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APPLICATION NUMBER:

205266Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

Clinical Pharmacology Review

NDA	205-266 \\CDSESUB1\evsprod\NDA205266\205266.enx
Type/Category	New Molecular Entity
Brand Name	Odomzo
Generic name	Sonidegib (LDE 225)
Indication	Basal cell carcinoma
Dosage Form	Capsule
Route of Administration	Oral
Dosing Regimen and Strength	200 mg once daily
Applicant	Novartis
OCP Division	DCP V
OND Division	DOP 2
Submission Date	26 September 2014
PDUFA	24 July 2015
Primary Reviewers	Stacy S. Shord, Pharm.D. Ping Zhao, Ph.D.
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1 EXECUTIVE SUMMARY

Sonidegib is a Hedgehog pathway inhibitor. The recommended indication will be for the treatment of locally advanced basal cell carcinoma (BCC) at a dose of 200 mg once daily in the fasted state. This review addressed five key questions. Overall, this NDA is acceptable from a clinical pharmacology perspective.

1. *Is the proposed dose of 200 mg once daily reasonable?* The proposed dose of 200 mg over a dose of 800 mg is supported by the lack of an exposure–response (E-R) relationship observed for best overall response and the mean probability of grade 3 or 4 creatine kinase (CK) elevation that increased with higher sonidegib concentrations in the registration trial.
2. *What is an appropriate dose modification for patients with grade 3 or 4 CK elevation?* It is recommended that sonidegib be permanently discontinued. The clinical data suggest that patients experience a durable response despite discontinuing therapy and that patients who experience severe musculoskeletal adverse reactions discontinue sonidegib following recurrence of these adverse reactions despite a dose reduction.
3. *What is an appropriate dose regimen for patients taking acid-reducing agents (ARA)?* The population pharmacokinetic (PK) analysis indicates that sonidegib steady-state exposure (as measured by $AUC_{0\text{-}24h}$) is 34% lower in cancer patients concurrently taking an ARA with a 200 mg sonidegib dose compared to patients not concurrently taking an ARA. A dedicated study in healthy subjects is ongoing to determine an appropriate dose regimen for patients concurrently taking an ARA.
4. *What is an appropriate dose for patients with hepatic impairment?* No dose adjustment is needed for patients with mild hepatic impairment (as defined by National Cancer Institute). A dedicated study in subjects with hepatic impairment is ongoing to determine if there is a need for dose adjustment for patients with moderate or severe hepatic impairment.
5. *What is an appropriate dose for patients taking a CYP3A modulator?* It is recommended to avoid coadministration of strong and moderate CYP3A modulators. If no alternative therapy is available, coadministration of a moderate inhibitor may be considered for up to 14 days with careful adverse event monitoring. An alternative sonidegib dose or schedule to provide similar sonidegib exposure to the recommended 200 mg dose is not feasible due to only one dose strength available.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective.

Decision	Acceptable to OCP?	Comment
Overall	Yes	
Evidence of effectiveness†	Yes	
Proposed dose for general population	Yes	
Proposed dose adjustment for others	Yes	A postmarketing requirement will be recommended for a study in subjects with hepatic impairment and for a study in patients taking an ARA.
Pivotal bioequivalence	Not Applicable	
Labeling	Yes	

†This decision is from a clinical pharmacology perspective only. The determination of the overall safety and effectiveness is made by the clinical review team.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Post Marketing Requirements

Drug Development Question	Rationale	PMR
Should the dose of sonidegib be reduced in patients with moderate or severe hepatic impairment?	The mass balance study indicates that ~70% of the absorbed dose is eliminated in the feces, indicating that hepatic elimination is the major elimination pathway. Higher sonidegib steady-state exposure is associated with greater probability of developing severe musculoskeletal toxicity.	Complete the ongoing pharmacokinetic (PK) trial to determine an appropriate dose of sonidegib in patients with moderate and severe hepatic impairment. Trial Completion: September 2015 Final Report Submission: July 2016
What is an appropriate dose for patients taking an acid-reducing agents (ARA)?	A population PK analysis suggests that ARAs reduce mean sonidegib steady-state exposure by 34%.	Submit the final study report for the completed PK trial to determine how to dose sonidegib in patients taking an ARA. Final Report Submission: July 2015

1.2.2 Post Marketing Commitments

None.

1.2.3 Additional Comment

1. Complete the ongoing PK trial (Study A2112, started April 2013) to determine the appropriate dose of sonidegib in patients taking sensitive or narrow therapeutic substrates metabolized by CYP2B6 and CYP2C9 and submit the final study report in September 2019 as planned.

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DCPV: DDD - B Booth

A Required OCP Office Level Briefing was held on 5 May 2015.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Sonidegib is a Hedgehog pathway inhibitor that is a Smoothened antagonist. The labeled indication will be for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that is not amenable to curative surgery or radiation therapy at a dose of 200 mg once daily in the fasted state (e.g., at least one hour before or 2 hours after a meal).

A single randomized, double-blind trial was conducted to evaluate the efficacy and safety of two sonidegib doses in patients with locally advanced or metastatic BCC. No exposure-response (E-R) relationship was observed for best overall response, but the mean probability of grade 3 or 4 creatine kinase (CK) elevation increased with higher sonidegib minimal concentrations (C_{min}). The proposed starting dose of 200 mg once daily is supported by available safety and efficacy data and the E-R analyses. Sonidegib should be discontinued in patients who experience a grade 3 or 4 musculoskeletal adverse event.

Sonidegib exposure increased in a less than dose proportional manner with doses up to 3000 mg in fasted conditions consistent with dose-dependent absorption (b) (4) The median T_{max} was observed between 2 hours and 4 hours under fasted conditions. The administration of a single 800 mg dose with a high-fat meal (1000 calories with 50% from fat) resulted in a 7.4-fold increase in area under the curve (AUC_{inf}) in healthy subjects. The population pharmacokinetic (PK) analysis suggests that geometric mean sonidegib steady-state AUC is 34% lower in cancer patients concomitantly taking an ARA with a sonidegib dose of 200 mg compared to patients not concomitantly taking an ARA. A dedicated study in healthy subjects is ongoing to determine an appropriate dose regimen for patients concomitantly taking an ARA.

Sonidegib is metabolized by CYP3A4 to several inactive metabolites. Ketoconazole increased sonidegib AUC_{0-10d} by 2.2-fold and rifampicin decreased sonidegib AUC_{0-10d} by 72% following a single 800 mg dose in healthy subjects. Simulation suggests that moderate inhibitors given for 14 days will increase steady-state exposure of sonidegib by1.8-fold and moderate inducers given for 14 days will decrease steady-state exposure of sonidegib by 56%. It is recommended that patients avoid taking strong and moderate CYP3A modulators with sonidegib. Dose interruption or an alternative sonidegib dose or schedule to provide similar sonidegib exposure to the 200 mg dose is not feasible, because sonidegib demonstrates non-linear PK with a long elimination half-life.

Sonidegib inhibited CYP2B6 and CYP2C9 in vitro. A study to assess the effects of sonidegib on the PK of a CYP2B6 and a CYP2C9 probe substrate is ongoing. Sonidegib does not induce or inhibit other major cytochrome P450 enzymes. Sonidegib inhibited ABCG2 in vitro, but it is not a substrate or inhibitor of several other transporters.

Approximately 70% and 30% of the absorbed dose was excreted in feces and urine, respectively following a single 800 mg oral dose of [^{14}C]-labeled sonidegib in healthy men. No dose adjustment is recommended for patients with mild hepatic impairment (as defined by National Cancer Institute) or mild or moderate renal impairment (as defined by Cockcroft-Gault) based on population PK analysis.

2 QUESTION BASED REVIEW

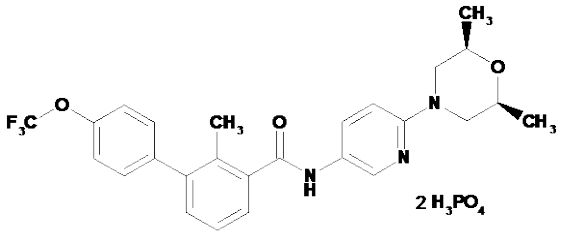
2.1 GENERAL ATTRIBUTES

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 related to clinical pharmacology and biopharmaceutics review?

Sonidegib is a Hedgehog pathway inhibitor with a molecular weight of 682 Daltons (diphosphate salt). The chemical structure is shown in **Figure 1**.

The drug product is available as 200 mg hard gelatin capsules.

Figure 1. Chemical structure of sonidegib



(b) (4)

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

Mechanism of Action

Sonidegib is a Smoothened (Smo) antagonist (IC_{50} of 11 nM). Smo is a G protein-coupled receptor-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Hh pathway activation of Smo leads to activation and nuclear localization of Glioma-Associated Oncogene (Gli) transcription factors. Sonidegib binds Smo to inhibit Gli mediated target gene activation thereby inhibiting Hh signaling.

Proposed Indications

The proposed indications are for the treatment of adult patients with locally advanced BCC who are not amenable to curative surgery or radiation therapy [redacted].

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

The proposed dose is 200 mg once daily orally on an empty stomach (e.g., at least one hour before or 2 hours after a meal).

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?

Clinical Pharmacology Studies

The clinical pharmacology program is comprised of 6 clinical trials as described in **Table 2**. This program is supported by additional studies conducted using human biomaterials and in animals, four reports of analyses of data from more than one study (population PK, E-R for efficacy, E-R for safety, ethnic sensitivity) and four simulation reports (drug interactions and hepatic impairment).

Table 2. Description of clinical pharmacology studies

Study No.	Assessment	Dosage and Administration	N
Studies in healthy subjects			
A2114	Food effect and relative bioavailability – [redacted] capsule, [redacted]	200 mg, 600 mg, 800 mg, 1200 mg, or 1400 mg single dose	146
A1102	Dose escalation - Japan	200 mg, 400 mg, 800 mg single dose	36
A2110	ADME	800 mg single dose	6
A2108	Drug interaction – rifampin, ketoconazole	800 mg single dose	50
Studies in patients with cancer			
X2101	Dose escalation – Europe, USA	100 mg, 200 mg, 400 mg, 800 mg, 1000 mg, 1500 mg, 3000 mg daily or 250 mg, 400 mg, 750 mg twice daily	103
X1101	Dose escalation – Japan	400 mg, 600 mg daily	21

Clinical Studies

The proposed indication is based on the results of a randomized, double blind, placebo controlled trial that evaluated the efficacy and safety of sonidegib in 230 patients with locally advanced (84%) or metastatic (16%) BCC (Study A2201). The patients were randomized 2:1 to receive an 800 mg dose or a 200 mg dose once daily on an empty stomach. Treatment arms were well balanced with respect to demographic characteristics and history of prior therapy. The Applicant states that an 800 mg dose was identified as the maximum tolerated dose (MTD) and a 200 mg dose was identified as the lowest tolerable dose with observed efficacy in the dose escalation trial (Study X2101). The overall response rate (ORR) per central review was 58% (95% CI: 45%, 70%) for the 200 mg dose and 44% (95% CI: 35%, 53%) for the 800 mg dose after a median follow-up of 20 months for patients with locally advanced BCC (FAS population, 12-month analysis). The median duration of response was not evaluable for the 200 mg dose and was 15.7 months for the 800 mg dose. [redacted]

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

For the registration trial Study A2201, the primary endpoint ORR (i.e., defined as the proportion of patients who achieved a complete response (CR) or partial response (PR)) was a composite endpoint based on modified Response Evaluation Criteria in Solid Tumors (RECIST) (locally advanced) or RECIST 1.1 (metastatic), clinical photography and histology. The primary analysis was based on evaluation by central review. ORR is considered a surrogate endpoint that can support accelerated or regular approval.

For the clinical pharmacology studies, PK parameters were estimated using non-compartmental (NCA) or population analysis. The geometric mean ratio (GMR) and 90% confidence intervals (CI) were determined for comparative studies.

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. Sonidegib was appropriately identified and measured in human samples to assess its PK parameters and E-R relationships (*see Section 2.6*).

2.2.4 Exposure-response

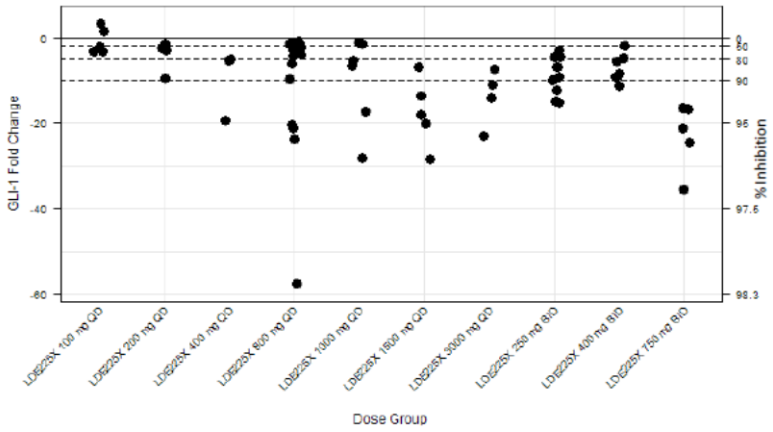
2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

No E-R relationship was identified for the best overall response in the registration trial. The proposed dose of 200 mg once daily was selected based on the observed exposure-safety relationship (*see Section 2.2.4.2*). The Applicant supported a dose selection of 200 mg and 800 mg for the registration trial based on the observed activity and adverse events in the dose escalation trial (Study X2101). Overall, the dose appears reasonable based on the available safety and efficacy data.

