no vismodegib-associated clinical benefit as measured by PFS in patient subgroups defined by chemotherapy regimen or by biomarkers (Hh ligand expression in tumor tissue and KRAS mutation status).

• In general, plasma levels of vismodegib, 5-FU, oxaliplatin, irinotecan, SN-38, SN-38G, and serum levels of bevacizumab from this study were in agreement with published data from other trials with similar dosing regimens. Furthermore, there were no clinically meaningful differences in 5-FU, oxaliplatin, irinotecan, SN-38, SN-38G, and bevacizumab levels with or without vismodegib. A limitation of these comparisons was the small sample size. Taken together, these results suggest that vismodegib did not appear to be a perpetrator or a victim of a drug-drug interaction when combined with FOLFOX-bevacizumab or FOLFIRI-bevacizumab.

• Cumulative exposure to all regimen components was lower among patients randomized to vismodegib regardless of the chemotherapy regimen given although patients who received FOLFIRI-bevacizumab were able to tolerate more therapy overall than patients who received FOLFOX-bevacizumab.

• Adverse events that have previously been reported in association with vismodegib monotherapy (e.g., vomiting, asthenia, decreased weight, decreased appetite, muscle spasms, and dysgeusia) are those that were more prevalent among vismodegib-treated patients in the current study (Von Hoff et al. 2009). In addition, dehydration was noted more frequently in vismodegib-treated patients in this study. While the majority of these were Grade 1 or 2 in intensity, their more frequent occurrence may have contributed to increased treatment discontinuation among patients in the vismodegib arm.

• Comparisons of Grade 3–5 adverse events suggest that vismodegib may have increased the frequency of severe fatigue, weight loss, decreased appetite, and dehydration. Among patients in the FOLFOX-bevacizumab stratum, the incidence of Grade 3-5 peripheral neuropathy appears increased among vismodegib-treated patients.

In summary, no clinical benefit was observed from combining vismodegib with standard-of-car treatment for first-line metastatic colorectal cancer.

Reviewer Comments:

- *Irinotecan is not a sensitive BCRP substrate. The results could not preclude the possibility between vismodegib (as a BCRP inhibitor) with other BCRP substrates.*

- *Overall the applicant's conclusions appear reasonable from a clinical pharmacology perspective.*

Study SHH4683g

Title: A Phase I, Open-Label Absorption, Distribution, Metabolism, and Excretion (ADME) Study of the Hedgehog Pathway Inhibitor GDC-0449 in Healthy Female Subjects of Non-Childbearing Potential

Objectives

Primary:

Part A:

To determine the absolute bioavailability, clearance, and volume of distribution of GDC-0449 after a single 150-mg oral dose of GDC-0449 in combination with a single IV dose of 10 μg of GDC-0449 containing 18.5 kBq (500 nCi) of ^{14}C-GDC-0449.

Part B:

To determine the routes of excretion and extent of GDC-0449 metabolism following administration of a 30-mL suspension containing 150 mg of GDC-0449 and the appropriate amount of ^{14}C-GDC-0449 to give a radioactivity of 37 kBq (1000 nCi).

Part C:

To determine the clearance and volume of distribution of GDC-0449 after seven daily 150-mg oral doses. On Day 7, a single IV dose of 10 μg of GDC-0449 containing 18.5 kBq (500 nCi) of ^{14}C-GDC-0449 was given.

Part D:

To determine the oral exposure (AUC) from a radiolabeled tracer dose of GDC-0449 on Day 7 following six daily doses of 150-mg capsules. On Day 7, subjects drank a 30-mL suspension containing 150 mg of GDC-0449 and the appropriate amount of ^{14}C-GDC-0449 to give a radioactivity of 37 kBq (1000 nCi).

Secondary:

Part A:

Safety data following a single dose in healthy volunteers were collected.

Part B:

To identify GDC-0449 metabolites in plasma, urine, and feces, if needed, on the basis of the initial results of Part B. The need for this assessment was determined by the Sponsor and was based on a comparison of the total radioactivity and non-labeled GDC-0449 plasma concentration versus time profiles. If the comparison suggested extensive metabolism; i.e., if total radioactivity (which represents parent plus metabolites) concentrations in plasma were much greater than non-labeled GDC-0449 (parent only), metabolite identification was considered. Safety data following a single dose in healthy volunteers were also collected.

Part C:

Safety data following multiple doses in healthy volunteers were collected.

Part D:

Safety data following multiple doses in healthy volunteers were collected.

Design:
This was an open-label, Phase I, single-center study to thoroughly investigate the plasma pharmacokinetics of GDC-0449 after a single dose (Part A) and after multiple doses (Parts C and D), and to determine the routes of excretion and extent of metabolism of GDC-0449 (Part B). Parts C and D were added by protocol amendment. In each part, 6 healthy female subjects of non-childbearing potential, between 18 and 65 years of age (inclusive), were dosed. Subjects enrolled in Part A could not be enrolled in Part B of the study. Likewise, subjects enrolled in Part C could not be enrolled in Part D of the study. Parts A and B were conducted sequentially, with ≥ 7 days between dosing the sixth subject in Part A and dosing the first subject in Part B. Likewise, Parts C and D were conducted sequentially, with ≥ 7 days between dosing the sixth subject in Part C and dosing the first subject in Part D. Parts C and D were initiated after completion of the clinical phase of Parts A and B.

Study treatment:
General:
Dosing was in the morning after a ≥ 4-hour fast. Fasting (no food or water) continued for 4 hours after the oral dose in Parts A and B or for 2 hours after the oral dose on Days 1−6 and 4 hours after the oral dose on Day 7 in Parts C and D. Subjects were not allowed to lie down during the post-dose fasting period to facilitate drug absorption.

Part A:
On Day 1, subjects received a single oral dose of 150 mg of non-labeled GDC-0449 administered in capsule form with approximately 240 mL of water. Starting approximately 2 hours after oral administration (at approximately Tmax), a tracer-dose of 10 μg (2 mL) of ^{14}C-GDC-0449 containing approximately 18.5 kBq (500 nCi) of radiocarbon, was administered as an IV injection over 1 minute and flushed with 5 mL of 5% dextrose immediately after the injection.

Part B:
On Day 1, subjects received a 30-mL oral suspension containing 150 mg of GDC-0449 with 6.5 μg of ^{14}C-GDC-0449 to give a radioactivity of approximately 37 kBq (1000 nCi). After administering the suspension, the container was rinsed 3 times with approximately 50 mL of bottled water (150-mL total volume of water), which the subject also drank. The solution, including the rinse, was consumed within 5 minutes.

Part C:
On Days 1−7, subjects received a single oral dose of 150 mg non-labeled GDC-0449 administered in capsule form with approximately 240 mL water. On Day 7, starting approximately 2 hours after oral administration, a tracer dose of 10 μg (2 mL) ^{14}C-GDC-0449 containing approximately 18.5 kBq (500 nCi) radiocarbon, was administered as an IV injection over 1 minute and flushed with 5 mL of 5% dextrose immediately after the injection.

Part D:
On Days 1−6, subjects received a single oral dose of 150 mg non-labeled GDC-0449 administered in capsule form with approximately 240 mL water. On Day 7, subjects received a

30-mL oral suspension containing 150 mg of GDC-0449 with 6.5 μg of ^{14}C-GDC-0449 to give a radioactivity of approximately 37 kBq (1000 nCi). After administering the 30-mL suspension, the container was rinsed 3 times with approximately 50 mL bottled water (150-mL total volume of water), which the subject also drank. The solution, including the rinse, was consumed within 5 minutes.

Number of Patients (Planned and Analyzed):
24 healthy female subjects of non-childbearing potential, 6 subjects per study part. Twenty-two subjects each participated in one part of the study, whereas one subject participated in two parts, Parts A and D.

Duration of Treatment:
Part A:
On Day 1, subjects received a single oral dose of non-labeled GDC-0449 and a single IV tracer dose of ^{14}C-GDC-0449.

Part B:
On Day 1, subjects received a single oral dose of ^{14}C-GDC-0449.

Part C:
On Days 1−7, subjects received a single oral dose of non-labeled GDC-0449. On Day 7, subjects also received a single IV tracer dose of ^{14}C-GDC-0449.

Part D:
On Days 1−6, subjects received a single oral dose of non-labeled GDC-0449. On Day 7, subjects received a single oral dose of 14C-GDC-0449.

Pharmacokinetic:
GDC-0449 and ^{14}C-GDC-0449 were measured in plasma (Parts A, C, and D). For Part B, GDC-0449 was measured in plasma and total radioactivity was measured in plasma, whole blood, urine, and feces. The following PK parameters were determined using non-compartmental methods:

- Maximum observed plasma concentration (Cmax)
- Time to maximum plasma concentration (Tmax)
- Area under the plasma concentration−time curve (AUC)
- Absolute bioavailability (%F)
- Total plasma clearance (CL)
- Volume of distribution (Vss)
- Plasma terminal phase half-life ($t_{1/2}$)
- Cumulative percent excretion in urine and feces (Part B)

Summary of Results and Conclusions

Safety Conclusions:

- The majority of the 60 reported treatment-emergent AEs (TEAEs) were of mild severity (58 TEAEs) and considered by the investigator not to be related to study drug treatment (57 TEAEs).
- An SAE of cancer of the left breast was reported for a 50-year old subject participating in Part D. One subject in Part C had a vomiting event of moderate severity after the first oral dose. Both events were considered by the investigator not to be related to study drug treatment.
- All TEAEs, except the SAE, were transient and had resolved without sequelae by follow-up.
- The most frequently reported TEAEs (reported by 3 or more subjects) were headache,
- diarrhoea, flatulence and back ache.
- There were no findings of clinical relevance with respect to clinical laboratory, vital signs, ECG or physical examination.

Pharmacokinetic Conclusions:

- Part A Single Dose PK: Following IV administration, mean clearance, volume of distribution, and absolute bioavailability were 0.0434 L/hr, 16.4 L, and 31.8%, respectively. The parallel GDC-0449 profiles following single dose oral and IV administration of GDC-0449 suggest elimination rate limited pharmacokinetics.

- Part B Mass Balance, Metabolite Profiling and Identification: Over a 56-day collection period, 86.6% of the administered dose was recovered, on average with 82.2% and 4.43% recovered in feces and urine, respectively. GDC-0449 was slowly eliminated by a combination of metabolism and excretion of parent drug, the majority of which was recovered in feces. GDC-0449 was predominant in plasma, representing greater than 98% of the total circulating drug-related components. Metabolic pathways of GDC-0449 in human included oxidation, glucuronidation, and uncommon pyridine ring cleavage. No metabolites unique to human were identified in this study.

- Part C Multiple Dose PK: Steady state concentrations were achieved within 7 days of daily oral administration of 150-mg GDC-0449. Following IV administration at steady state, mean clearance and volume of distribution were 0.0785 L/hr and 26.8 L, respectively. Relative to single dose, GDC-0449 CL and Vss increased 55% and 62%, respectively, indicative of time-dependent changes in PK.

- Part D Oral Suspension PK: The PK profile of 14C-GDC-0449 administered as a single suspension dose at steady state was similar to the PK profile of GDC-0449 administered as a single 150-mg capsule dose under non-steady state conditions.

Overall Conclusions:

- Administration of study drug was well-tolerated by the healthy female subjects in all study parts.

- There were no findings of clinical relevance with respect to clinical laboratory, vital signs, ECG or physical examination.

- GDC-0449 exhibited a very long terminal half-life (9-12 days) after oral and IV administration, moderate absolute bioavailability (31.8%), and non-linear PK (CL and Vss) after repeated dosing.

- The majority of GDC-0449-related radioactivity was recovered in feces (82.2%) with low urinary recovery (4.43%); GDC-0449 was the predominant species in human plasma, urine, and feces, with no unique metabolites to human identified.

Reviewer's comments:

- *Urine and feces samples were not collected after the IV dose.*

- *Part B: Following administration of ^{14}C-GDC-0449 oral suspension (Part B) the total estimated excretion was 86.6% of the administered dose over a collection period of 56 days, with the majority of GDC-0449-related radioactivity recovered in feces (>80%) and low recovery in urine (<5%). Notably, detectable drug remained in plasma in all patients on Day 56, which suggests that recovery could have been even more complete if urine and feces collections would have continued beyond Day 56.*

- *A limitation of the Part C study design is that 150 mg GDC-0449 was only administered through Day 7 which likely resulted in an underestimation of the true steady state CL and V_{ss}. Time dependent changes in unbound fraction of GDC-0449 could be responsible for the changes in CL and V_{ss}; additional experiments are needed to assess this hypothesis.*

- *Overall the applicant's conclusions appear reasonable from a clinical pharmacology perspective.*

Study SHH8395g

OBJECTIVES

The primary objectives:

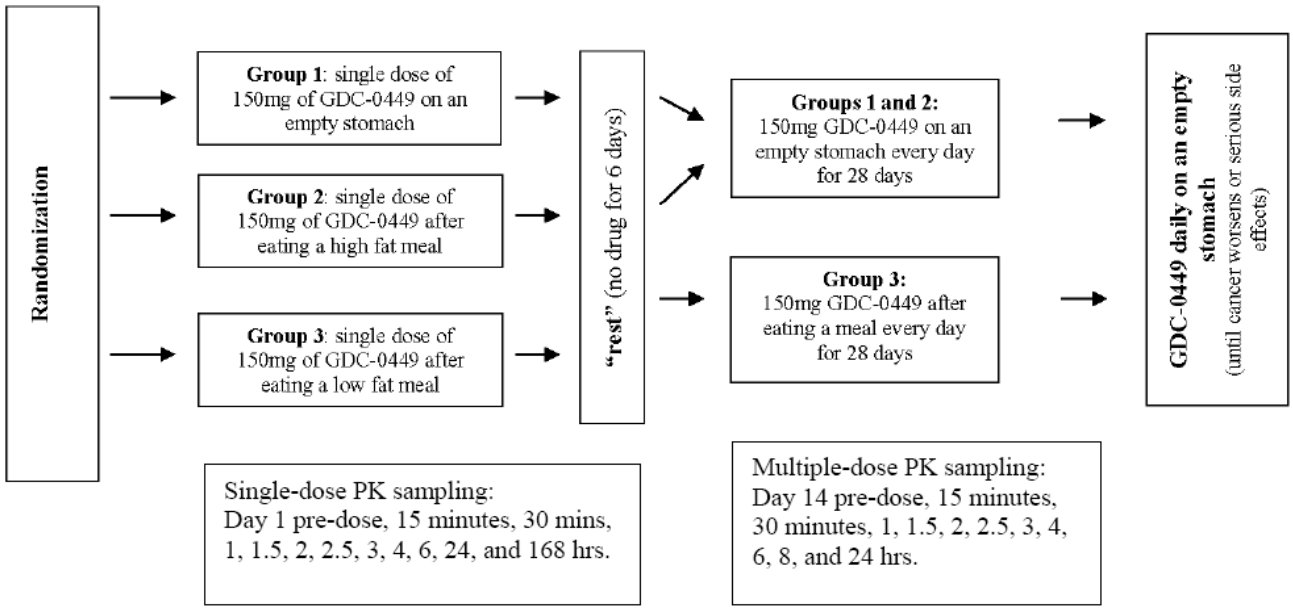
- To evaluate the effect of prandial states on the PK parameters of vismodegib
- To evaluate the effect of fat content of meals on the PK parameters of vismodegib

The secondary objectives:

- To evaluate the effect of prandial states and fat content of meals on the safety profile of vismodegib
- To describe any anticancer activities of vismodegib

STUDY DESIGN

This study was conducted in two parts: 1) a single-dose part and 2) a consecutive daily dosing part. Given the long half-life of vismodegib, a parallel design was used.



TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Vismodegib was administered orally. For Part I of the study, patients took their first dose of vismodegib (150 mg) in the clinic. For patients in the fasted group, following an overnight fast of at least 10 hours, patients entered the clinic and received vismodegib with 240 mL of water. For patients in the fed (HF and LF) groups, following an overnight fast of at least 10 hours, patients entered the clinic and received breakfast 30 minutes before vismodegib was administered. Vismodegib was administered with 240 mL of water.

For patients in all three groups, no food was allowed for at least 4 hours after receiving vismodegib. Patients remained in the clinic all day for PK sampling.

In Part II of the study, patients in both the fasted and HF groups from Part I were assigned to receive 150 mg vismodegib once daily in a fasted state (i.e., the fasted group). Patients in the LF

group from Part I received vismodegib once daily 30 minutes after a healthy breakfast. All patients in Part II were required to fast overnight for at least 10 hours and for at least 4 hours after receiving vismodegib.

PHARMACOKINETIC SAMPLING AND ANALYSES

In Part I of this study, blood samples were collected from patients prior to dosing, and 15 minutes, 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 24, and 168 hours after a single dose of vismodegib. C_{max}, t_{max}, and $AUC_{(0\text{-}168)}$ were estimated and summarized. These PK parameters were then compared among the fasted, LF, and HF groups.

In Part II of the study, blood samples were collected prior to Day 14 dosing with vismodegib and at 15 minutes, 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing on Day 14. Steady-state C_{max}, t_{max}, and $AUC_{(0\text{-}24)}$ were estimated and summarized. A mixed-effects model on log-transformed AUC and C_{max} was used to estimate GMRs and 90% CIs for the ratios. These analyses were performed using the WinNonLin built-in bioequivalence module with the effect of food as a fixed effect and no random effect.