Dose Selection

A dose finding trial was conducted in patients with advanced solid tumors receiving sonidegib as monotherapy once or twice daily in a fasted state (Study X2101). The Applicant supported the dose selection for the registration trial (Study A2201) based on safety and activity observed in this trial. The change in Gli-1 mRNA expression was measured in biopsies of normal skin at screening and at the end of cycle 1, cycle 2 and therapy. Increased sonidegib dose and minimal concentrations were generally associated with increased Gli-1 inhibition (**Figure 2**); the mean Gli-1 inhibition was 69% at a dose of 200 mg and 74% at a dose of 800 mg. Paired tumor biopsies similarly showed a dose dependent decrease in Gli-1 expression; the changes were more pronounced in tumor tissue compared to skin tissue. The Applicant stated that the 200 mg dose was the lowest dose associated with activity. Partial response (n=1) and stable disease (n=2) were observed in patients treated at this dose; all patients responding to sonidegib in the dose escalation study were diagnosed with BCC or medulloblastoma.

Figure 2. Fold change and percent inhibition in Gli-1 mRNA expression increases with dose in biopsies of normal skin

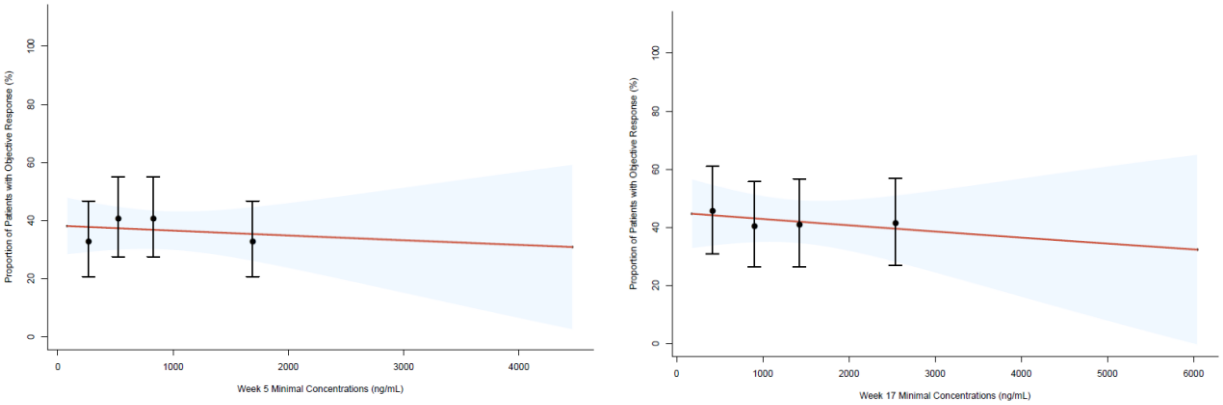


Source: Clinical Study Report, Study X2101, Figure 10-4

Basal Cell Carcinoma

A single randomized double-blind trial was conducted in patients with BCC (Study A2201) given a dose of 200 mg or 800 mg once daily. The primary efficacy endpoint was ORR as described in *Section 2.2.2*. On treatment imaging and color photography schedule included assessments on week 5, week 9, week 17 and then every 8 weeks for the first 12 months. Sonidegib minimal concentrations were measured on week 1, 3, 5, 9 and then every 4 weeks for the first 6 months. Median time to tumor response in the 200 mg arm was 3.9 months (95% CI: 3.6, 4.2) and in the 800 mg arm was 3.7 months (95% CI: 2.6, 3.8) for patients with locally advanced BCC. No E-R relationship was observed between the best overall response and C_{min} at week 5 or at week 17 (steady-state) (**Figure 3**). No covariates were identified that affected the exposure-efficacy relationship, but patients with poorer performance status (ECOG 1 or 2) had a lower probability of an overall response compared to patients with no altered performance status (ECOG 0) at baseline (data not shown, *see Appendix 4.1*). The Applicant similarly demonstrated no E-R relationship between best overall response and simulated average AUC (calculated using the dose intensity divided by the individual post-hoc clearance from the population PK model; Response to FDA information request #11).

Figure 3. No exposure-response relationship observed for best overall response and sonidegib minimal concentrations observed on Week 5 (left) or Week 17 (steady-state, right)



Data source: adpkeff.xpt

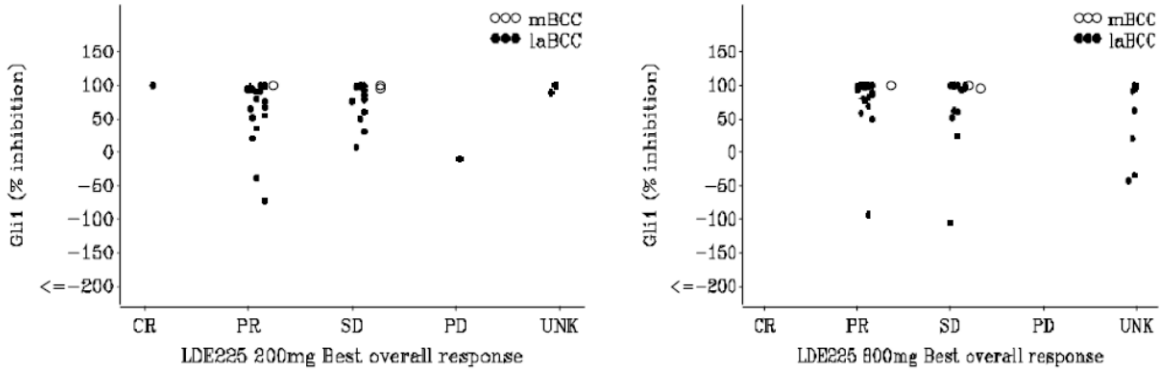
Gli-1 mRNA was measured in archival tissue samples at baseline and from fresh tumor tissue on week 9, week 17 and end of therapy. The Applicant stated that the reduction in Gli-1 mRNA expression (**Table 3**) corresponds with a 91% disease control rate per central review for the 200 mg dose and with an 80% disease control rate per central review for the 800 mg dose; however, the strip plot (**Figure 4**) included in the clinical study report suggests that no reduction in Gli-1 mRNA expression was observed in few patients with a partial response.

Table 3. Percent change in baseline Gli-1 expression in tumor tissue

	200 mg (n=79)	800 mg (n=150)
Locally Advanced, mean± SD	73.2 ± 39.1 (n=45)	73.3 ± 48.4 (n=48)
Metastatic, mean ± SD	98.4 ± 1.7 (n=3)	98.4 ± 2.2 (n=3)

Source: From Table 11-29 in Clinical Study Report for Study A2201

Figure 4. Change from baseline in Gli-1versus best overall response at week 17



Source: Clinical Study Report for Study A2201, Figure 11-5

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

The E-R analyses demonstrate that the mean probability of grade 3 or 4 CK elevation increased with higher observed sonidegib C_{min} as measured on week 5 (Cycle 2, Day 1). Grade 3 CK

elevation is defined as > 5x ULN to 10x ULN and grade 4 elevation in CK is defined as > 10x ULN (Common Terminology Criteria for Adverse Events, v4.0). The selection of the 200 mg once daily for the product labeling was based on a more favorable safety and tolerability profile compared to an 800 mg dose. Overall, the dose appears reasonable based on the available safety and efficacy data.

Dose Selection

The Applicant supported their dose selection for the registration trial (Study A2201) based on safety and activity observed in a dose escalation trial (Study X2101). The primary dose limiting toxicity observed in the dose escalation trial was grade 3 or 4 CK elevation and it appears that the probability of grade 3 or 4 CK elevation was related to dose. Dose limiting toxicity was only observed in one patient at 800 mg once daily and one patient at 1000 mg once daily, so the dose escalation continued to a dose of 3000 mg once daily. Additional patients who experienced grade 3 or 4 CK elevation were administered a dose of 800 mg (n=1), 1000 mg (n=1), 1500 mg (n=3) and 3000 mg (n=1). These events occurred after cycle one (cycle = 28 days). Based on these observations, the Applicant identified 800 mg once daily as the maximum tolerated dose (MTD).

Other related adverse events include muscle spasms (32%), myalgia (16%), asthenia (13%), and increased blood myoglobin (3%). Rhabdomyolysis was reported in 3 patients receiving 800 mg once daily or 3000 mg once daily. The Applicant stated that additional analyses suggest that the observed CK elevations reflect skeletal muscle injury, not cardiac muscle injury.

Overall, the mean exposure to sonidegib was 102 days ranging from 2 days to 970 days. The longest mean exposure was observed in patients given 100 mg once daily (294 days) and 200 mg once daily (208 days).

Pooled Analysis

Data from 336 patients enrolled into Studies B2209 (placebo controlled, 400 mg once daily x 12 weeks, nevoid BCC syndrome), X1101, X2101 and A2201 were pooled to conduct an exposure-safety analysis to examine the probability of grade 3 or 4 CK elevation as a function of sonidegib exposure. The analysis set included all patients with at least one post-dose CK assessment and at least one PK parameter (**Table 4**). CK elevation was determined only from laboratory tests, not from reported adverse events. Occurrence of grade 3 or 4 CK elevation (defined as worse grade within 30 days of the last dose) was utilized as a categorical variable (yes, no) via logistic regression to explore the association between PK and grade 3 or 4 CK elevation. The assumptions of this model were that the PK exposure at a given time point is predictive of grade 3 or 4 CK elevation regardless of when the CK elevation occurred with respect to when the PK was assessed and that no grade 3 or 4 CK elevation occurred prior to Cycle 1 Day 15. This pooled analysis suggests that sonidegib exposure was higher in patients with grade 3 or 4 CK elevation.

Table 4. Summary of pharmacokinetic parameters by absence or presence of grade 3 or 4 creatine kinase elevation

Grade 3 or 4 CK elevation	Statistics	C1D15 AUC (ng*hr/mL)	C1D15 Cmax (ng/mL)	C2D1 Cmin (ng/mL)
Yes (N=52)	n	17	25	45
	Mean (SD)	27344.3 (12769.71)	1717.8 (946.17)	1471.8 (850.52)
	CV% mean	46.7	55.1	57.8
	Geo-mean	24335.6	1496.2	1266.2
	CV% geo-mean	56.6	58.8	60.9
	Median	25253.9	1270.0	1390.0
	[Min; Max]	[6378.8;52669.0]	[404.0;4290.0]	[412.0;4460.0]
No (N=284)	n	55	77	262
	Mean (SD)	10747.0 (6337.80)	731.8 (458.49)	782.4 (657.49)
	CV% mean	59.0	62.6	84.0
	Geo-mean	8885.4	588.9	589.9
	CV% geo-mean	73.7	80.3	89.5
	Median	9634.9	613.0	602.0
	[Min; Max]	[1417.6;28602.5]	[82.2;1890.0]	[14.6;4450.0]

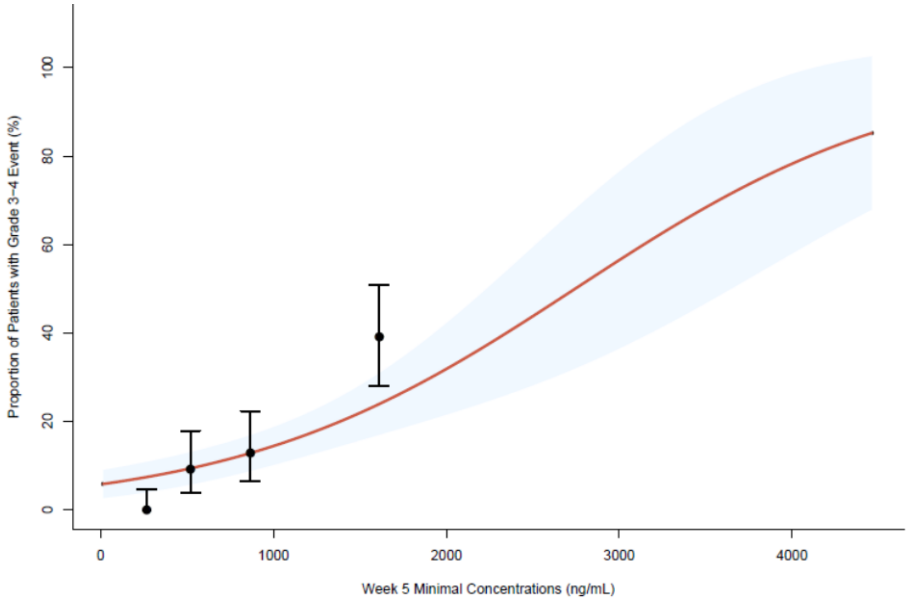
Source: Exposure-safety report, Table 3-2

Basal Cell Carcinoma

The logistic regression model showed a significant relationship between the sonidegib C_{min} measured on week 5 (n=310, Study A2201) and grade 3 or 4 CK elevation, suggesting increasing sonidegib exposure increases the probability of developing grade 3 or 4 CK elevation. **Figure 5** illustrates the probability of grade 3 or 4 CK elevation as a function of sonidegib C_{min} on week 5. Given the similar efficacy of sonidegib observed at 200 mg and 800 mg doses and the observed exposure-safety relationship, the proposed dose of 200 mg is reasonable.

No covariates (such as baseline weight, race, sex, and age) were found to influence the observed relationship between sonidegib exposure and the probability of grade 3 or 4 CK elevation; however, men appear to have a 2.4-fold higher incidence of grade 3 or 4 CK elevation compared to women at baseline (data not shown, *see Appendix 4.1*).

Figure 5. Probability of grade 3-4 creatinine kinase elevation increases with higher sonidegib minimal concentrations on week 5



Source: adpkck.xpt

Dose Modifications

The 200 mg and 800 mg dose levels provided a similar ORR (*see Section 2.1.1.*), but the 800 mg dose was associated with more grade 3 or 4 CK elevation and more dose modifications (**Table 5**). The most common reason for dose interruptions was adverse events: 28% for 200 mg dose and 44% for 800 mg dose (6-month analysis, Summary of Clinical Safety). The protocol included dose reduction from a 200 mg dose to placebo (such that the drug was withdrawn). The other reasons for dose interruptions were dosing error, technical problems and dispensing error.