Figure 19: Mean (SD) Plasma Concentration-Time Profiles after a Single Dose of Vismodegib by Prandial State from 0−168 Hours (A) and from 0−24 Hours (B)

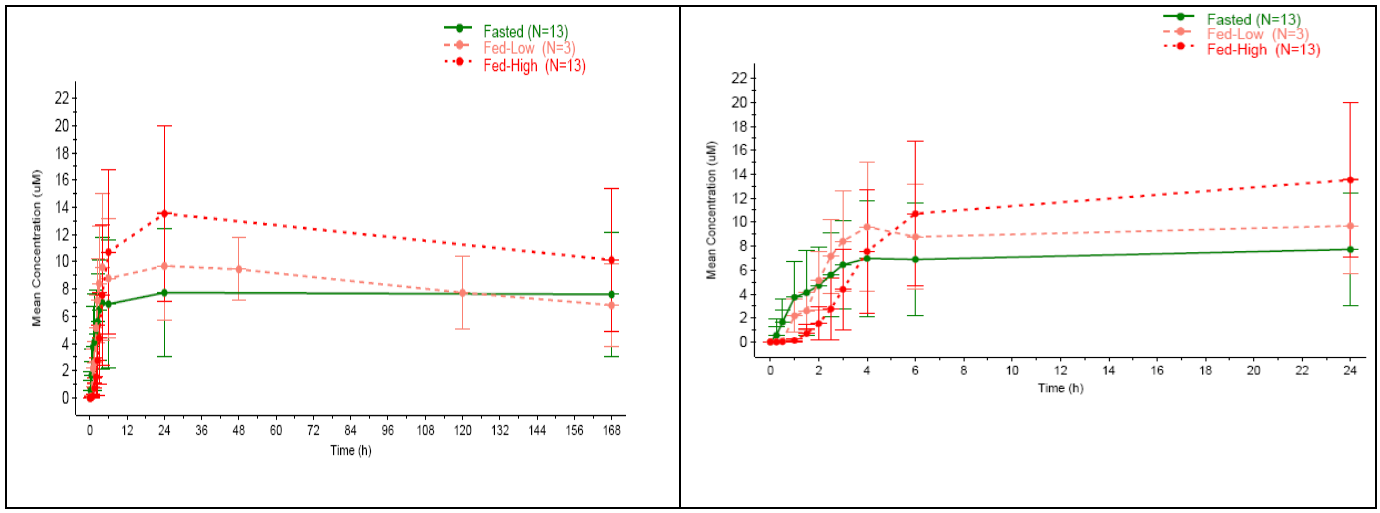


Table 29: PK Parameters after a Single Dose of Vismodegib

Group	t_{max} (hour) (Median [Range])	C_{max} (µM) (Mean ± SD)	$AUC_{0\text{-}168}$ (µM*hour) (Mean ± SD)
Fasted (n = 13)	26.9 (0.583, 170)	10.0 ± 5.73	1270 ± 749
Low-fat (n = 3)	4 (4, 120)	11.3 ± 3.32	1410 ± 368
High-fat (n = 13)	24.8 (6, 169)	13.8 ± 6.35	1680 ± 1100

Figure 20: Single-Dose Distribution of Vismodegib Cmax and AUC(0-168) by Prandial State

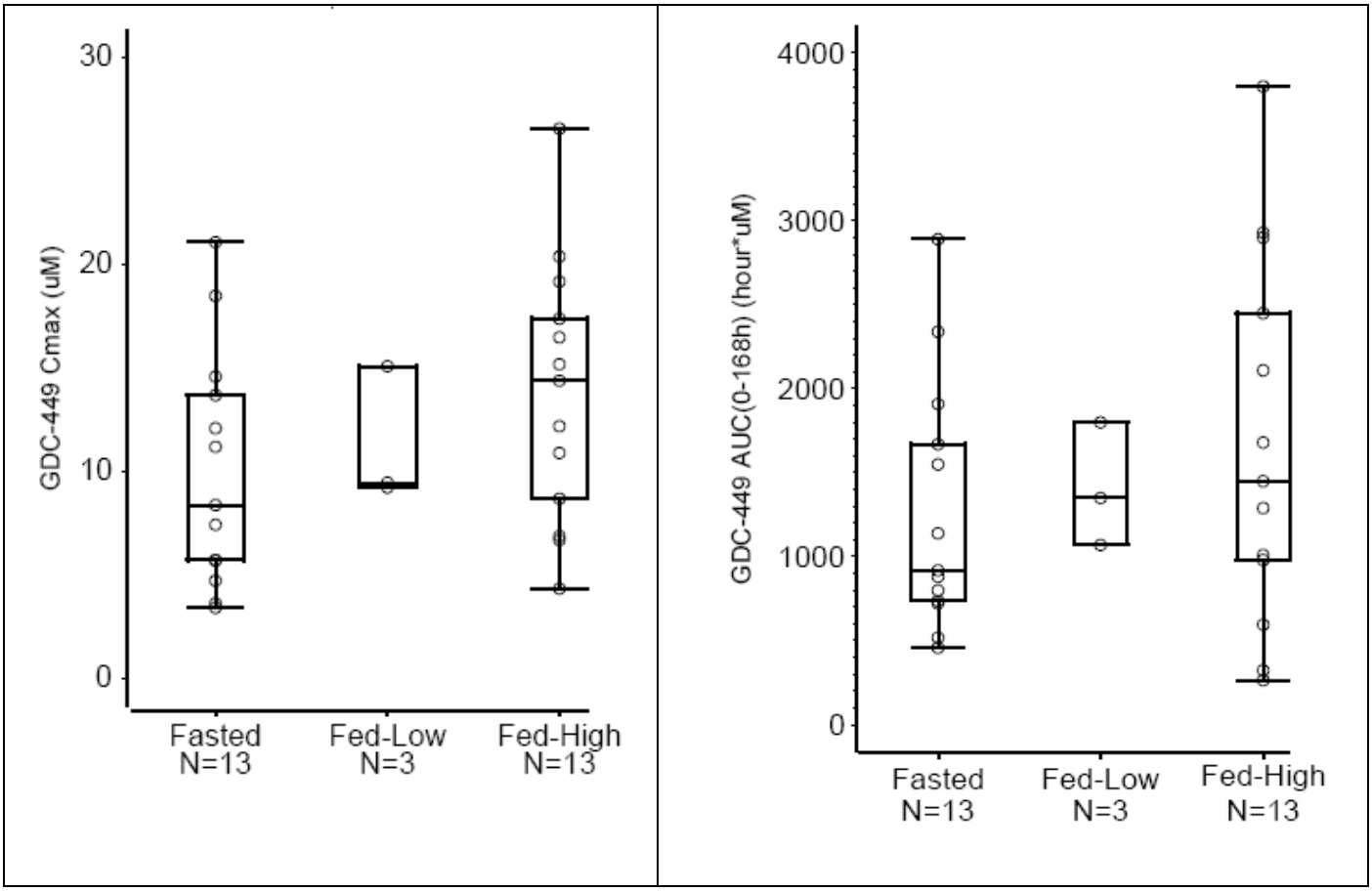


Figure 21: Plasma Concentration-Time Profiles by Prandial State on Day 14 following 150 mg Daily Vismodegib

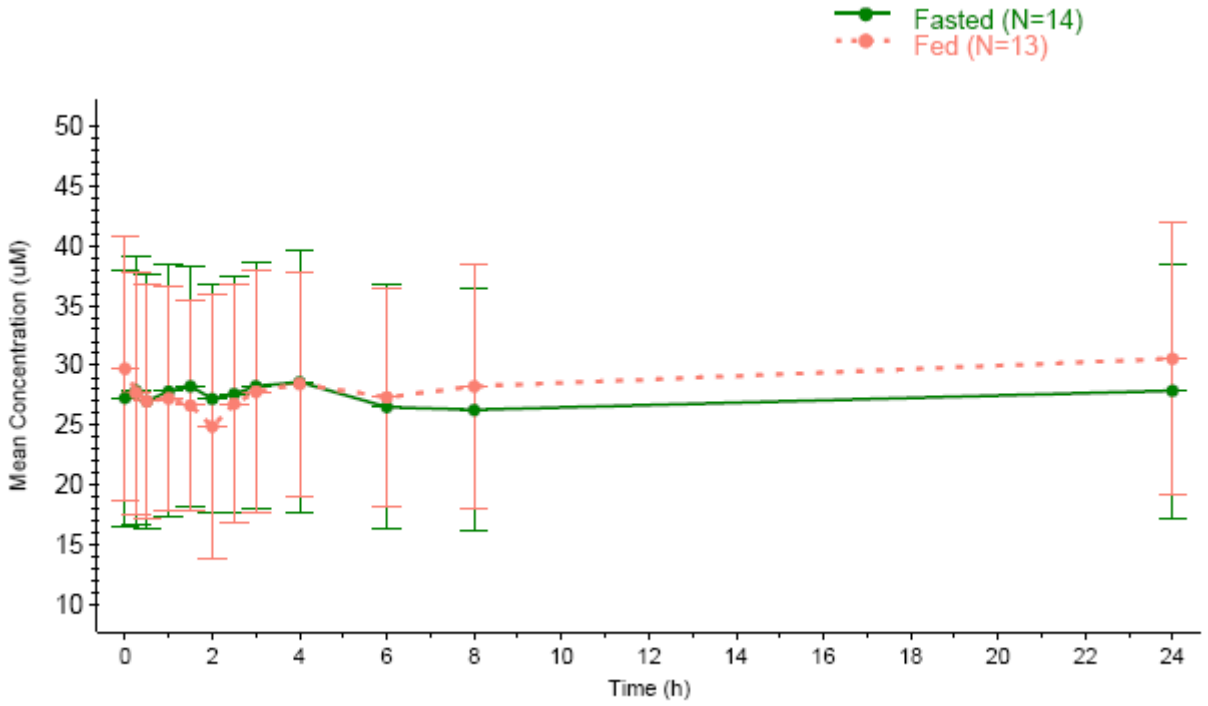


Table 30: PK Parameters on Day 14 following 150 mg Daily Vismodegib for Patients Enrolled in Part II of the Study

Group	Vismodegib		
	t_{max} (hour) (Median [Range])	C_{max} (µM) (Mean ± SD)	AUC_{0-24} (µM*hour) (Mean ± SD)
Fasted (n = 13)	4.33 (1, 28.7)	29.2 ± 11.0	698 ± 274
Fed (n= 13)	22.2 (2.5, 26.5)	30.9 ± 11.2	727 ± 280

Figure 22: Distribution of Day 14 Vismodegib Cmax and AUC(0-24) by Prandial State

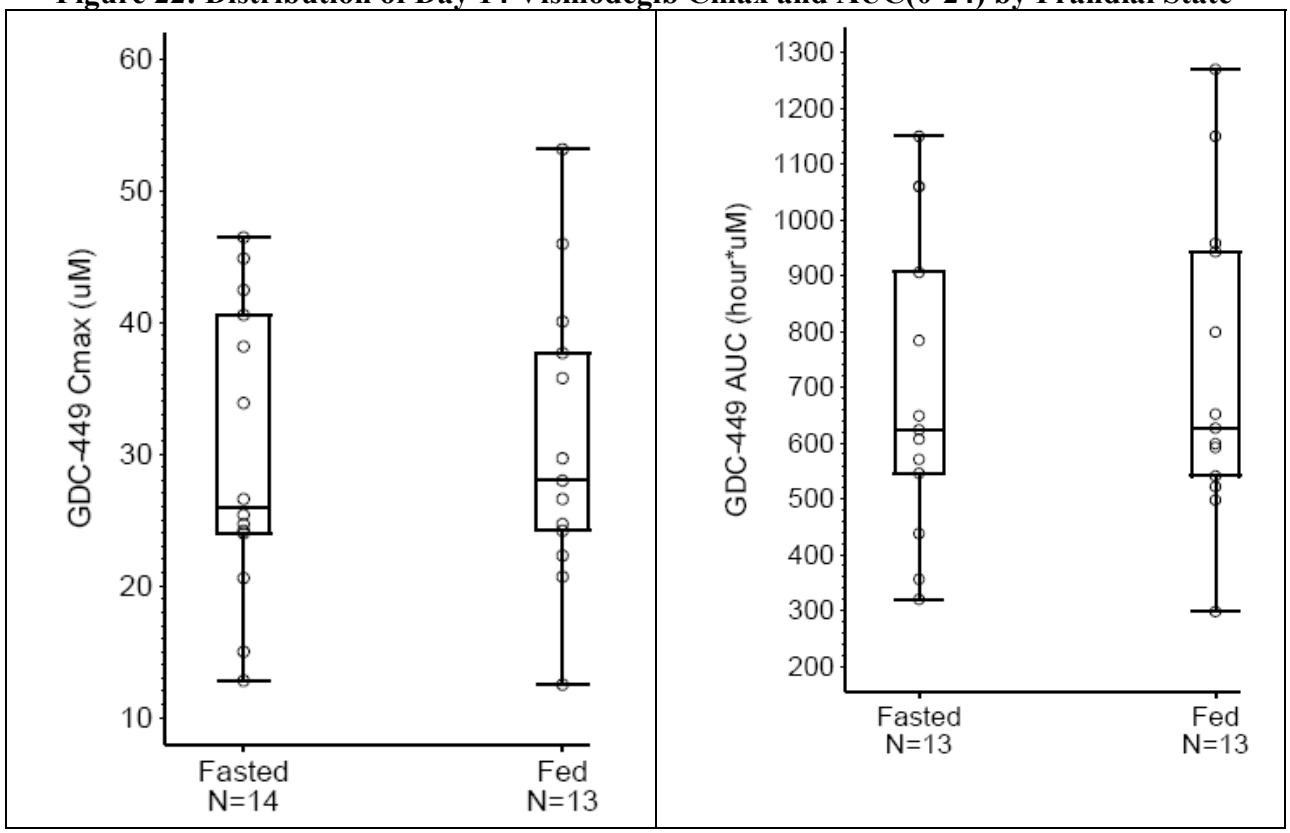


Table 31: Statistical Analysis of Steady-State Vismodegib Cmax and AUC0-24 for Fed (n=13) versus Fasted (n=13) Groups

PK Parameter	Treatment Ratio	GMR	Lower End of 90% CI	Upper End of 90% CI
Cmax	Fed/fasted	106.6%	81.9%	138.8%
AUC0-24	Fed/fasted	104.7%	80.0%	137.2%

PK RESULTS AND CONCLUSIONS

No apparent effect of food on vismodegib plasma exposure was observed at steady-state. The geometric mean ratios and corresponding 90% confidence intervals (CIs) for the comparison of steady-state vismodegib Cmax and AUC_{0-24} (fed:fasted) were 107% (90% CI: 82%, 139%) and 105% (90% CI: 80%, 137%), respectively(Table 22).

The mean concentration-time profile following a single 150 mg dose of vismodegib indicates that food and fat content had a slight effect on the exposure and caused delayed absorption of vismodegib. An increase in C_{max} and AUC_{0-168} (1.38-fold maximum, HF group) with food was observed in the single-dose (Part I) of the study.

SAFETY
Three serious adverse events (erectile dysfunction, fatigue, and WBC decreased) that were considered by the investigator to be possibly related to vismodegib therapy were each reported in 1 patient. Those adverse events were generally consistent with those seen in other studies with vismodegib.

SUMMARY AND CONCLUSIONS
Although food slightly impacted single-dose vismodegib plasma exposure as indicated by an increase in C_{max} and AUC_{0-168} (1.38-fold maximum, HF group), there was no apparent impact of food on vismodegib plasma exposure at steady-state.

Reviewer's comment:

- *The formulation used in the food-effect study is the same as the to-be-marketed formulation.*

- *It has been previously shown that there is a strong correlation between vismodegib steady-state plasma concentration and level of alpha-1-acid glycoprotein (AAG), and that AAG levels explain > 70% of the observed PK variability. Under single-dose conditions, vismodegib concentrations are not sufficient to saturate AAG binding allowing for an effect of food on the extent of absorption. In contrast, AAG binding is saturated with continuous daily dosing (at steady-state) under which conditions food would not be expected to have an impact on vismodegib exposure.*

- *In the pivotal phase 2 trials, information on prandial state was not collected from investigators or patients. In the Phase II studies (SHH4476g, SHH4429g, SHH4489g), patients were instructed to take vismodegib with or without food, at the same time each day.*

- *For the food-effect study, SHH4893s (NCI 8395), the applicant states that the PK results provided in the synoptic report are considered to be final. The applicant states that although the study is ongoing, the primary endpoints have been met.*

- *Overall the applicant's conclusions appear reasonable from a clinical pharmacology perspective.*

4.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW Application Number	NDA 203388
Submission Number (Date)	September 8, 2011
Compound	Vismodegib
Clinical Division	DHP
Primary PM Reviewer	Bahru A Habtemariam, Pharm.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

4.2.1 Summary of Findings

4.2.1.1 Key Review Questions

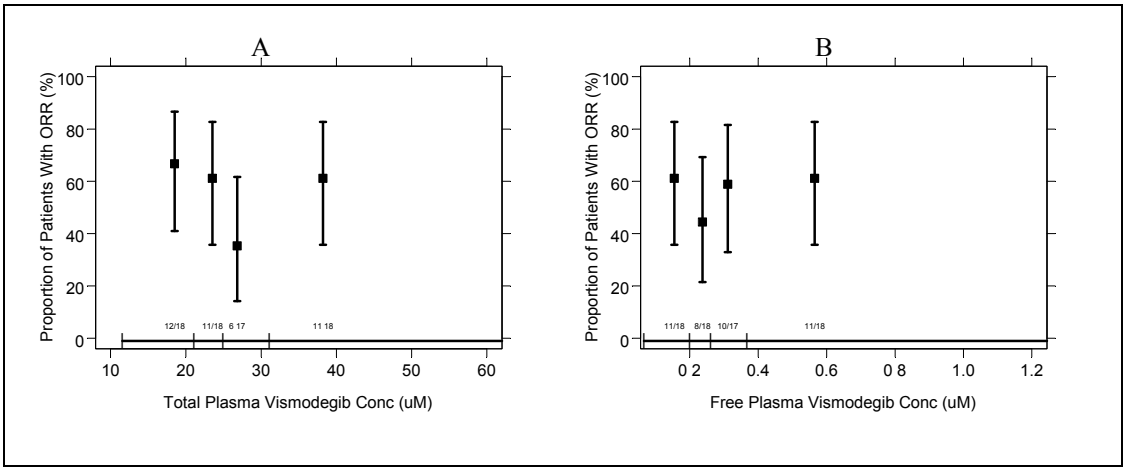
The purpose of this review is to address the following key questions.

Is there evidence of exposure-response for efficacy in the pivotal phase 2 trials?

There is no evidence of an exposure-response for ORR following 150 mg of vismodegib once daily. Since data were available following one dose level, exposure-response analyses were intended to account for inter-individual variability.

The phase 2 study enrolled a total of 104 patients with metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) where patients were treated with 150 mg of vismodegib once daily. Steady state plasma concentrations of total and free vismodegib were available from 71 patients. Total vismodegib concentration refers to all circulating drug including those bound to plasma proteins and those unbound (free). It appears that vismodegib binds to alpha-1-acid glycoprotein with high affinity. Free drug concentration refers to circulating drug that is unbound to any plasma protein. Figure 23 shows that increasing concentrations of total or free vismodegib does influence the proportion of patients with ORR.

Figure 23. Proportion of objective response rate (ORR) is not influenced by increasing steady total concentrations (A) or steady state free vismodegib concentrations (B).