Table 5. Dose interruptions and reductions

	200 mg (n=79)	800 mg (n=150)
Reductions, n (%)	11 (14)	45 (30)
Interruptions, n (%)	49 (62)	91 (61)

Source: Summary of Clinical Safety – 6-month safety analysis

Twenty-nine patients experienced grade 3 or 4 CK elevation. The median time to onset and resolution (grade $\leq$ 1) was longer for patients given an 800 mg dose relative to a 200 mg dose (**Table 6**). These data support the findings from the E-R analysis that sonidegib causes dose dependent increase in the probability of grade 3 or 4 CK elevation; however, the increases in CK typically resolved within 2 weeks following onset. It is unlikely that sonidegib exposure substantially declined within the two weeks given the terminal elimination half-life of 28 days.

Table 6. Median time to onset and resolution of grade 3 or 4 creatine kinase elevation

	200 mg (n=79)	800 mg (n=150)
Patients, n	5	24
Time to Onset (weeks), median (minimum, maximum)	15.1 (8, 48)	6.1 (3, 17)
Resolved, %	80%	75%
Time of Resolution (days), median (95% confidence interval)	8 (4, NE)	15 (13, 22)

Source: Summary of Clinical Safety – 6-months safety analysis

Dose Recommendations following Grade 3 or 4 Musculoskeletal Adverse Reaction

It is recommended that sonidegib be permanently discontinued following the onset of grade 3 or 4 musculoskeletal adverse reaction. The proposed labeling recommends (b) (4)

[redacted]

Objective Responses Observed with a 200 mg Dose: **Table 7** provides a summary of the laboratory and clinical data for patients randomized to receive 200 mg once daily who experienced musculoskeletal adverse reactions (Response to FDA information request #7). All patients with an action taken listed as dose adjusted or dose interrupted subsequently received placebo in accordance with the clinical protocol (SDN 21). Three patients had an objective response with a duration of response of at least 100 days from the last dose despite discontinuing sonidegib (Response to FDA information request #18).

Tolerability Observed with an 800 mg Dose: Forty-nine patients given 800 mg once daily experienced a musculoskeletal adverse reaction that required a dose interruption (n=20), dose reduction (n=36) and/or discontinuation (n=17) (Response to FDA information request #18). Grade 3 or 4 musculoskeletal adverse reactions occurred in 24 of these patients. Sonidegib was ultimately discontinued in 10 of these 24 (42%) patients. For patients who continued treatment after a dose interruption for a musculoskeletal adverse event (n=18), these adverse events recurred in at least 12 (67%) patients.

Table 7. Summary of musculoskeletal adverse reactions for patients given a 200 mg dose

Patient ID	Preferred term (CTC grade)	Creatine phosphokinase level (U/L)[a]	Sonidegib PK level (ng/mL)[b]	Time of onset (days)	Action taken	Time to resolution (days)	Confirmed BOR	Time to BOR (days)	DOR (days)
1150-007	Blood creatine phosphokinase increased (G3)	1019	1530	170	Drug interrupted	6	PR	121	162
1197-008	Muscle spasms (G3)	272	553	141	Drug withdrawn	Ongoing	UNK	-	-
1237-003	Muscular weakness (G1)	273	827	224	Dose adjusted	Ongoing	CR[c]	57	365[d]
1238-001	Muscle spasms (G3)	109	1350	140	Drug withdrawn	104	SD	-	-
1350-003	Blood creatine phosphokinase increased (G2)	706	570	72	Drug interrupted	9	PR	57	449[e]
1512-002	Blood creatine phosphokinase increased (G4)	1977, 2145[f]	1550	107	Drug interrupted	2	SD	-	-
	Blood creatine phosphokinase increased (G2)	953	1550	109	Drug withdrawn	25			
	Myalgia (G2)	645	670	120	Drug interrupted	3			
1513-005	Muscle spasms (G2)	110	1690	108	Drug withdrawn	34	SD	-	-
1515-004	Blood creatine phosphokinase increased (G4)[g]	2107	1610	85	Drug interrupted	Ongoing	SD	-	-
1532-001	Blood creatine phosphokinase increased (G3)	1698, 2162[f]	875	335	Drug interrupted	4	SD	-	-
	Rhabdomyolysis (G3)	1698, 2162[f]	875	335	Drug interrupted	4			
1536-001	Blood creatinine increased (G2)	18	522	141	Drug interrupted	8	PD	-	-

BOR = Best overall response, DOR = Duration of response
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UNK = unknown
[a] Creatine phosphokinase levels at the closest available time point to the AE start date.
[b] Sonidegib PK levels (trough) at the closest available time point on the same day or prior to the event are provided.
[c] BOR changed to PR in 12-month analysis.
[d] DOR increased to 526 days in 12-month analysis.
[e] DOR increased to 533 days in 12-month analysis.
[f] Two assessments on the same day.
[g] On the same day of CK increase, the patient also experienced a grade 4 CKMB increase, which caused the study drug to be withdrawn. Of note, no ECG abnormalities were reported at the same time point.

Source: Response to FDA Information Request #7, Received 18-Dec-2014 and #18, Received 03-Mar-2015

2.2.4.3 *Does this drug prolong the QT or QTc interval?*

No large mean change (i.e., > 20 ms) in the QTc interval was detected when sonidegib was administered at a dose of 200 mg; however, a clear concentration-ΔQTcF relationship was observed using ECG data collected as part of Study A2201. No cases of ventricular arrhythmia (Torsade's de pointes) and no deaths associated with QT prolongation were reported during sonidegib clinical development. A thorough QT study was not conducted as the exposure to sonidegib following a single dose in healthy subjects would not reflect sonidegib exposure in cancer patients. Sonidegib exposure is higher in cancer patients compared to healthy subjects (i.e., clearance is 3-fold lower in cancer patients compared to healthy subjects) and sonidegib exposure accumulates 19-fold after daily dosing.

Pooled QT/QTc Analysis

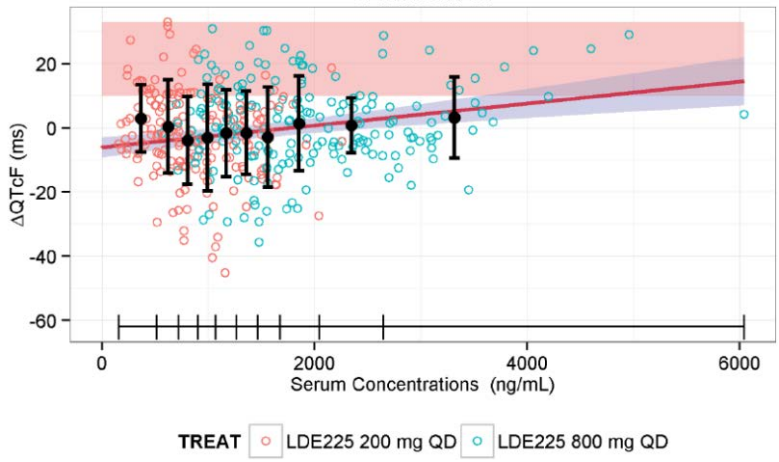
Using pooled data from Studies A2201 (n=229), B2209 (n=8), X1101 (n=21), and X2101 (n=103) in which time matched PK and ECG data were collected, sonidegib is unlikely to prolong the QT/QTc interval (report no. lde225hvscp). The mean (standard deviation) ΔQTcF was -4.4 msec (9.4). A linear mixed effect model analysis showed that the upper one-sided 95% confidence interval of the estimated ΔQTcF at steady-state concentration was less than 5 msec for a dose of 200 mg or 800 mg. The final model included baseline QTcF, sex and regimen as covariates and no

relationship was observed between ΔQTcF and sonidegib treatment.

Study A2201

The Applicant conducted additional analyses using time matched ECG and PK data collected at steady-state (Week 17) in 62 patients enrolled into Study A2201. The findings from this analysis were similar to the pooled analysis in that the upper one-sided 95% confidence interval for the estimated ΔQTcF at steady-state concentration (C_{ss}) was less than 10 msec at either dose (200 mg, 4.1 ms and 800 mg, 7.2 ms). The QT-IRT review states that a significant positive relationship between sonidegib concentration and QTc may exist and clear QTc changes were observed in patients with high sonidegib concentration (e.g. > 3500 ng/mL) (**Figure 6**).The plasma concentrations measured in Study A2201suggest that these concentrations will not be observed with a 200 mg dose, but could be observed with an 800 mg dose. Therefore, any extrinsic or intrinsic factors that could increase sonidegib exposure more than 2.3-fold could potentially prolong the QTc interval.

Figure 6. Concentration-ΔQTcF relationship for sonidegib in cancer patients



Source: QT-IRT Review, Figure 1

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

Yes, the dose and dosing regimen selected by the Applicant is based on two dose levels studied in the registration trial and supported by the known exposure-safety and exposure-efficacy relationships. There is no unresolved dosing or administration issues.

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?*

Sonidegib demonstrates non-linear PK with dose-dependent bioavailability and substantial accumulation following repeated doses. Nonlinear absorption (b) (4) that results in less than dose proportional increase in sonidegib exposure with doses greater than 400 mg.

Dose Escalation Study

A dose escalation study (X2101) was completed in 103 patients with solid tumors who received sonidegib as a single dose followed by repeated once daily dosing starting seven days after the

single dose. The PK could not be adequately characterized in this study as the sampling period was relatively short following a single dose (up to 168 hours) compared to the terminal elimination half-life (~28 days) and PK sampling was not performed at steady-state (**Table 8**).

Table 8. Summary of mean (standard deviation) pharmacokinetic parameters of sonidegib following a single dose and repeated doses

Single Dose	$AUC_{0\text{-}168h}$ (ng*h/mL)	C_{max} (ng/mL)
100 mg (n=6)	1883 (1150)	86 (52)
200 mg (n=6)	3673 (2133)	160 (115)
400 mg (n=5)	7448 (8534)	267 (239)
800 mg (n=25,24)	7867(6950)	430 (381)
1000 mg N=11)	7396 (6343)	322 (288)
1500 mg (n=9)	12633 (7113)	376 (199)
3000 mg (n=10)	11757 (11209)	429 (237)
Repeated Dose – Cycle 1 Day 15	$AUC_{0\text{-}24h}$ (ng*h/mL)	C_{max} (ng/mL)
100 mg (n=3)	2691 (1337)	155 (63)
200 mg (n=3,5)	5916 (3886)	269 (163)
400 mg (n=4)	10178(5880)	558 (286)
800 mg (n=16,20)	12781 (6351)	840 (457)
1000 mg (n=6,8)	15168 (18471)	1232 (1395)
1500 mg (n=3,8)	27420 (14291)	1323 (657)
3000 mg (n=4,6)	24580 (8768)	1673 (1045)

Source: Clinical Study Report, LDE225X2101, Table 10-9

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 population apparent oral clearance (CL/F) is about 3-fold higher in healthy subjects compared to cancer patients, suggesting that the exposure will be higher in cancer patients compared to healthy subjects taking the same dose. The geometric mean (% coefficient of variation) CL/F was 10.0 L/h (74%) in cancer patients compared to 35.2 L/h in healthy subjects based on the original full population PK model. No cross study comparison is feasible with the available PK data. The reason for the exposure differences is unknown.

2.2.5.3 *What are the characteristics of drug absorption?*

The absolute bioavailability of sonidegib was not evaluated in humans. The human mass balance study suggests that < 10% of the dose is absorbed (Study A2201). The capsule given in the mass balance study (b) (4)) differs from the to-be-marketed capsule (b) (4)), but the mean exposure as measured by the AUC_{inf} was similar in this study relative to another study and both studies were conducted in healthy subjects (Study A2201: 9090±2530 ng*h/mL vs. Study A2108: 7970±3670 ng*h/mL). Therefore, the oral bioavailability of the to-be-marketed capsule is likely similar to oral bioavailability observed for the radiolabeled capsule. The relative bioavailability of different formulations is discussed in *Section 2.5.2*.

The median T_{max} occurred between 2 hours and 4 hours after a single dose of sonidegib under fasted conditions in cancer patients (n=103, Study X2101). Sonidegib is not a substrate of ABCB1 (P-glycoprotein) or ABCG2 (Breast Cancer Resistance Protein) in vitro.

2.2.5.4 *What are the characteristics of drug distribution?*

The population estimated apparent central volume of distribution (V_{ss}/F) of sonidegib was 9,166 L

based on the original full population PK model.

Sonidegib is greater than 97% bound to human plasma proteins independent of sonidegib concentrations (report no.0700955-03).

Sonidegib is predominantly distributed to plasma. The average blood-to-plasma concentration ratio ranged from 0.19 to 0.73 (report no. 0700955-03).

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

The mass balance study suggests that liver is the major route of elimination (64% to 73% of the absorbed dose).

Clinical

Six healthy White men were given a single 800 mg dose containing a trace amount of [^{14}C] sonidegib (~74 kBq) under fasted conditions (Study A2110). Serial PK samples were collected up to 14 weeks after administration of the radiolabeled dose. Complete urine and fecal outputs were collected for 3 weeks after administration and then 24-hour urine and fecal samples were collected during subsequent 24-hour visits until day 183. Only 5.6% to 7.2% of the dose was absorbed. The percent of the radioactive dose recovered from pooled feces was 93.4±1.9% and from urine was 2.0±0.8%; therefore, it is estimated that about 27% to 36% of the absorbed drug was eliminated in the urine and the remaining portion was eliminated in the feces (64% to 73%). A study in subjects with impaired hepatic function is ongoing (*see Section 2.3.2.6*).

Nonclinical

Following single oral administration of a 25 mg/kg dose to rats, sonidegib was not identified in bile. Two metabolites (M16 and M31) that were identified in rat bile, accounted for ~3% and ~8% of the dose, respectively. Two glucuronides (M35 and M61) and one glutathione conjugate (M66) were identified at low levels.