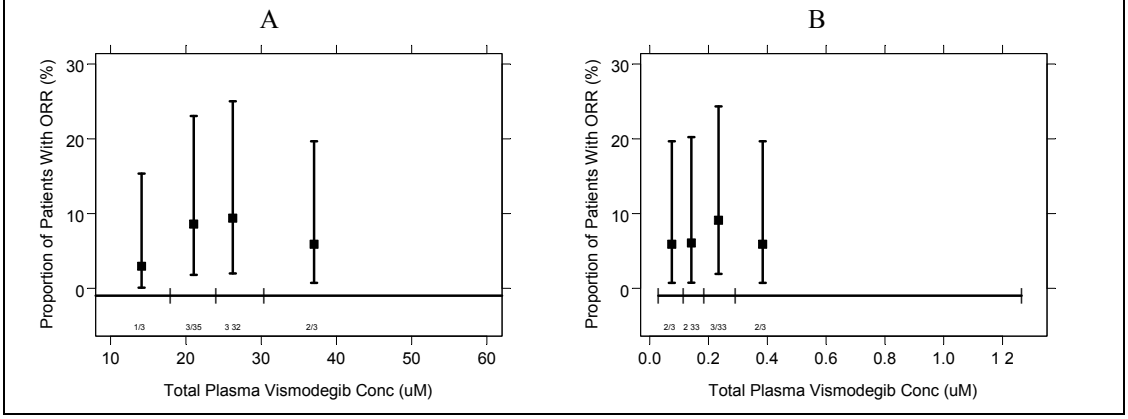


Is there exposure-response relationship safety?

There is no evidence for exposure-response for Grade 3+ weight loss or fatigue.

Safety data for vismodegib were available from 138 advanced BCC patients that took part in phase 1 and phase 2 trials. The most frequent Grade 3 or more adverse events (Grade 3+) were weight loss (n=10) and fatigue (n=9), which were observed at frequencies of 7.2 % and 5.1 %, respectively. Pharmacokinetic data were available from 138 patients that took part in the phase 1 and phase two studies. As shown in below, the proportion of patients with Grade 3 or more weight lose (Grade 3+) does not increase with increasing total of free vismodegib concentrations (**Figure 24**). A similar trend was observed for Grade 3+ fatigue.

Figure 24. Proportion of patients with Grade 3+ weight loss does not increase with increasing total (A) or free (B) vismodegib concentrations.



4.2.2 Recommendations

Exposure-response analyses indicate that following vismodegib dose of 150 mg once daily, the proportion of patients with ORR remained similar across the observed ranges of vismodegib total and free concentrations. Similarly, the proportion of patients with Grade 3+ weight loss and

fatigue did not increase with increasing total or free vismodegib concentrations.

4.2.3 Labeling Statements

12.3 Pharmacokinetics

Absorption

Vismodegib is a highly permeable compound with low aqueous solubility (BCS Class 2). The single dose absolute bioavailability of vismodegib is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg and 540 mg vismodegib. Under clinically relevant conditions (steady state), the PK of vismodegib is not affected by food. Therefore, vismodegib may be taken without regard to meals.

Distribution

The volume of distribution for vismodegib is low, ranging from 16.4 to 26.6 L. In vitro binding of vismodegib to human plasma proteins is high (97%) at clinically relevant concentrations. Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG). In vitro binding to AAG is saturable at clinically relevant concentrations. Ex vivo plasma protein binding in human patients is >99%. Vismodegib concentrations are strongly correlated with AAG levels, showing parallel fluctuations of AAG and total drug over time and consistently low unbound drug levels.

Metabolism

Vismodegib is slowly eliminated by a combination of metabolism and excretion of parent drug. Vismodegib is predominant in plasma, with concentrations representing greater than 98% of the total circulating drug-related components. Metabolic pathways of vismodegib in human include oxidation, glucuronidation, and an uncommon pyridine ring cleavage. The two most abundant oxidative metabolites recovered in feces are produced in vitro by recombinant CYP2C9 and CYP3A4/5.

Elimination

After a single oral dose, vismodegib demonstrates a unique PK profile with sustained plasma levels and an estimated terminal half-life of 12 days.

After continuous once-daily dosing, the pharmacokinetics of vismodegib appear to be nonlinear. Considering the single dose half-life, steady-state plasma concentrations in patients are achieved faster than expected (typically within approximately 7 days of continuous daily dosing), with lower than expected accumulation. The apparent half-life of vismodegib at steady-state is estimated to be 4 days with continuous daily dosing.

After oral administration of radiolabeled drug, vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug, the majority of which is recovered in the feces (82% of the administered dose), with 4.4% of the administered dose recovered in urine. Vismodegib and associated metabolic products are eliminated primarily by the hepatic route.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses showed that weight (range: 41-146 kg), age (range: 26-89 years), creatinine clearance (range: 30 to 80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.

4.2.4 Results of Sponsor's Analysis

Population PK Model

Using plasma concentration data from 230 subjects that participates in 5 clinical studies, the sponsor conducted a population PK analyses to determine the influence of patient covariates on the disposition of vismodegib. Below are key finding of the population PK analysis results.

- The PK of vismodegib can be adequately described by a one-compartment model with first-order absorption, first-order elimination of unbound drug, and saturable binding to AAG with fast-equilibrium. See **Figure 25** below describing the structural PK model of vismodegib. **Table 32** summarizes the final PK parameter estimates.
- Variability of total vismodegib concentration at steady-state was predominantly explained by the range of AAG in patients. AAG was also the most influential factor for the steady-state concentration of unbound vismodegib, but the impact was not clinically significant, indicating that no dose adjustment would be necessary based upon AAG level in patients.
- Patient covariates such as age (range: 26-89), weight, creatinine clearance (range: 30 80 mL/min), and gender do not have meaningful influence the PK of vismodegib

Figure 25. Diagram of vismodegib Structural PK Model

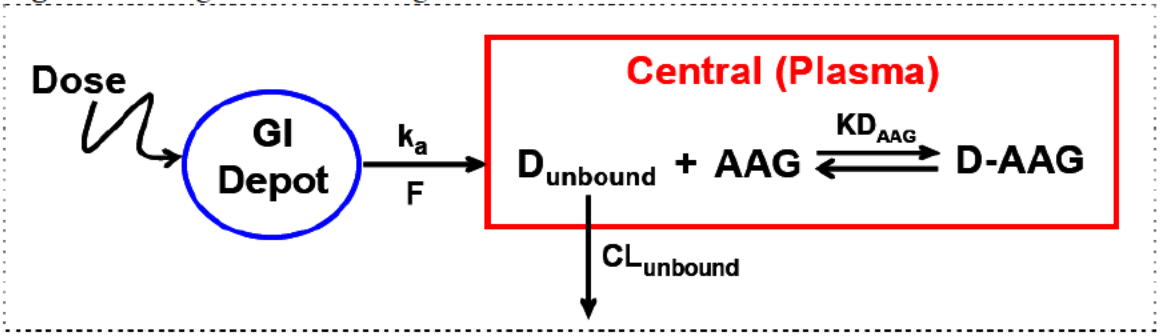


Table 32. Summary of Vismodegib Population PK Parameter Estimates

Parameter	Parameter Description	Population Estimate	Bootstrap Final Model Median (2.5^{th}, 97.5^{th} Percentiles)
$\exp(\theta_1)$	Apparent clearance of unbound, $CL_{unbound}$ (L/day)	1326	1332 (1196, 1467)
θ_9	Influence of age on $CL_{unbound}$	-0.527	-0.526 (-0.842,-0.248)
$\exp(\theta_2)$	Apparent volume of distribution of central compartment, V_c (L)	58.0	58.4 (53.2, 63.4)
θ_{10}	Influence of body weight on V_c	0.660	0.65 (0.31, 0.96)
$\exp(\theta_3)$	Dissociation constant, KD_{AAG} (μM)	0.056	0.056 (0.053, 0.058)
$\exp(\theta_6)$	Relative bioavailability for Phase I formulation in patients (Phase II formulation as reference), F	0.346	0.347 (0.293, 0.403)
θ_7	Influence of population on F	0.881	0.880 (0.566, 1.33)
$\exp(\theta_4)$	Absorption rate constant, k_a (day^{-1})	9.025	9.065 (6.870, 11.865)
θ_5	Influence of population on k_a	0.671	0.621 (0.215, 0.991)
θ_8	Influence of formulation on k_a	-0.602	-0.594 (-1.07, -0.11)
Inter-subject variability (%)	$CL_{unbound}$	48.7	47.4 (39.6, 57.5)
	V_c	45.5	44.8 (39.7, 50.8)
	KD_{AAG}	19.7	19.5 (15.0, 23.2)
Residual variability (%)	Total vismodegib plasma concentration	26.7	26.5 (24.7, 28.6)
	Unbound vismodegib plasma concentration	42.4	42.3 (39.5, 44.9)

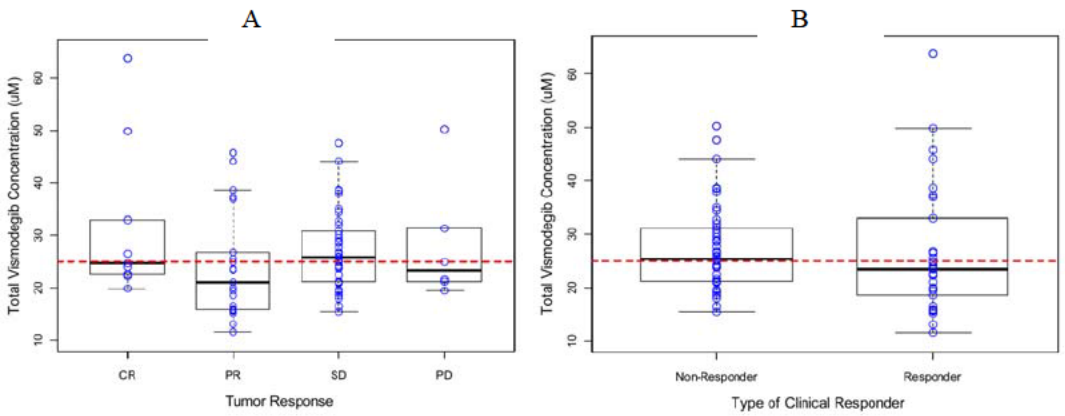
Reviewer's comments:
The sponsor's population PK analysis is adequate and the model appears to adequately describe the data. No major PK parameter-covariate relationships were discovered in the population PK model that warrants dose adjustment.