2.2.5.6 *What are the characteristics of drug metabolism?*

Sonidegib undergoes extensive metabolism with some involvement of CYP3A4 (**Figure 7**). It is unlikely that any of the metabolites will contribute to the observed efficacy, as no major circulating metabolites were identified and the active metabolites accounted for < 15% of the radiolabeled dose identified in the plasma.

- In vitro studies indicate that CYP3A4 is responsible for formation of M16 (LNC119), M23 (LMT323), M26 (LMR550), M33.2, and M48 (LGE899) (report no. DMPK R0800034).
- Plasma: The metabolite profiles showed unchanged sonidegib as the major circulating radiolabeled component in plasma, accounting for 36% of the $AUC_{0\text{-}504h}$ of total radioactivity in plasma. Multiple metabolites were identified in human plasma; the most abundant metabolites were M48 (LGE899) which accounted for 15% and M16 (LNC119) + M25 (LMT326) which accounted for 14% of the $AUC_{0\text{-}504h}$ of plasma radioactivity.
- Urine: M47e (CMN964) was the major component in urine, accounting for 91% of the dose eliminated in the urine. It only accounted for 1.3% of the cumulative excretion of the radiolabeled dose up to 504 hours.
- Feces: Sonidegib accounted for 89% of the cumulative excretion of the radiolabeled dose up to 504 hours. The other compounds identified in the fecal matter included M31 (< 1% of dose), followed by M50 and M43 (LNM147).

The pharmacologic activity of the following metabolites was evaluated: M48 (LGE899), M25 (LMT326), M16 (LNC119) and M23 (LMV128). M48 is an inactive metabolite; the other

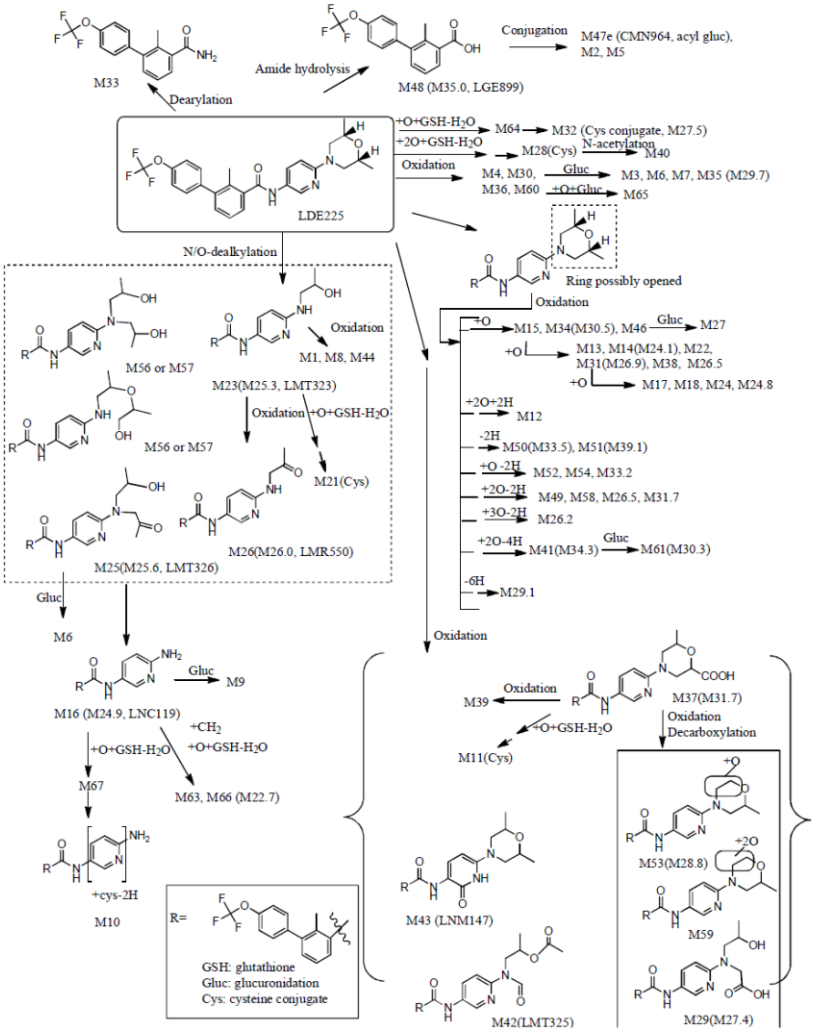
metabolites inhibited Smo with IC_{50} values at least 4-fold higher compared to the IC_{50} value of sonidegib (report no. RD-2013-50348 and Study A2110). It is unlikely that these metabolites will contribute to the observed efficacy, as only M25 and M16 were identified in the plasma at relatively low concentrations.

2.2.5.7 *What are the characteristics of drug excretion?*

Metabolism followed by fecal elimination is the primary route of sonidegib elimination as described above.

The median apparent oral clearance (CL/F) and elimination half-life could not be estimated for patients enrolled into dose finding trial (Study X2101) as the sampling duration was relatively short compared to sonidegib elimination half-life. The estimated population geometric mean (CV, %) CL/F was 10 L/h (74%) and elimination half-life was 28 days (108%) in cancer patients based on the original full population PK model.

Figure 7. Proposed metabolism of sonidegib in humans

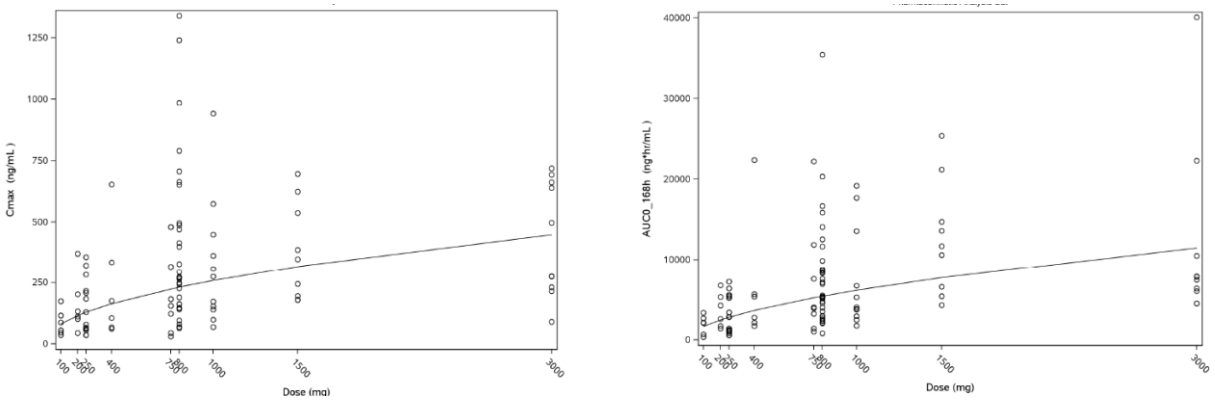


Source: Pharmacokinetics Written Summary, Figure 5.4

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

The Applicant used a power model with equivalence bounds of 0.93 and 1.07 to assess dose proportionality over the dose range tested in the dose escalation study (Study X2101) and demonstrated the lack of linear relationship between dose and exposure for both single dose and repeat dose assessments (**Figure 8**). The exposure appears to increase proportionally with doses up to 400 mg, then less than dose proportionally. From the original full population PK model, sonidegib has dose-dependent absorption, consistent with the observation that the dose-concentration relationship is nonlinear (**Figure 9**).

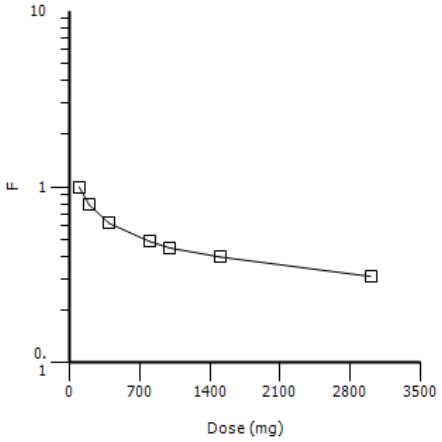
Figure 8. Mean maximal concentrations (left) and area under the curve from 0 to 168 hours (right) after a dose of 100 mg to 3000 mg in cancer patients



β = 0.50 and 90% CI: 0.35, 0.65 β = 0.57 and 90% CI: 0.42, 0.72

Source: Final Clinical Study Report X2101, Figure 14.2-3.3

Figure 9. Sonidegib demonstrates dose-dependent absorption after a single dose in cancer patients



Source: Population Pharmacokinetics Modeling Report, Table 5-5

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

Accumulation of sonidegib at steady-state is about 19-fold which was reached by week 17 based on the original full population PK model. **Table 9** lists the predicted PK parameters for sonidegib following a dose of 200 mg and 800 mg. Accumulation is anticipated as sonidegib is being

administered once daily and the elimination half-life is relatively long.

Table 9. Summary of mean (standard deviation) pharmacokinetic parameters of sonidegib following a single dose and repeated doses based on population PK model

Regimen	Day	AUC0-24h (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
200 mg qd	Day 1	1122 (249, 2575)	125 (23.6, 321)	20.9 (5.21, 52.1)
	Steady state	22348 (5967, 53263)	1030 (317, 2351)	890 (224, 2170)
800 mg qd	Day 1	2724 (695, 5958)	303 (60.9, 769)	48.0 (14.4, 112)
	Steady state	51982 (12889, 125322)	2405 (652, 5396)	2065 (491, 5097)
Note: values are presented as mean (90% prediction intervals) /vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/Prediction_Intervals_3.R				

Source: Population PK Modeling Report, Table 5-6

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

The revised population PK model incorporated data from 436 patients and healthy subjects and estimated the inter-individual variability in CL/F to be 67% (RSE 4.3%) and in Vc/F to be 213% (RSE 14.8%). Several covariates incorporated into the revised full population PK model had a clinically meaningful impact on sonidegib exposure: disease state (healthy subjects vs. cancer patients), dose, high-fat meal and ARA coadministration.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on effectiveness or safety responses?

The original full population PK model included several covariates that had a statistically significant effect on sonidegib PK, including disease state, dose, high-fat meal, baseline albumin, concurrent proton pump inhibitor (PPI), baseline weight, and baseline age; however, few covariates had a clinically meaningful effect on sonidegib PK. The original full population PK model suggests that high fat meal, disease state (healthy subjects vs. cancer patients) and dose had a clinically meaningful effect on sonidegib PK and that coadministration of an ARA might have a clinically meaningful effect on sonidegib PK (*see Section 2.1.1*). The remaining covariates assessed in the population PK model had no clinically meaningful impact on sonidegib PK, including baseline albumin, baseline bilirubin, baseline ALT levels, sex, ethnicity, baseline weight, baseline age, and baseline creatinine clearance.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups, healthy subjects vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.2.1 *Elderly*

None. The median (min, max) age was 58 (20, 93) years. The original final model suggests baseline age has a statistically significant, but not clinically meaningful effect on sonidegib clearance. The geometric mean $AUC_{0\text{-}24h}$ and C_{max} ratio at steady- state in subjects ≥ 65 years was 1.1-fold of that in subjects < 65 years.

2.3.2.2 *Pediatric*

A disease specific waiver from pediatric studies for the proposed indication for BCC was requested.

Sonidegib does not have orphan designation.

2.3.2.3 *Sex*

None. About 68% of the subjects included in the population PK model were men. The original final model suggests sex has a statistically significant, but not clinically meaningful effect on sonidegib clearance. The geometric mean $AUC_{0\text{-}24h}$ and C_{max} ratio at steady-state in women was 1.1-fold of that in men. Of note, men have a higher mean probability of grade 3 or 4 CK elevation compared to women at baseline (*see Section 2.2.4.2*).

2.3.2.4 *Race*

None. The exposure observed in Japanese subjects at a dose of 200 mg is not likely to exceed the exposure observed at a dose of 800 mg in the registration trial and therefore, a 200 mg dose in Japanese subjects should be well-tolerated.

Japanese subjects constituted about 13% of the population included in the population PK model. Ethnicity appears to have no statistically effect on sonidegib CL/F or steady-state exposure, but relatively few Japanese subjects were included in the model compared to Whites. The population model was not likely sensitive enough to detect potential differences in exposure between White subjects and Japanese subjects.

In contrast, a pooled analysis suggests that sonidegib exposure is higher in Japanese subjects compared to Western subjects, including White (33%) and Black (67%) subjects. In Study A2114 (Western) and Study A1102 (Japanese), healthy subjects received a single sonidegib dose in the fasted state. The exposure in Japanese subjects (n=12) was generally higher than the exposure in Western subjects (n=12). Following administration of a single 200 mg dose, the C_{max} was 1.6-fold (90% CI: 0.98, 2.49) higher and the AUC_{inf} was 1.7-fold (90% CI: 0.98, 2.91) higher for Japanese subjects compared to Western subjects. The exposure difference at an 800 mg dose was not clinically meaningful. The reasons for the higher exposure at a single 200 mg dose are not known, but differences in baseline body size were noted. A covariate analysis suggested that body size did not contribute to the observed differences, consistent with the findings from the population PK model, in which body weight had no clinically meaningful effect on sonidegib exposure.