Exposure-Response Analyses

The sponsor performed exploratory exposure response analysis for efficacy and safety. The findings of the sponsor's exposure-response analysis were as follows:

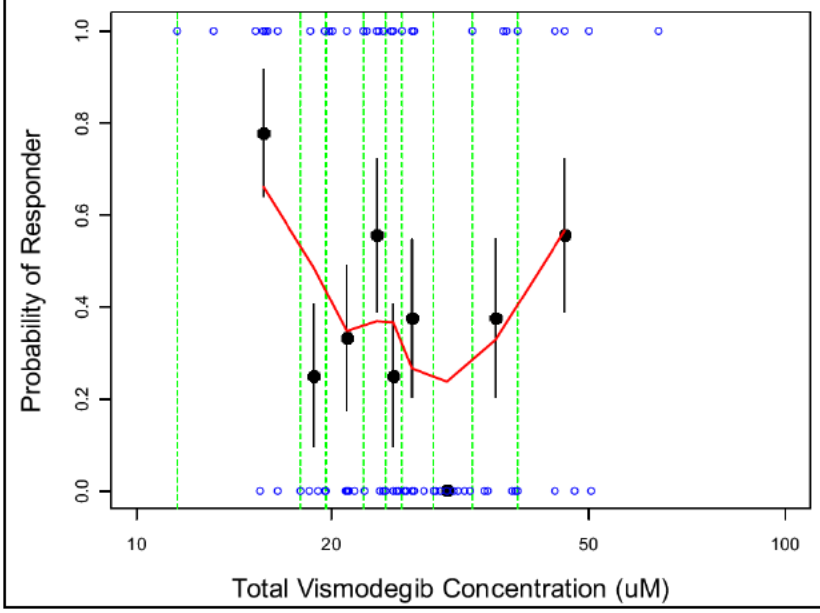
- No exposure-relationship was observed for tumor response (complete response, partial response, stable disease, progressive disease) and type of clinical responder (responder/non-responder) following treatment with 150 mg daily in study SHH4476g (**Figure 26A**).
- The lack of E-R relationship for efficacy suggested additional benefit would not be expected with higher exposures of vismodegib (**Figure 26B and Figure 27)**.
- No clinically relevant exposure-response relationship was for safety (weight loss, alopecia, dysgeusia, fatigue, muscle spasms, or nausea) in BCC patients treated with vismodegib doses of 150, 270, 540 mg daily in studies SHH3925g and SHH4476g.

Figure 26. Exposure-Response Relationship for Tumor Response (A) and Type of Clinical Responder (SHH4476g) (B).



Source: Sponsor's analysis

Figure 27. Probability of clinical responder versus total plasma concentrations of vismodegib in study (SHH4476g).



Source: Sponsor's analysis

Reviewer's comments:

- *The sponsor's exposure-response analyses for efficacy assessed whether there are exposure differences among the different tumor responses (CR, PR, SD, and PD) and types of responders (responders and non-responders) and concluded there are no exposure differences in different tumor responses and types of responders. Sponsor's logistic regression analysis also showed the lack of exposure-response relationship for*

efficacy. We agree with the sponsor's conclusions. However, because protein biding was found to be an important component of the vismodegib PK, the reviewers extended the sponsor's exposure-response analysis by looking at the proportion of respondents across free and total vismodegib concentration quartiles.

- *The sponsor's exposure-response analyses for safety included data for all grade adverse events and concluded there is no exposure-response relationship. The sponsor's conclusion is acceptable. The reviewers performed additional exposure-response analysis for safety by looking at the occurrences of grade 3 ore more weight loss and fatigue. Limiting analyses for severe adverse events (grade 3 or more) is important because such severe adverse events can trigger dose modifications.*

4.2.5 Reviewer's Analysis

Introduction

The sponsor performed population PK analysis of vismodegib to identify sources of vismodegib PK variability. The sponsor also performed exploratory exposure response analysis for safety and efficacy. The sponsor analyses did not reveal any coviate-PK or exposure-response relationships that could lead to dose adjustments. The reviewers performed additional analyses to further elucidate the exposure-response properties of vismodegib.

Objectives

Exposure-response and dose-response analyses were performed to characterize the exposure-response relationship for safety and efficacy endpoints in order to justify any dose adjustments, if needed. The efficacy endpoint was ORR and the safety endpoints were Grade 3+ weight loss and Grade 3+ fatigue.

Methods

Efficacy, safety, trough concentrations, and dosing data were available from three studies. These studies consist of one phase 1 dose escalation study, one extension study, and one phase 2 pivotal study. Summary of the studies and available data are described in **Table 33**.

In the phase 2 study, ORR data were available from 96 patients. This study was designed to show whether vismodegib improves objective response rate (ORR) (partial or complete response) in patients with mBCC or laBCC.

Table 33. Summary of Clinical Studies and Data Used for Exposure-Response Analyses

Study (Phase)	Design/Dose	Population	Endpoint	N	PK
SHH3925G (Ph 1)	dose escalation: 150, 270, or 540 mg PO QD	Solid tumors	Safety*	68	68
SHH4437G (Ph 2)	Extension: 150 or 300 mg PO QD	Patients were previously treated with vismodegib in a phase 1 or 2 studies	Safety Efficacy	15	-
SHH4476G (Ph 2)	150 mg PO QD	Locally advanced or metastatic BCC	ORR	104	71

*Safety data were available from 33 advanced BCC patients.

The exposure-response analysis for efficacy looked at proportion of respondents at each concentration quartiles of total and free vismodegib concentrations. Because the proportion of respondents was similar across all concentration quartiles, univariate logistic regression analysis was not conducted. A similar analysis method was used for exposure-safety analysis.

Data Sets

Data sets used are summarized in **Table 34** below.

Table 34: Analysis Data Sets.

Study Number	**Name (description)**	**Link to EDR**
SHH3925G, SHH4433G, SHH4476G, SHH4610G, and SHH4683G	poppkmdl.xpt (PK)	\\Cdsesub1\evsprod\NDA203388\0000\m5\datasets\11-2188\analysis\datasets
SHH3925G, SHH4437G, and SHH4476G	adae.xpt (safety)	\\Cdsesub1\evsprod\NDA203388\0000\m5\datasets\iss\analysis\datasets
SHH4476G	adrsp.xpt (PK)	\\Cdsesub1\evsprod\NDA203388\0000\m5\datasets\shh4476g\analysis\datasets

Software

S-PLUS was used for the reviewer's analyses.

4.3 Pharmacogenomic Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	203388
Submission Date	September 08, 2011
Applicant Name	Genentech, Inc.
Generic Name	Vismodegib
Proposed Indication	Advanced Basal Cell Carcinoma
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Rosane Charlab Orbach, Ph.D.

1 Background

Vismodegib is an oral, small molecule inhibitor of the Hedgehog (Hh) pathway. It inhibits the G protein coupled receptor‐ like smoothened (SMO). The key purpose of this memo is to assess whether the data is suggestive of a potential association between the level of Hh pathway activation and clinical response, and to outline any outstanding issues from a Genomics perspective.

2 Submission Contents Related to Genomics

Expression levels of Hh pathway components measured by qRT-PCR were assessed in tumor tissue in the pivotal study SHH4476g. This was a phase II multicenter, single-arm, two-cohort (locally advanced or metastatic) study in patients with advanced BCC (N=104; 33 patients with metastatic/71 patients with locally advanced). All efficacy-evaluable patients (N=96) were White. Tumor biopsies were mandatory for locally advanced BCC patients at baseline and on treatment. In addition, archival tumor samples were obtained from all patients prior to study entry. Limited data from this study was submitted in the NDA. Germline DNA for pharmacogenetic analyses was not collected.

3 Key Issues and Summary of Findings

3.1 Hh pathway molecular alterations in BCC

Most sporadic BCCs have been associated with upregulation of Hh signaling by ligand overexpression, or alterations at the PTCH/SMO level. About 70%-90% of these tumors show PTCH1 loss-of-function and another 10% -20% have activating mutations in SMO (PMID: 20546211; 21614026). However, mutations in genes downstream of SMO (e.g., SUFU) have also been described. This is important given that vismodegib is a SMO inhibitor and tumors with activation downstream of SMO may not be responsive. Availability of tumor samples from the pivotal study may represent an opportunity to perform exploratory analyses in the future if warranted.