2.3.2.5 *Renal impairment*

None. It is unlikely that renal impairment will have a clinically meaningful effect on sonidegib exposure, since less than 1% of the absorbed radiolabeled dose was eliminated in urine as unchanged sonidegib and the population PK model suggests mild or moderate renal impairment is unlikely to influence sonidegib exposure. The population PK model evaluated creatinine clearance (CLcr) calculated using the Cockcroft-Gault formula as a covariate. Patients with normal renal function (CLcr $\geq$ 90 mL/min, n=161), as well as patients with mild (CLcr 60 to 89 mL/min, n=129), moderate (CLcr 30 to 59 mL/min, n=60) and severe (CLcr 15 to 29 mL/min, n=1) renal impairment were included in the population analysis. Using the original full population PK model, the results showed that baseline CLcr had no statistically significant effect on sonidegib apparent oral clearance and mild or moderate renal impairment had no effect on sonidegib exposure (**Table 10**). Furthermore, a radiolabeled dose was not eliminated in bile based on a nonclinical studies conducted in rats (see *Section 2.2.5*). No additional studies are recommended to evaluate the effect of renal impairment on sonidegib exposure.

Table 10. Sonidegib steady-state exposure in cancer patients with mild and moderate renal impairment similar to cancer patients with normal renal function

Organ Impairment	$AUC_{0\text{-}24h}$ (ng*h/mL)	C_{max} (ng/mL)
Moderate: Normal	1.08 (0.62, 1.94)	1.07 (0.64, 1.84)
Mild: Normal	1.10 (0.64, 1.98)	1.10 (0.65, 1.88)

Geometric mean ratio (90% confidence interval)
Source: Population Pharmacokinetic Modeling Report, Table 5-11

2.3.2.6 *Hepatic impairment*

Sonidegib is eliminated via hepatic route with about 70% of the absorbed dose excreted in fecal matter, so it is possible that sonidegib exposure could increase in patients with hepatic impairment. No dose adjustment is needed for patients with mild hepatic impairment based on the population PK analysis, but it is not known if the dose needs to be reduced for patients with moderate or severe hepatic impairment. A study in non-cancer subjects with normal hepatic function or varying degrees of hepatic impairment: mild, moderate and severe hepatic impairment defined by Child Pugh is ongoing (see *Section 1.2.1)*. FDA will issue a postmarketing requirement (PMR) for the final study report.

The original full population PK model suggests that mild hepatic impairment defined by the National Cancer Institute does not affect sonidegib exposure. The geometric mean sonidegib steady-state AUC decreased by 26% (GMR 0.74; 90% CI 0.38, 1.37) and sonidegib steady-state C_{max} decreased by 24% (GMR 0.76; 0.42 1.35) in cancer patients with mild hepatic impairment (n=35, total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to ≤ 1.5 ×ULN and AST any value) compared to cancer patients with normal hepatic function (n=315, total bilirubin ≤ ULN and AST ≤ ULN). It is not clear why sonidegib exposure decreased, but these populations were not balanced in regards to baseline age, albumin or ARA coadministration. Only one patient had moderate hepatic impairment and no patients had severe hepatic impairment.

Baseline albumin had a statistically significant impact on apparent oral central volume of distribution (Vc/F) and CL/F, whereas ALT and bilirubin had no effect on CL/F based on the original full population PK model.

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

No clinical trials in pregnant or lactating women have been conducted, but sonidegib is embryotoxic, fetotoxic, and teratogenic in animals. It is not known whether sonidegib is excreted in human milk.

According to Division of Risk Management review, a Pregnancy Pharmacovigilance Study will be required to collect pregnancy registry data to evaluate pregnancy and infant outcomes following sonidegib exposure as a PMR.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Coadministration with a strong CYP3A inhibitor and inducer affected sonidegib exposure. Simulations suggest that a moderate CY3A inhibitor or inducer will also affect sonidegib exposure.

It is recommended to avoid concomitant administration of strong or moderate CYP3A inhibitors,

because the exposure following co-administration of a single 200 mg sonidegib dose with a strong or moderate CYP3A inhibitor is associated with a greater risk of grade 3 or 4 CK elevation. The co-administration of a moderate CYP3A inhibitor for up to 14 days may be considered if an alternative therapy is not available.

It is recommended to avoid concomitant administration of strong or moderate CYP3A inducers, because sonidegib exposure is likely to be lower than the exposure at the lowest clinically active dose. An increase in dose to provide similar exposure to sonidegib 200 mg is not recommended, since sonidegib has a long elimination half-life and non-linear PK at doses greater than 400 mg.

2.4.2 Drug-drug interactions

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

Yes, as sonidegib is metabolized by CYP3A4 and it inhibits CYP2C9 and CYP2B6 in vitro.

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

Sonidegib undergoes metabolism by CYP3A4 (at least 29% of its overall metabolism) based on the metabolites CYP3A forms in vitro and the relative amount of these metabolites observed in human plasma (report no. DMPK R0800034 and A2201). Genetic differences will likely have no effect on sonidegib metabolism.

A parallel study was conducted in 50 healthy subjects to assess the effects of ketoconazole (inhibitor) and rifampin (inducer) on sonidegib exposure after a single 800 mg dose given under fasted conditions (Study A2108). Subjects received sonidegib alone (day 1) or sonidegib (day 5) + ketoconazole 200 mg twice daily (days 1 to 14) or sonidegib (day 5) + rifampin 600 mg once daily (days 1 to 14). Serial PK samples were collected from pre-dose to 336 hours following the sonidegib dose. **Table 11** lists the geometric mean ratios with 90% CI for sonidegib exposure with and without ketoconazole or rifampin.

Table 11. Effect of ketoconazole and rifampin on the pharmacokinetics of sonidegib

					Treatment comparison		
						90% CI	
PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUC0-240h (ng*hr/mL)	LDE225	16	5620				
	LDE225+keto	15	12700	LDE225+keto/ LDE225	2.25	1.78	2.86
	LDE225+rifam	16	1550	LDE225+rifam/ LDE225	0.276	0.219	0.349
Cmax (ng/mL)	LDE225	16	212				
	LDE225+keto	15	316	LDE225+keto/ LDE225	1.49	1.11	1.99
	LDE225+rifam	16	97.7	LDE225+rifam/ LDE225	0.461	0.346	0.613

Source: Table 11-5, (Table 14.2-1.1)
- Model is a linear model of the log-transformed PK parameters. Included in the model is treatment as a fixed effect.
Results were back transformed to get adjusted geo-mean, geometric mean ratio, and 90% CI.
- n* = number of subjects with non-missing values.

Source: Final Study Report, A2108, Table 11-3

CYP3A4 Inhibition

Ketoconazole increased sonidegib exposure 2.2-fold, resulting in an exposure similar to the exposure observed with an 800 mg dose. The Applicant completed simulations using Simcyp which

predicted a 2.4-fold increase in sonidegib exposure following a single 200 mg dose (report no. DMPKR140013). Additional simulations were completed to estimate the effect of a strong and a moderate CYP3A inhibitor on steady-state sonidegib exposure following a dose of 200 mg in cancer patients (**Table 12**) (report no. DMPKR140013, DMPKR140013A DMPKR140013B). It is anticipated that coadministration of a strong or a moderate inhibitor would increase sonidegib exposure to an exposure level that likely exceeds the exposure with an 800 mg dose given alone. Therefore, it is recommended to avoid coadministration of sonidegib with strong and moderate CYP3A inhibitors, as patients with increased exposure will have a greater risk of severe musculoskeletal adverse events. The co-administration of a moderate CYP3A inhibitor for up to 14 days may be reasonable if no alternative therapy is available. Patients should be monitored for adverse events when taking a moderate inhibitor with sonidegib and after completing treatment with a moderate inhibitor.

Table 12. Simulated effect of strong and moderate CYP3A4 modulators on sonidegib exposure in cancer patients

Sonidegib Dose and Administration	Perpetrator Dose and Administration	Sampling	AUC_{0-24h} Ratio	C_{max} Ratio
Inhibitors				
200 mg QD days 1-120	Ketoconazole 200 mg BID days 1-120	Day 120	3.5	3.0
200 mg QD days 1-133	Ketoconazole 200 mg BID day 120-133	Day 133	2.0	1.8
200 mg QD days 1-120	Erythromycin 500 mg QID day 1-120	Day 120	2.8	2.4
200 mg QD days 1-133	Erythromycin 500 mg QID day 120 -133	Day 133	1.8	1.6
Inducers				
200 mg QD days 1- 120 (EMAX = 8)	Rifampicin 600 mg QD days 1-120	Day 120	0.26	0.36
200 mg QD days 1-120 (EMAX = 16)	Rifampicin 600 mg QD days 1-120	Day 120	0.12	0.20
200 mg QD days 1-120	Efavirenz 600 mg QD days 1-120	Day 120	0.31	0.40
200 mg QD days 1-133	Efavirenz 600 mg QD days 120-133	Day 133	0.44	0.51

CYP3A4 Induction

Rifampicin decreased sonidegib exposure by 72% in healthy subjects given a single 800 mg dose. Simulations using Simcyp predict a 76% decrease in sonidegib exposure following a single 200 mg dose (report no. DMPKR140013). Additional simulations were completed to estimate the effect of a moderate CYP3A inducer on steady-state sonidegib exposure following a dose of 200 mg in cancer patients (**Table 12**) (report no. DMPKR140013, DMPKR140013A DMPKR140013B). These simulations suggest that strong and moderate inducers will significantly reduce sonidegib exposure. Therefore, it is recommended to avoid concurrent administration of strong or moderate inducers, since a 200 mg dose is the lowest clinically active dose. A dose escalation to provide similar exposure to sonidegib 200 mg is not recommended, since sonidegib has a long elimination half-life and non-linear PK at doses greater than 400 mg.

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

Sonidegib could inhibit CYP2B6 and CYP2C9 in humans assuming a mean C_{max} of 1,030 ng/mL (1.5 μM; 200 mg dose at steady-state, **Table 9**). A study to assess the effect of sonidegib on the PK of a CYP2B6 and a CYP2C9 probe substrate is ongoing.

- Sonidegib inhibited CYP2B6 (Ki 0.045 μM; R_1 value ~34) and CYP2C9 (Ki 1.7 μM; R_1 value ~ 1.8) in vitro (report No. DMPKR0700986).
- No competitive inhibition of CYP1A2, 2C8, 2C19, 2D6 or 3A was observed at sonidegib concentrations of up to 100 μM.
- No time-dependent inhibition of CYP1A2, 2C9, 2D6 or 3A was observed at sonidegib concentrations of up to 50 μM.
- CYP1A2, 2B6 and 3A mRNA and activity were not increased compared to positive controls in vitro (report No. DMPKR1200636).
- No activation of the human pregnane X receptor was observed in a CYP3A reporter gene assay (report No. DMPKR0800482).

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

Sonidegib is not a substrate (efflux ratio < 2) or inhibitor of P-glycoprotein transport process in vitro. The net flux of a P-glycoprotein substrate was not affected by sonidegib (report No. DMPKR0700984, DMPKR0700988)

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

Yes. Sonidegib may be an inhibitor of BCRP in vivo.

- Sonidegib was not a substrate or an inhibitor of MRP2 up to concentrations of 25 μM in vitro (report No. DMPKR0700984, DMPKR0800540).
- Sonidegib is not a substrate of BCRP (efflux ratio < 2) in vitro, but it is an inhibitor of this transporter (IC_{50} 1.5 μM; $(I)_1/IC_{50}$ ~0.98) (report No. DMPKR1300665, DMPKR0800323-01).
- Sonidegib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 in vitro (report No. DMPKR1200563, DMPK R1200564, DMPK R1200565).
- Sonidegib is not a substrate of hepatic uptake transporters in vitro (DMPR1200562).
- The Applicant did not determine if sonidegib is a substrate of the renal transporters in vitro.

2.4.2.6 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

Sonidegib is to be given as monotherapy.

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Patients taking sonidegib will likely be taking other medications to prevent or treat adverse events or concurrent illnesses.

2.4.2.8 *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?*

Yes. [redacted] (b) (4) It is possible that an ARA could affect sonidegib bioavailability, [redacted] (b) (4) The Applicant completed an exploratory analysis to assess the effects of an ARA on the PK of sonidegib as part of the

population analysis. Histamine 2 receptor antagonists (H2RA) and PPI were included as two separate dichotomous variables in the original full population PK analysis. Fifty-eight patients were taking a PPI and 10 patients were taking an H2RA for more than 80% of the time in which sonidegib PK were assessed (N=351). This exploratory analysis suggests that sonidegib steady-state AUC following a 200 mg daily dose is about 34% lower in cancer patients concurrently taking an ARA compared to patients not concurrently taking an ARA (**Table 13**).

The Applicant also conducted an additional exploratory analysis of the ORR using the primary efficacy analysis set for Study A2201. ARA did not affect the ORR based on the geometric mean, but the 90% Clopper-Pearson exact confidence intervals were relatively wide likely due to the relatively small subsets (No, n=43 and Yes, n=12). A dedicated study is ongoing to assess (b) (4) how to dose sonidegib with an ARA.

Table 13. Geometric mean ratios at steady-state in patients taking sonidegib with an acid-reducing agent compared to patients taking sonidegib without an acid-reducing agent based on population pharmacokinetic analysis

	$AUC_{0\text{-}24h}$ (ng*h/mL)	C_{max} (ng/mL)
Geometric Mean No PPI or H2RA Yes PPI or H2RA	 21067 13560	 976 644
Geometric Mean Ratio	0.66	0.67
90% Confidence Interval	0.41, 1.09	0.43, 1.10

Source: Modeling Population Pharmacokinetic Report, Table 5-11, 5-12

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

No.

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

No.

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

None.

2.5 General Biopharmaceutics

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

(b) (4) but the amount of the dose absorbed in the mass balance study is small in humans (Study A2110). About 88% of the radiolabeled dose was rapidly excreted unchanged into the feces within 0 to 144 hours, but rapid biliary excretion or direct secretion of the radiolabeled dose is unlikely, as sonidegib demonstrates relatively low clearance and long terminal half-life.

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

The drug product administered in the registration trial supporting the proposed indication (Study A2201) is the to-be-marketed product and the same product that was used in the drug interaction (Study A2108) and relative bioavailability study (Study A2114). No relative bioavailability study was needed to compare the trial product to the to-be-marketed product.

Hard gelatin capsules at dose strengths of 50 mg, 100 mg, **200 mg** and 250 mg were used in the earlier clinical trials.

A randomized parallel study was conducted in 134 healthy subjects to compare the relative bioavailability of the two earlier (b) (4) formulations and an (b) (4) (Study A2114) to the to-be marketed hard gelatin capsule. (b) (4) bioavailability relative to the hard gelatin capsule. These formulations will not be marketed.

2.5.2.1 *What data support or do not support a waiver of in vivo BE data?*

Not applicable.

2.5.2.2 *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?*

Not applicable.

2.5.2.3 *If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the 'to-be-marketed' product?*

Not applicable.

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?

Sonidegib was given in the fasted state in the registration trial. A high-fat breakfast (1000 calories with 50% calories from fat) increased sonidegib AUC_{inf} 7.4-fold following a single 800 mg dose in healthy subjects. This observed food effect is anticipated based on the physiochemical properties (b) (4) of sonidegib. It is recommended sonidegib be taken in the fasted state, as increases in exposure of 2.3-fold have been associated with more grade 3 or 4 CK elevation\

Food Effect Study

A parallel study in 25 healthy subjects was completed to determine the effects of a high-fat breakfast on sonidegib exposure following a single 800 mg dose (Study A2114). Serial PK samples to measure sonidegib and LGE899 plasma levels were collected up to 12 weeks after dose administration. Sonidegib AUC_{inf} was 7.4-fold higher in the group where sonidegib was taken with a high-fat meal compared to the group where sonidegib was taken under a fasted state (**Table 14**). The T_{max} was delayed from a median of 2 hours in the fasted state to a median of 3 hours in the fed state. It is recommended sonidegib be taken in the fasted state as the exposure of a single 200 mg dose with a high-fat meal would be expected to exceed the exposure observed with an 800 mg dose in the fasted state and this exposure is associated with an increased risk of grade 3 or 4 CK

elevation.

Table 14. Effect of high-fat breakfast on the pharmacokinetics of sonidegib

PK Parameter (unit)	Treatment 800 mg	n*	Adjusted Geo-mean	Comparison	Treatment Comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
AUCinf (ng·h/mL)	fasted	12	10739.44				
	high fat meal	12	79296.03	high fat/fasted	7.38	4.94	11.04
AUClast (ng·h/mL)	fasted	11	10348.35				
	high fat meal	12	77691.84	high fat/fasted	7.51	5.34	10.56
Cmax (ng/mL)	fasted	13	216.49				
	high fat meal	12	1684.89	high fat/fasted	7.78	5.13	11.81

Model is a linear model of the log-transformed PK parameters. Included in the model was treatment as a fixed effect. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.

n* = number of subjects with evaluable PK data.

Source: Summary Clin Pharm BCC Table 2-2

Population Analysis

The Applicant added a compliance factor to the relative bioavailability (F) in the base population PK model after finding evidence that an increase in bioavailability was observed in cancer patients after the first dose. The Applicant suspected the increase in bioavailability may have been due to noncompliance with food restrictions. The non-compliance with food restriction was found to be have a statistically significant effect on bioavailability in the original full population PK model, but non-compliance does not appear to have a clinically meaningful effect on exposure (mean: 1.2; 95% CI: 1.0, 1.3).

The Applicant included 2 hour fast after a light meal (cancer patients) versus an overnight fast of a minimum of 10 hours (healthy subjects) as a covariate in the original full population PK model. The fasting duration (2 hours vs. 10 hours) had no statistically significant effect on bioavailability.

These findings do not influence the recommendations to take sonidegib fasted; however, these data seem to suggest that occasional non-compliance with fasted conditions will not substantially increase the risk of grade 3 or 4 CK elevation.

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

No BE study is necessary as the registration trial (Study A2201) used the to-be-marketed formulation.

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

Refer to the review by Office of New Drug Products (ONDP).

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

Not applicable; only one dose strength will be commercially available.

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 'to-be-marketed' product? 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 relation to in vitro dissolution of 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 and the other matrices?

High performance liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) methods were developed and validated for the identification and quantification of sonidegib in human plasma and urine samples.

2.6.2 Which metabolites have been selected for analysis and why?

CYP3A metabolism of sonidegib forms LGE899. Plasma concentrations of LDE899 were measured, as this metabolite was one of two metabolites identified in human plasma.

2.6.3 For all moieties measured is free, bound or total measured?

Total concentrations were measured for sonidegib and LGE899.

2.6.4 What bioanalytical methods are used to assess concentrations?

Table 15 lists the biological methods used to measure sonidegib for each study that included PK sampling. Three different validated analytical methods were used for the quantification of sonidegib in human plasma. Two analytical methods (report no. DMPK R070065802 and DMPK R070065804) are identical except for the assay range. The third analytical method (report no. DMPK R1000477f) was validated to simultaneously quantify sonidegib and its primary circulating metabolite LGE899 with a lower limit of quantification (LLOQ) of 0.500 ng/mL. The Applicant states that the validated methods used to support the sample analysis for clinical studies included in the current submission have been successfully cross-validated. The parameters described for the various methods indicate that the methods were adequate to estimate the concentration data.

Table 15. Bioanalytical methods

Bioanalytical Method	Study
DMPK R0700658-02 DMPK R0700658-04	X2101 X1101 B2209 A2114
DMPK R100477f	A2201 A2108 A2110 A1102

Source: Summary Biopharm BCC

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Table 16 lists the range of the standard curve and the curve fitting techniques used for the three methods used to measure sonidegib in human plasma. The dilution of plasma samples by a factor of 1000-fold was validated. This standard curve range was adequate for the purposes of determining plasma concentrations of sonidegib in the clinical studies.

Table 16. Bioanalytical methods summary

Parameter	DMPK R070065802	DMPK R070065804	DMPK R1000477f
Standard Curve			
- Range	0.0500 to 100 ng/mL	0.0254 to 50.8 ng/mL	0.0500 to 100 ng/mL
- Model	Linear	Linear	Linear
- Weighting Factor	$1/x^2$	$1/x^2$	$1/x^2$
Lower Limit of Quantification	0.0500 ng/mL	0.0254 ng/mL	0.0500 ng/mL
Upper Limit of Quantification	100 ng/mL (x1000)	50.8 ng/mL (x1000)	100 ng/mL (x1000)
Accuracy	Mean bias within ±15% (±20% at LLOQ)		
Precision	<15% (<20% at LLOQ)		
Sample Stability			
- Post preparative	48 hours at 25° C		
- Freeze-Thaw	3 at ≤ -18°C		
- Long-term stability			
- Spiked	15.5 weeks at ≤ -15°C		
- Incurred	14.5 weeks at ≤ -65°C		
QC Concentrations	0.0500 ng/mL 0.150 ng/mL 7.50 ng/mL 75.0 ng/mL	0.0254 ng/mL 0.0762 ng/mL 3.81 ng/mL 38.1 ng/mL	0.500 ng/mL 1.50 ng/mL 2.50 ng/mL 7.50 ng/mL 50.0 ng/mL 70.5 ng/mL

2.6.4.2 *What are the lower and upper limits of quantification?*

Table 16 provides the lower and upper limits of quantification.

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

Table 16 provides the accuracy and precision at these limits. The specificity or selectivity of the assay was demonstrated by evaluating the apparent peak area in blank samples and in LLOQ samples for sonidegib and the internal standard. Minimal carryover was adequately demonstrated.

2.6.4.4 *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Table 16 provides the sample stability under multiple conditions.

2.6.4.5 *What is the QC sample plan?*

Table 16 provides the QC concentrations. QC samples were prepared from different batches of matrix for each validation run. A minimum of five replicates prepared from the same matrix for each QC concentration were analyzed in each validation run.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested changes to the proposed labeling are shown in underline blue text and removal of content shown by red strikethroughs. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on ~~ODOMZO~~Sonidegib

(b) (4) *Strong and Moderate CYP3A Inhibitors*

(b) (4)

–Avoid concomitant (b) (4) –administration of ODOMZO with strong CYP3A inhibitors, including but not limited to (b) (4) ,–saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone.– (b) (4) *[see Clinical Pharmacology (12.3)]*.

Avoid concomitant administration of ODOMZO with moderate CYP3A inhibitors, including but not limited to atanzavir, diltiazem, and fluconazole. If a moderate CYP3A must be used, usedadminister the moderate CYP3A4 inhibitor for less than 14 days and monitor closely for adverse reactions, particularly musculoskeletal adverse reactions *[see Clinical Pharmacology (12.3)]*.

(b) (4) *Strong and Moderate CYP3A Inducers*

(b) (4)

–Avoid concomitant (b) (4) administration of ODOMZO with strong and moderate CYP3A inducers, including but not limited to carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin and St John's Wort *(Hypericum perforatum)*,– (b) (4) –*[see Clinical Pharmacology (12.3)]*.

(b) (4) —

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

4 APPENDIX

4.1 PHARMACOMETRICS REVIEW

4.2 PHYSIOLOGIC BASED PHARMACOKINETIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

NDA	205-266 \\CDSESUB1\evsprod\NDA205266\205266.enx
Submission Type	Original
Submission Date	26 September 2014
Generic Name	Sonidegib
Applicant	Novartis
Primary Reviewer	Stacy S. Shord, Pharm.D.
Secondary Reviewer	Yaning Wang, Ph.D.
Clinical Division	Division of Oncology Products 2 (DOP2)

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Figure 2. The relationship between the observed sonidegib minimal concentrations as week 17 and ORR in patients with locally advanced or metastatic basal cell carcinoma in Study A2201. The solid black symbols represent the observed ORR per central review in each quartile of observed minimal concentrations. The vertical black bars represent the 95% confidence interval (CI). The red line and the shaded area represent the logistic regression model predicted mean and 95% CI of the probability of ORR by average observed minimal concentrations. 4

Figure 3. The relationship between observed sonidegib minimal concentrations measured on Week 5 and grade 3 or 4 creatinine kinase elevation in patients with BCC. The solid black symbols represent the observed incidence of grade 3 or 4 CK elevation in each quartile of observed minimal concentrations. The vertical black bars represent the 95% confidence interval (CI). The red lines and shaded area represents the logistic regression model predicted mean and 95% CI of incidence of grade 3 or 4 CK elevation by observed minimal concentrations..... 6

Figure 4. The relationship between observed minimal sonidegib concentrations measured on week 5and grade 3 or 4 creatinine kinase elevation in men (top) and women (bottom). The solid black symbols represent the observed incidence of grade 3 or 4 CK elevation in each quartile of average observed minimal concentrations, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The red line and shaded area represent the logistic regression model predicted mean and 95% CI of incidence of grade 3 or 4 CK elevation by observed minimal concentrations. 7

Figure 5. Fold change of sonidegib steady-state exposure (AUC – left and maximal concentrations – right) relative to reference covariate group for cancer patients randomized to a 200 mg dose based on the original full population model (Source: Population Pharmacokinetic Modeling Report, Figure 5-27 and 5-28). 9

1 SUMMARY OF FINDINGS

1.1 BACKGROUND

Sonidegib (LDE 255, Odomzo) is a Hedgehog pathway inhibitor. The labeled indication will be for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) with lesions that are not amenable to curative surgery or radiation therapy. The indication is based on the results of a single placebo-controlled, double-blind trial that randomized 229 patients with locally advanced or metastatic BCC to a sonidegib dose of 200 mg (n=79) or 800 mg (n=150) orally, once daily, until disease progression or intolerable toxicity (Study A2201). A dose of 200 mg once daily provided an overall response rate (ORR) per central review of 58% (95% CI: 45%, 71%) and a dose of 800 mg once daily provided an ORR per central review of 44% (35%, 53%) for patients with locally advanced BCC (12-month analysis, FAS population). The median duration of response was not evaluable for patients randomized to a 200 mg dose. Grade 3 or 4 creatine kinase (CK) elevation were observed in 13% of patients, with the incidence lower in patients randomized to a 200 mg dose (6%) compared to an 800 mg dose (16%) (6-month analysis). Dosing interruptions occurred in 28% of patients and dose reductions occurred in 14% of patients for adverse events.

The main purpose of this pharmacometric review is to evaluate the appropriateness of the proposed dosing regimen by addressing the following key questions.

1.2 KEY REVIEW QUESTIONS

1.2.1 Are there significant exposure-response relationships for efficacy?

No. No exposure-response (E-R) relationship was identified for best overall response (BOR) in the registration trial. Based on this analysis, it appears that the E-R curve reached a plateau (**Figure 1** and **Figure 2**). No covariates affected the exposure-efficacy relationship. The proposed dose of 200 mg once daily was selected based on the observed E-R relationship for safety. The dose appears reasonable based on the available safety and efficacy data.

Overall Response Rate (ORR)

E-R analyses were conducted using a logistic regression model for the primary endpoint of ORR and the observed sonidegib minimal concentrations (C_{min}) measured at two time points [Week 5 (n=218) and Week 17 (steady-state, n=183)] for patients with locally advanced or metastatic BCC who were randomized to a sonidegib dose of 200 mg or 800 mg given once daily (Study A2201). The primary endpoint ORR [defined as the proportion of patients who achieved a complete response (CR) or partial response (PR)] was a composite endpoint based on modified Response Evaluation Criteria in Solid Tumors (RECIST) (locally advanced) or RECIST 1.1 (metastatic), clinical photography and histology. On treatment imaging and color photography schedule included assessments on week 5, week 9, week 17 and then every 8 weeks for the first 12 months. Sonidegib concentrations were measured on week 1, 3, 5, 9 and then every 4 weeks for the first 6 months. It was reasonable to evaluate the E-R relationship at these two time points, because week 5 corresponds to the timing of the first efficacy assessment and week 17 corresponds to steady-state concentrations. Median time to tumor response in the 200 mg arm was 3.9 months (95% CI: 3.6, 4.2) and in the 800 mg arm was 3.7 months (95% CI: 2.6, 3.8) for patients with locally advanced BCC. No E-R relationship was observed with the observed sonidegib week 5 (**Figure 1**) or with 17 (**Figure 2**) C_{min} and BOR.