3.2 Correlation of clinical response to vismodegib with the expression of Hh target genes

The mRNA expression of Hh target genes is frequently increased in BCCs and can be assessed as a measure of pathway activation. The overall response rate (ORR) in the pivotal study SHH4476g as assessed by the IRF was 43% (95% CI 30%, 56%) in patients with locally advanced disease and 30% (95% CI 16%, 48%) in patients with metastatic disease. The sponsor performed subgroup analyses for ORR, duration of objective response, and PFS to explore whether patient subsets that may have had a

differential treatment effect could be distinguished based on their relative expression levels of Hh target genes GLI1 and PTCH2 in archival tumor samples. Data from 75 efficacy-evaluable patients were used (22 metastatic and 53 locally advanced) and results for each cohort were summarized by tertiles. Responses were reported in all tertiles, and no evidence supporting an association was observed in this preliminary assessment. However results should be interpreted with caution. Some of the subgroups were small (as low as N=5), and the subgroups were defined post-hoc. The maximum allowable time between archival biopsy sample acquisition and GLI1 and PTCH2 testing was not defined, and the potential impact of archival sample quality on RNA expression is not clear. Moreover, the choice of PTCH2 expression as a measure of Hh pathway activation in BCC is not in full agreement with the literature (PMID: 11348463). Furthermore, as previously noted (section 3.1), molecular stratification based on Hh pathway activity will not likely differentiate tumors with alterations downstream of SMO, that would be resistant to treatment with a SMO inhibitor such as vismodegib, from those likely to respond to therapy.

3.3 Potential influence of pharmacogenetic variability on the pharmacokinetics of vismodegib

Although a contribution of the polymorphic CYP3A4, CYP3A5 and CYP2C9 drug metabolizing enzymes to vismodegib metabolism was identified in vitro, available data suggest that vismodegib is not extensively metabolized. Therefore a significant impact of drug metabolizing enzyme polymorphisms on vismodegib pharmacokinetics is not anticipated.

4 Summary and Conclusions

No conclusion regarding a potential association between the expression levels of Hh target genes and efficacy outcomes could be drawn from the limited, exploratory data available for analysis. As for other targeted therapies, outstanding issues include (1) selection of patients most likely to respond to therapy, and (2) identification of resistance mechanisms likely to limit vismodegib efficacy.

5 Recommendations

The data support approval of vismodegib for metastatic and locally advanced BCC from the Genomics Group perspective.

5.1 Post-marketing studies

No recommendations from the Genomics Group for PMR/PMC.

5.2 Label Recommendations

None.

_____
Christian Grimstein, Ph.D.
Reviewer, Genomics Group, OCP

_____
Rosane Charlab Orbach, Ph.D.
Secondary reviewer, Genomics Group, OCP

4.4 OCP Filing and Review Form

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202324

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203388**	**Brand Name**	**Erivedge (under review)**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Vismodegib**
Medical Division	**Oncology**	**Drug Class**	**First-in-class small molecule Hedgehog pathway inhibitor**
OCP Reviewer	**Jian Wang, Ph.D.**	**Indication(s)**	**Advanced basal cell carcinoma (BCC)**
OCP Team Leader	**Hong Zhao , Ph.D.**	**Dosage Form**	**150 mg capsules**
Pharmacometrics Reviewer	**TBA , Ph.D.**	**Dosing Regimen**	**150 mg QD daily**
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Pharmacogenomics Reviewer	**Rosane Charlab-Orbach, Ph.D.**		
Pharmacometrics Team Leader	**Issam Zineh, Pharm.D.**		
Date of Submission	**9/22/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Genentech**
Medical Division Due Date	**01/06/2012**	**Priority Classification**	**Priority**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		**Plasma: total vismodegib, unbound vismodelgib, [^{14}C] vismodegib and total [^{14}C], AAG, Moxifloxacin**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**SHH4683g (Part B)**
Isozyme characterization:		**2**		**12 recombinant human CYP isoforms**
Blood/plasma ratio:	**X**	**1**		**blood-plasma partitioning**
Plasma protein binding:	**X**	**2**		**Cross-species, AAG and HAS**
Pharmacokinetics -				
Healthy Volunteers-				
single dose:	**X**	**3**		**SHH4433g, SHH4683g(ADME, Part A), SHH4871g(QTc)**

multiple dose:		**2**		**SHH4683g (Part C), SHH4871g (QTc)**
Patients-				
single dose:	**X**	**2**		**SHH3925g, SHH4610g(dose schedule)**
multiple dose:	**X**	**4**		**SHH3925g, SHH4610g, SHH4318g, SHH4476g**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		**SHH3925g**
fasting / non-fasting multiple dose:	**X**	**1**		**SHH3925g**
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**		**In combination with bevacizumab or FOLFOX in CRC patients**
In-vivo effects of primary drug:	**X**	**1**		**the same as above**
In-vitro:	**X**	**8**		**CYP inhibition and induction, PXR binding, BCRPinhibition, MDR1 and BCRP substrate**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:	**X**	**2**		**Cancer patients; healthy volunteers**
Phase 2:	**X**	**1**		**104 BCC patients**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		**SHH3925g, SHH4476g**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**4**		**SHH3925g (cancer patients), SHH4610g(cancer patients), SHH4433g(healthy subjects), SHH4683g(healthy subjects),**
Data sparse:	**X**	**1**		**SHH4476g (cancer patients)**
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		**SHH4683g**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		**SHH3925g**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**SHH8395g (ongoing)**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**47**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

Note: Ongoing studies:
1: Food effect study (SHH8395g); interim report available
2: *in vivo* DDI study with rosiglitazone (CYP2C8) and oral contraceptive (CYP3A) (SHH4593g); no report available

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

Please send an information request to the Applicant containing the following:

1. Module 5.3.3 "*Reports of Human Pharmacokinetic Studies"* listed only three studies- SHH4433g, SHH4683g and SHH4610g. All clinical pharmacology study reports and raw data sets in electronic format (i.e., SAS transport files) should be included in Module 5.3.3. Please provide links to the studies that are not included in Module 5.3.3.
2. Please provide the analysis and table(s) listing the [I]/Ki ratios for all the *in vitro* studies for CYP isoenzymes.
3. Please provide the relevant data (e.g. calculate [I]/IC_{50} (or Ki) ratio or net flux ratio) to determine whether vismodegib is a substrate or inhibitor of P-gp and BCRP. Refer to the following two links:

http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269215.pdf

http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269213.pdf

4. Please provide the relevant data to determine whether vismodegib is a substrate or inhibitor of OATP1B1 and OATP1B3. Refer to the following three links.

http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269211.pdf

http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269216.pdf

http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269218.pdf

5. Please provide a table listing different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies, if this is the case.
6. Please confirm that the formulation used in the food effect study SHH8395g is the to-be-marketed formulation.
7. Please provide the raw data sets and file definitions in electronic format (i.e., SAS transport files) for each of the *in vitro* studies. If this information has already been submitted, please provide the location in the eCTD.
8. Please provide interim report for DDI study SHH4593g, if it is available.
9. Please provide timelines for submitting the final study reports for food effect study SHH8395g and DDI study SHH4593g.
10. Please provide mile stone timelines for the renal and hepatic impairment trial (GP27839) as this trial will be conducted under post market requirement (PMR).
11. Please provide available dosing information with or without food in the phase 2 trials to assess the possible effect of food on exposure. It would be informative, if investigators or patients reported administration was mostly in a fasted state, or was mostly in a fed state.
12. In section 12.3 of the annotated label, the PK of vismodegib is reported as follows: (b) (4) [redacted]. It is not clear where these PK parameters reported in the label come from. Are they from the NCA analysis for studies SHH4433g and SHH4683g as well as the PopPK analysis? Please provide your clarification.

Please explain why you chose to report the single-dose PK (e.g. single-dose terminal $t_{1/2}$ of 12 days) from the trials in healthy subjects, but not from the trials in BCC patients.

Please explain why you chose to report the multiple-dose PK (e.g. steady-state $t_{1/2}$ of 4 days) from the PopPK analysis, but not from the NCA analyses for the trials in BCC patients.

Please provide the dataset that were used in the NCA analyses to obtain the PK parameters in healthy subjects and in BCC patients.

Please provide this information within ten business days. If this information has already been submitted, please provide the location in the eCTD.

13. For Question 7, FDA requests the individual data for *in vitro* studies, especially for CYP the induction and inhibition studies. If this information has already been submitted, please provide the location in the eCTD.
14. For question 15, FDA requests the analysis datasets that support the NCA analysis. Either XPT or PWO format is acceptable as long as the individual data are listed. Please also provide the dataset grouping by studies and patient type.

###

Potential PMC/PMR:

1. Renal and hepatic impairment trials
2. DDI trials

Jian Wang, Ph.D. 9-17-11

Clinical Pharmacology Reviewer **Date**

Hong Zhao, Ph.D. 9-17-11

Clinical Pharmacology Team Leader **Date**

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

/s/

JIAN WANG
01/06/2012

BAHRU A HABTEMARIAM
01/06/2012

CHRISTINE E GARNETT
01/06/2012

CHRISTIAN GRIMSTEIN
01/06/2012

ROSANE CHARLAB ORBACH
01/06/2012
Had problems with pdf files.

HONG ZHAO
01/06/2012
I concur.