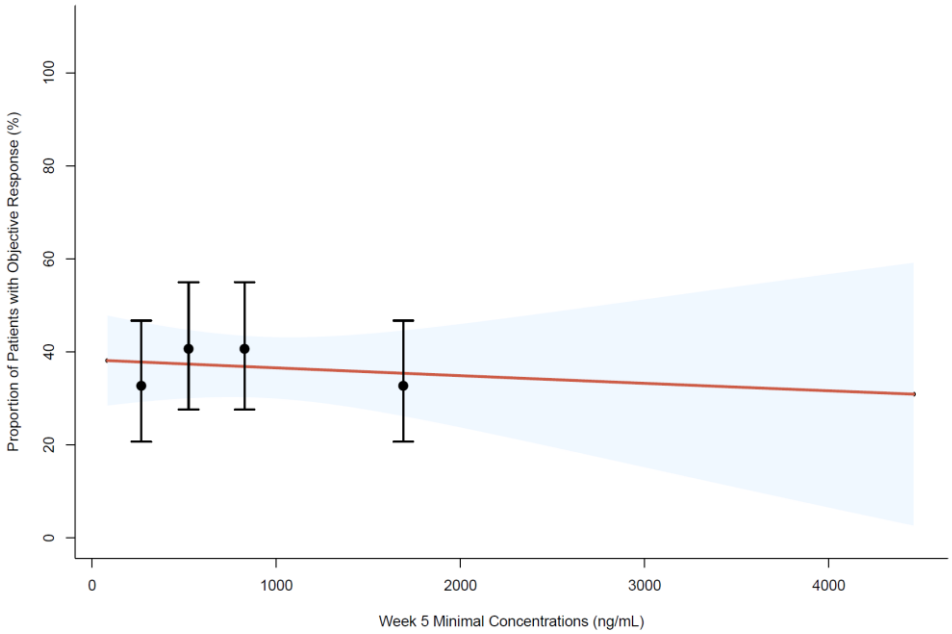


Figure 1. The relationship between the observed sonidegib minimal concentrations measured on week 5 and ORR in patients with locally advanced or metastatic BCC in Study A2201. The solid black symbols represent the observed ORR per central review in each quartile of observed minimal concentrations. The vertical black bars represent the 95% confidence interval (CI). The red line and the shaded area represent the logistic regression model predicted mean and 95% CI of the probability of ORR by observed sonidegib minimal concentrations.

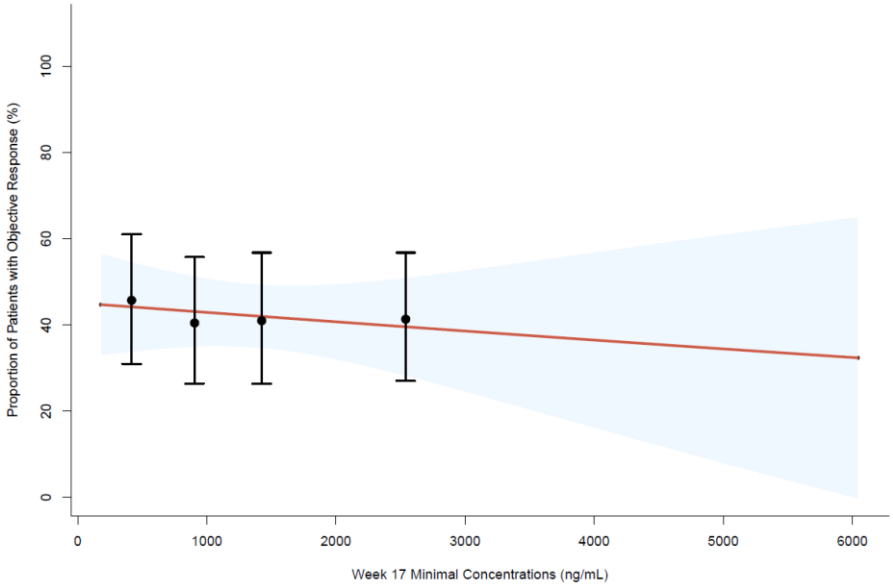


Figure 2. The relationship between the observed sonidegib minimal concentrations as week 17 and ORR in patients with locally advanced or metastatic basal cell carcinoma in Study A2201. The solid black symbols represent the observed ORR per central review in each quartile of observed minimal concentrations. The vertical black bars represent the 95% confidence interval (CI). The red line and the shaded area represent the logistic regression model predicted mean and 95% CI of the probability of ORR by sonidegib observed minimal concentrations.

A logistic regression model was used to analyze BOR versus the observed sonidegib C_{min} measured on week 5 and week 17 with the potential baseline covariates, including age, sex, race, height, weight and ECOG performance status. Patients with ECOG performance status of 1 or 2 appear to have higher mean probability of an overall response compared to patients with ECOG performance status of 0 (data not shown) at baseline**.** No covariates appear to influence the exposure-efficacy relationship.

1.2.2 Are there significant exposure-response relationships for safety?

Yes. E-R analyses demonstrate that the mean probability of grade 3 or 4 creatine kinase (CK) elevation increased with higher sonidegib C_{min} measured on week 5. No covariates affected the exposure-safety relationship. E-R analyses for other adverse events were not conducted, since serious adverse events other than muscle toxicity occurred in < 5% of the population, with the exception of grade 3 or 4 lipase elevation.

Grade 3 or 4 Creatine Kinase Elevation

In the registration trial Study A2201, CK elevation were observed in 30% of patients randomized to a 200 mg dose (6.3% grade 3 or 4) and 37% of patients randomized to an 800 mg dose (13% grade 3 or 4) (6-month analysis); these data, along with the reported dose limiting toxicities and serious adverse events in the dose escalation trial Study X2101, suggested that the probability of developing grade 3 or 4 CK elevation increases with higher sonidegib exposure. Therefore, E-R analyses for grade 3 or 4 CK elevation were conducted using the observed sonidegib C_{min} at week 5 as a measure of sonidegib systemic exposure in 310 patients enrolled into Study A2201, Study X2101 or Study X1101 (dose escalation). Grade 3 CK elevation was defined as > 5x upper limit of normal (ULN) to 10x ULN and grade 4 CK elevation was defined as > 10x ULN (Common Terminology Criteria for Adverse Events, v4.0). This analysis shows that the mean probability of grade 3 or 4 CK elevation increases with higher sonidegib C_{min} (**Figure 3**). About one percent of patients discontinued sonidegib for grade 3 or 4 CK elevation and about 6% of patients required dose interruption or dose adjustment as summarized by the Applicant; however, the protocol included dose reduction from a 200 mg dose to placebo such that the drug was withdrawn (18-month analysis). Essentially, about 8% of patients randomized to the 200 mg dose discontinued sonidegib for elevated CK levels.

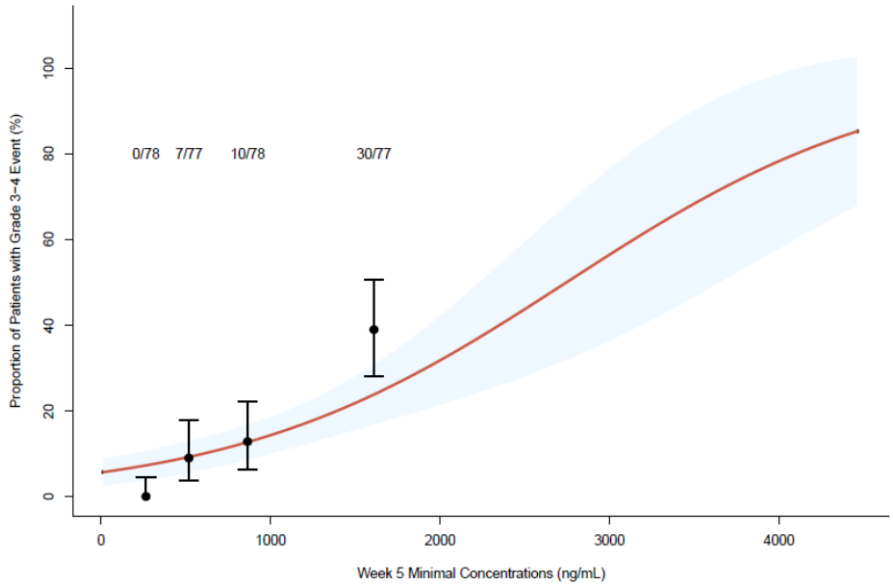
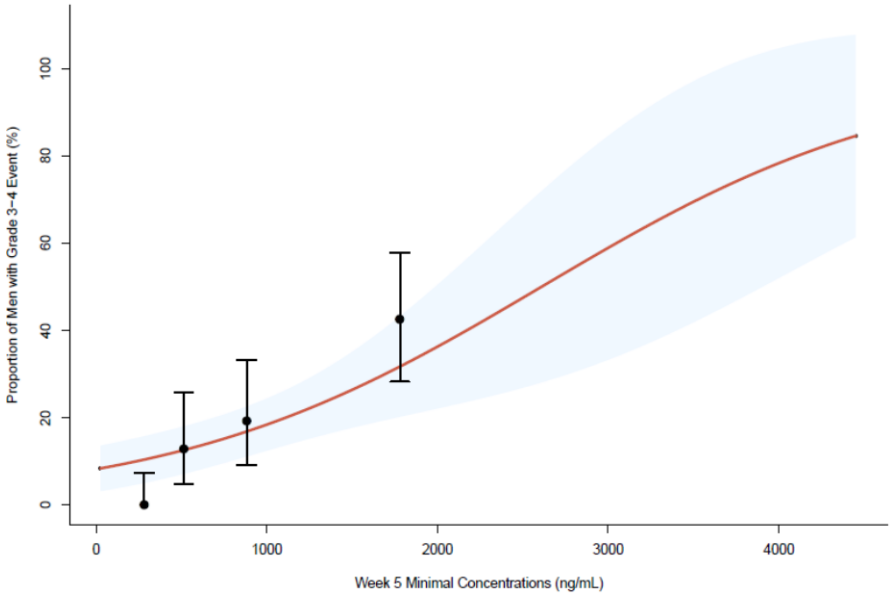


Figure 3. The relationship between observed sonidegib minimal concentrations measured on Week 5 and grade 3 or 4 creatinine kinase elevation in patients with BCC. The solid black symbols represent the observed incidence of grade 3 or 4 CK elevation in each quartile of observed minimal concentrations. The vertical black bars represent the 95% confidence interval (CI). The red lines and shaded area represents the logistic regression model predicted mean and 95% CI of incidence of grade 3 or 4 CK elevation by observed minimal concentrations.

A logistic regression model was used to analyze the occurrence of a grade 3 or 4 CK elevation versus the observed sonidegib C_{min} measured on week 5 with the potential baseline covariates, including age, sex, race and weight. No covariates affected the exposure-safety relationship, but men appear to have a higher mean probability of grade 3 or 4 CK elevation compared to women at baseline (**Figure 4**).



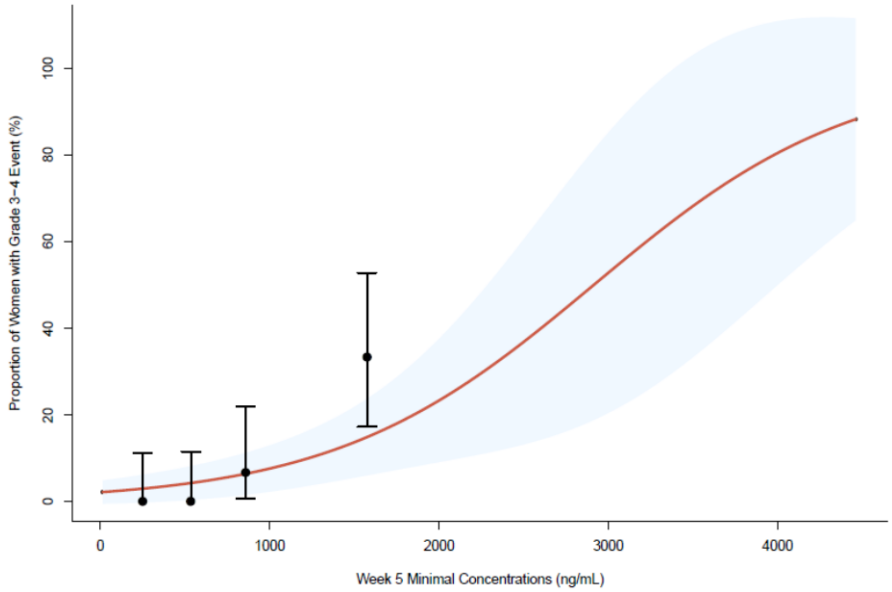


Figure 4. The relationship between observed minimal sonidegib concentrations measured on week 5 and grade 3 or 4 creatinine kinase elevation in men (top) and women (bottom). The solid black symbols represent the observed incidence of grade 3 or 4 CK elevation in each quartile of average observed minimal concentrations, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The red line and shaded area represent the logistic regression model predicted mean and 95% CI of incidence of grade 3 or 4 CK elevation by observed minimal concentrations.

Other Grade 3 or 4 Adverse Events

The most common adverse reactions that occurred in ≥10% of patients were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus (as summarized in the proposed FDA labeling). The most common grade 3 or 4 adverse events observed in patients randomized to a 200 mg dose were increased lipase and increased CK levels. Grade 3 or 4 decreased weight and muscle spasms were also frequently observed in patients randomized to an 800 mg dose.