NAM ATIQUR RAHMAN
01/09/2012

ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA#:	203-388
Submission Date:	09/08/2011
Brand Name:	Erivedge
Generic Name:	Vismodegib
Formulation:	Capsules
Strength:	150 mg
Applicant:	Genentech, Inc.
Type of submission:	Original NDA, 505(b)(1), Priority Review
Reviewer:	Zedong Dong, Ph.D.

SUBMISSION:

NDA 203-388 is submitted under FDC 505(b)(1) category for vismodegib capsules (150 mg) for the treatment of patients with advanced basal-cell carcinoma. As a BCS 2 new molecular entity (NME), vismodegib was formulated in capsules throughout clinical studies, however, via different manufacturing processes and in different strengths, (b) (4) for Phase I studies, (b) (4) for Phase II studies, and (b) (4) for Phase II pivotal clinical trial, primary stability and commercialization.

BIOPHARMACEUTICS REVIEW:

The Biopharmaceutics review will be focused on the evaluation of the information/data supporting the proposed dissolution method and acceptance criterion.

The dissolution method development report is provided in the submission. The proposed dissolution method uses (b) (4) (b) (4) The dissolution method development report will be reviewed, and the acceptability of the proposed dissolution method and specification will be determined. The analytical procedures of the dissolution method and method validation report were also included in the submission.

REVIEWER COMMENT

The following comment was sent to the Applicant on 10/11/2011:

- Provide the dissolution profiles and the actual individual test results (n=12, mean, minimun and maximum, RSD) for your pivotal Phase 2 and primary stability lots of drug product.

RECOMMENDATION

NDA 203-388 for Vismodegib Capsules is fileable from the Biopharmaceutics perspective.

_____ _____

Zedong Dong, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Supervisory Lead
ONDQA Biopharmaceutics

CC: NDA 203-388
Mona Patel, Deborah Mesmer

APPENDIX A

Formulation Compositions for Vismodegib Capsules Throughout Clinical Studies

Ingredient	Function	Specification	Phase I Capsules 25 mg	Phase I Capsules 125 mg	Phase I Capsules 270 mg	Phase II Capsules 150 mg	Phase II Pivotal/ Primary Stability/ Commercial/ Scale-up[a] Capsules 150 mg
Drug Product Process:					(b) (4)		(b) (4)
(% w/w of blend)							
Vismodegib	API	In-house monograph			(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose	(b) (4)	USP/NF/Ph. Eur.				NA	NA
Microcrystalline Cellulose		USP/NF/Ph. Eur.	NA	NA	NA		(b) (4)
Lactose Monohydrate		USP/NF/Ph. Eur.	NA	NA	NA		
Sodium Lauryl Sulfate		USP/NF/Ph. Eur.			(b) (4)		
Talc		USP/Ph. Eur.					
Sodium Starch Glycolate		USP/NF/Ph. Eur.					
(b) (4)							(b) (4)
Sodium Starch Glycolate		USP/NF/Ph. Eur.	NA	NA	NA	NA	
(b) (4)							
Magnesium Stearate		USP/NF/Ph. Eur.			(b) (4)	(b) (4)	
Povidone		USP/NF/Ph. Eur.	NA	NA	NA		
(b) (4)		USP/Ph. Eur.	NA	NA	NA		
Subtotal Weight of Blend (mg/capsule)	—	—	(b) (4)		(b) (4)		
Capsule Shell	—						(b) (4)
(b) (4)							

APPENDIX B

Proposed Dissolution Method : Equipment and Conditions

(b) (4)

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

/s/

ZEDONG DONG
10/19/2011

ANGELICA DORANTES
10/19/2011

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202324

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203388**	**Brand Name**	**Erivedge (under review)**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Vismodegib**
Medical Division	**Oncology**	**Drug Class**	**First-in-class small molecule Hedgehog pathway inhibitor**
OCP Reviewer	**Jian Wang, Ph.D.**	**Indication(s)**	**Advanced basal cell carcinoma (BCC)**
OCP Team Leader	**Hong Zhao , Ph.D.**	**Dosage Form**	**150 mg capsules**
Pharmacometrics Reviewer	**TBA , Ph.D.**	**Dosing Regimen**	**150 mg QD daily**
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Pharmacogenomics Reviewer	**Rosane Charlab-Orbach, Ph.D.**		
Pharmacometrics Team Leader	**Issam Zineh, Pharm.D.**		
Date of Submission	**9/22/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Genentech**
Medical Division Due Date	**01/06/2012**	**Priority Classification**	**Priority**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		**Plasma: total vismodegib, unbound vismodelgib, [^{14}C] vismodegib and total [^{14}C], AAG, Moxifloxacin**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**SHH4683g (Part B)**
Isozyme characterization:		**2**		**12 recombinant human CYP isoforms**
Blood/plasma ratio:	**X**	**1**		**blood-plasma partitioning**
Plasma protein binding:	**X**	**2**		**Cross-species, AAG and HAS**
Pharmacokinetics -				
Healthy Volunteers-				
single dose:	**X**	**3**		**SHH4433g, SHH4683g(ADME, Part A), SHH4871g(QTc)**
multiple dose:		**2**		**SHH4683g (Part C), SHH4871g (QTc)**
Patients-				

single dose:	X	2		SHH3925g, SHH4610g(dose schedule)
multiple dose:	X	4		SHH3925g, SHH4610g, SHH4318g, SHH4476g
Dose proportionality -				
fasting / non-fasting single dose:	X	1		SHH3925g
fasting / non-fasting multiple dose:	X	1		SHH3925g
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		In combination with bevacizumab or FOLFOX in CRC patients
In-vivo effects of primary drug:	X	1		the same as above
In-vitro:	X	8		CYP inhibition and induction, PXR binding, BCRPinhibition, MDR1 and BCRP substrate
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:	X	2		Cancer patients; healthy volunteers
Phase 2:	X	1		104 BCC patients
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		SHH3925g, SHH4476g
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	4		SHH3925g (cancer patients), SHH4610g(cancer patients), SHH4433g(healthy subjects), SHH4683g(healthy subjects),
Data sparse:	X	1		SHH4476g (cancer patients)
II. Biopharmaceutics				
Absolute bioavailability	X	1		SHH4683g
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		SHH3925g
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		SHH8395g (ongoing)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		47		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

Note: Ongoing studies:
1: Food effect study (SHH8395g); interim report available
2: *in vivo* DDI study with rosiglitazone (CYP2C8) and oral contraceptive (CYP3A) (SHH4593g); no report available

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

Please send an information request to the Applicant containing the following:

1. Module 5.3.3 "*Reports of Human Pharmacokinetic Studies"* listed only three studies- SHH4433g, SHH4683g and SHH4610g. All clinical pharmacology study reports and raw data sets in electronic format (i.e., SAS transport files) should be included in Module 5.3.3. Please provide links to the studies that are not included in Module 5.3.3.
2. Please provide the analysis and table(s) listing the [I]/Ki ratios for all the *in vitro* studies for CYP isoenzymes.
3. Please provide the relevant data (e.g. calculate [I]/IC_{50} (or Ki) ratio or net flux ratio) to determine whether vismodegib is a substrate or inhibitor of P-gp and BCRP. Refer to the following two links:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269215.pdf

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269213.pdf

4. Please provide the relevant data to determine whether vismodegib is a substrate or inhibitor of OATP1B1 and OATP1B3. Refer to the following three links.

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269211.pdf

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269216.pdf

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269218.pdf

5. Please provide a table listing different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies, if this is the case.
6. Please confirm that the formulation used in the food effect study SHH8395g is the to-be-marketed formulation.
7. Please provide the raw data sets and file definitions in electronic format (i.e., SAS transport files) for each of the *in vitro* studies. If this information has already been submitted, please provide the location in the eCTD.
8. Please provide interim report for DDI study SHH4593g, if it is available.
9. Please provide timelines for submitting the final study reports for food effect study SHH8395g and DDI study SHH4593g.
10. Please provide mile stone timelines for the renal and hepatic impairment trial (GP27839) as this trial will be conducted under post market requirement (PMR).
11. Please provide available dosing information with or without food in the phase 2 trials to assess the possible effect of food on exposure. It would be informative, if investigators or patients reported administration was mostly in a fasted state, or was mostly in a fed state.
12. In section 12.3 of the annotated label, the PK of vismodegib is reported as follows: (b) (4) [redacted] It is not clear where these PK parameters reported in the label come from. Are they from the NCA analysis for studies SHH4433g and SHH4683g as well as the PopPK analysis? Please provide your clarification.

    Please explain why you chose to report the single-dose PK (e.g. single-dose terminal $t_{1/2}$ of 12 days) from the trials in healthy subjects, but not from the trials in BCC patients.

    Please explain why you chose to report the multiple-dose PK (e.g. steady-state $t_{1/2}$ of 4 days) from the PopPK analysis, but not from the NCA analyses for the trials in BCC patients.

    Please provide the dataset that were used in the NCA analyses to obtain the PK parameters in healthy subjects and in BCC patients.

Please provide this information within ten business days. If this information has already been submitted, please provide the location in the eCTD.

###

Potential PMC/PMR:

1. Renal and hepatic impairment trials
2. DDI trials
3. A food effect trial

Jian Wang, Ph.D.	9-17-11
Clinical Pharmacology Reviewer	**Date**
Hong Zhao, Ph.D.	9-17-11
Clinical Pharmacology Team Leader	**Date**

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

/s/

JIAN WANG
10/05/2011

HONG ZHAO
10/05/2011
I concur.