No E-R analyses were conducted for these adverse events, because relatively few serious adverse events for each of these adverse events were observed, with the exception of grade 3 or 4 lipase elevation. No E-R analysis was conducted for grade 3 or 4 lipase elevation, because the incidence of all grades and grade 3 or 4 toxicity was similar for patients randomized to a 200 mg or an 800 mg dose (**Table 1**). The Applicant indicates that 5.1% of patients randomized to a 200 mg dose (n=4) and 4.0% of patients randomized to an 800 mg dose (n=6) required a dose adjustment or study drug interruption following the development of grade 3 or 4 lipase elevation. It is likely that the patients randomized to a dose of 200 mg permanently discontinued sonidegib, since the protocol included a dose reduction to placebo for grade 3 or higher non-hematologic adverse events. The clinical reviewer stated that no abdominal pain, vomiting or other evidence of pancreatitis was observed in these patients.

Table 1. Incidence of lipase elevation

Dose	All grades	Grade 3 or 4
200 mg (N=79)	6 (7.6%)	5 (6.3%)
800 mg (N=150)	12 (8.0%)	8 (5.3%)
Source: Addendum to Module 2.7.4 Summary of Clinical Safety in Advanced Basal Cell Carcinoma: 18-month Analysis		

Dose Modifications

The median duration of treatment was 11.0 months for patients randomized to a dose of 200 mg dose and 6.6 months for patients randomized to a dose of 800 mg based on the 18-month analysis. More patients randomized to a dose of 800 mg required a dose modification (**Table 2**). The most common reason for dose interruptions was adverse events: 28% for 200 mg dose and 51% for 800 mg dose (6-month analysis). The protocol included dose reduction from a 200 mg dose to placebo (such that the drug was withdrawn) for hematologic and non-hematologic serious adverse events. The other reasons for dose interruptions were dosing error, technical problems and dispensing error.

Table 2. Dose interruptions and reductions

Dose	200 mg (N=79)	800 mg (N=150)
Dose Interruption	54 (68%)	98 (65%)
Dose Reduction	13 (16%)	53 (35%)
Source: Addendum to Module 2.7.4 Summary of Clinical Safety in Advanced Basal Cell Carcinoma: 18-month Analysis		

1.2.3 What covariates affect the systemic exposure of sonidegib?

Based on the Applicant's population PK analyses, most covariates (e.g., age, sex, race, body weight, hepatic function and renal function) did not have clinically meaningful effect on sonidegib steady-state exposure [AUC or maximal concentrations (C_{max})]. No dose adjustments are needed for age, sex, weight, or organ function; however, usage of an acid-reducing agent (ARA) appears to affect sonidegib steady-state exposure. Since the Applicant is currently conducting a study to determine how to dose sonidegib with an ARA, no recommendations are being made at this time.

Population Model

The original full population model was described by a two-compartment disposition model with first-order oral absorption, linear elimination and non-linear bioavailability. The dichotomous covariates included in this model were disease status (healthy subject vs. cancer patient), high fat meal, proton pump inhibitor (PPI) and H_2-receptor antagonists (H2RA) usage (if more than 80% of the time during PK sampling), sex, and ethnicity. The continuous covariates included in this model were baseline weight, baseline creatinine clearance, baseline normalized ALT levels, baseline normalized albumin levels, baseline age, and planned dose level. Following an FDA information request, the Applicant subsequently redeveloped the population model to find a population model that converges on the data and to reduce the convergent model by backward elimination of covariates. The revised full population model converged with the inclusion of a fixed ALAG1. The reduced final model included age, albumin and disease status as a covariate

of apparent oral clearance (CL/F), weight and albumin as a covariate of apparent central volume of distribution (Vc/F) and food, compliance with food restriction with multiple dosing, dose and PPI usage as a covariate of oral bioavailability (F).

The original full population model suggested that a high-fat meal and dose have a clinically meaningful effect on F, that disease state (healthy subjects vs. cancer patient) has a clinically meaningful effect on CL/F, and that PPI usage might have a clinically meaningful effect on F; however, no covariates appear to have a significant effect on the estimated steady-state AUC following a dose of 200 mg in patients with cancer (**Figure 5**). The incorporation of these covariates into the reduced full model decreased the inter-individual variability (IIV) for CL/F from 106% to 67% compared to the base model. The IIV for Vc/F and Ka were similar in the base and reduced full model.

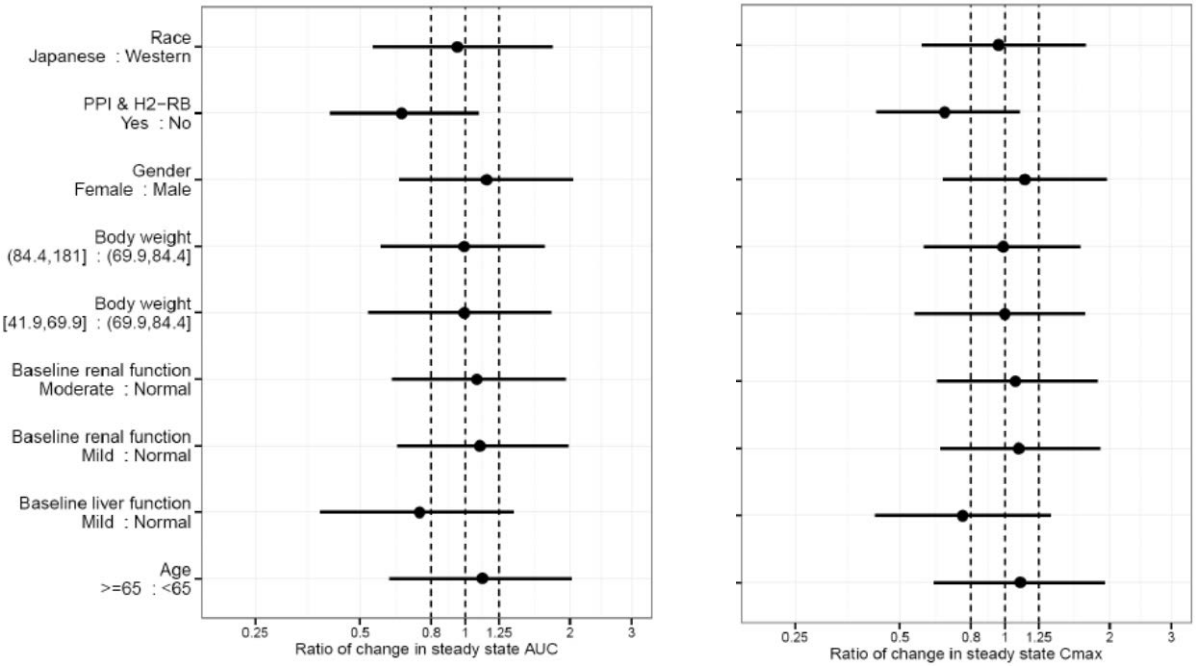


Figure 5. Fold change of sonidegib steady-state exposure (AUC – left and maximal concentrations – right) relative to reference covariate group for cancer patients randomized to a 200 mg dose based on the original full population model (Source: Population Pharmacokinetic Modeling Report, Figure 5-27 and 5-28).

Weight

The proposed flat dose of 200 mg once daily is acceptable. The population model suggests that baseline body weight has no clinically meaningful effect on sonidegib exposure (**Figure 5**). The median weight was 75 kg (min, max: 42, 181) for patients with cancer.

Organ Function

No dose adjustment is recommended for patients with renal impairment or mild hepatic impairment. The population model included renal function as measured by creatinine clearance (CLcr) calculated using the Cockcroft-Gault formula and hepatic function defined by the National Cancer Institute Organ Dysfunction Working Group (NCI ODWG). The population model included 129 patients with mild (CLcr 60 to 89 mL/min), 60 patients with moderate (CLcr 30 to 59 mL/min) and 1 patient with severe (CLcr 15 to 29 mL/min, n=1) renal impairment and

35 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to ≤ 1.5 ×ULN and AST any value). Baseline mild or moderate renal impairment or mild hepatic impairment has no effect on the sonidegib steady-state exposure as compared to patients with normal organ function (**Table 3**). No additional studies are recommended to evaluate the effect of renal impairment on sonidegib exposure. A study to determine an appropriate dose for patients with moderate and severe hepatic impairment is ongoing.

Table 3. Sonidegib steady-state exposure in cancer patients with hepatic and renal impairment compared to cancer patients with normal organ function

Organ Impairment	$AUC_{0\text{-}24h}$ (ng*h/mL)	C_{max} (ng/mL)
Renal		
Moderate: Normal	1.08 (0.62, 1.94)	1.07 (0.64, 1.84)
Mild: Normal	1.10 (0.64, 1.98)	1.10 (0.65, 1.88)
Hepatic		
Mild: Normal	0.76 (0.42 1.35)	0.74 (0.38, 1.37)

Geometric mean ratio (90% confidence interval)
Source: Population Pharmacokinetic Modeling Report, Table 5-11

Acid Reducing Agents (ARA)

The available data is insufficient to determine how to dose an ARA with sonidegib. H2RA and PPI were included as two separate dichotomous variables in the original full population model. Fifty-eight patients were taking a PPI and 10 patients were taking an H2RA for more than 80% of the time in which sonidegib PK samples were collected. The original full model suggests that sonidegib steady-state exposure following a 200 mg daily dose is about 34% lower in cancer patients concurrently taking an ARA compared to patients not concurrently taking an ARA (**Table 4**). The Applicant is currently conducting a study to determine how to dose ARA with sonidegib.

Table 4. Sonidegib steady-state exposure in patients taking sonidegib with an acid-reducing agent to patients taking sonidegib without an acid-reducing agent

	$AUC_{0\text{-}24h}$ (ng*h/mL)	**C_{max} (ng/mL)**
Geometric Mean		
No PPI or H2RA	21067	976
Yes PPI or H2RA	13560	644
Geometric Mean Ratio	0.66	0.67
90% Confidence Interval	0.41, 1.09	0.43, 1.10

Source: Population Pharmacokinetic Modeling Report, Table 5-11, 5-12

Ethnicity

No dose adjustment appears needed for Japanese patients compared to White patients, since the exposure observed for Japanese subjects at a dose of 200 mg is not likely to exceed the exposure observed at a dose of 800 mg in the registration trial. Japanese subjects constituted about 13% of the population included in the population PK model. Ethnicity appears to have no statistically effect on sonidegib clearance or steady-state exposure, but relatively few Japanese subjects were included in the model compared to Whites. The population model was not likely sensitive enough to detect potential differences in exposure between healthy White subjects and healthy Japanese subjects; however, the Applicant completed a pooled analysis that showed that the C_{max} was 1.6-fold (90% CI: 0.98, 2.49) higher and the AUC_{inf} was 1.7-fold (90% CI: 0.98, 2.91)

higher for Japanese subjects compared to Western subjects following the administration of a single 200 mg dose. The reasons for the higher exposure at a single 200 mg dose are not known, but differences in baseline body size were noted. The Applicant conducted a covariate analysis that suggested that body size did not influence the observed differences, consistent with the findings from the population PK model, in which body weight had no clinically meaningful effect on sonidegib exposure.

1.2.4 Is the proposed dosing regimen acceptable for the accelerated approval?

Yes. No E-R relationship was observed for BOR, but the mean probability of grade 3 or 4 CK elevation increased with higher observed sonidegib C_{min}. Sonidegib at a dose of 200 mg provided a similar ORR compared to a dose of 800 mg; however, fewer serious adverse events and dose modifications were observed with the 200 mg dose. The duration of response was not evaluable based on the 12-month analysis for the 200 mg dose. Therefore, the proposed starting dose of 200 mg once daily is acceptable from a clinical pharmacology perspective.

1.3 RECOMMENDATIONS

The pharmacometric reviewer finds that the NDA 205-266 is acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the Applicant and FDA regarding the labeling language.

1.4 POSTMARKETING REQUIREMENTS OR COMMITMENTS

The Office of Clinical Pharmacology will recommend the following two postmarketing requirements.

Drug Development Question	Rationale	PMR
Should the dose of sonidegib be reduced in patients with moderate or severe hepatic impairment?	The mass balance study indicates that ~70% of the absorbed dose is eliminated in the feces, indicating that hepatic elimination is the major elimination pathway. Higher sonidegib steady-state exposure is associated with greater probability of developing severe musculoskeletal toxicity.	Complete the ongoing pharmacokinetic (PK) trial to determine an appropriate dose of sonidegib in patients with moderate and severe hepatic impairment. Trial Completion: September 2015 Final Report Submission: July 2016
What is an appropriate dose for patients taking an acid-reducing agent (ARA)?	A population PK analysis suggests that ARAs reduce mean sonidegib steady-state exposure by 34%.	Submit the final study report for the completed PK trial to determine how to dose sonidegib in patients taking an ARA. Final Report Submission: July 2015

1.5 LABELING STATEMENTS

The following table provides a side-by-side comparison of the Applicant's and FDA's proposed labeling language. Only sections relevant to this review are provided in the table.

The Applicant's Proposed Language	FDA Proposed Language
8.6 Hepatic Impairment (b) (4)	**8.6 Hepatic Impairment** No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1.0 to 1.5 times ULN) ODOMZO has not been studied in patients with moderate or severe hepatic impairment [*see Clinical Pharmacology (12.3)*].
8.7 Renal Impairment (b) (4)	**8.7 Renal Impairment** No dose adjustment is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.
12.3 Pharmacokinetics (b) (4)	**12.3 Pharmacokinetics** Effect of Acid Reducing Agents on Sonidegib Based on population PK analysis, concomitant administration of a proton pump inhibitor or a histamine-2-receptor antagonist decreases the geometric mean steady-state AUC_{0-24h} to sonidegib by 34%. *Specific Populations* Hepatic Impairment Based on the population PK analyses, mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin ≤ 1.0 to 1.5 times ULN, n=35) had no effect on the sonidegib steady-state exposure as compared to patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN, n=315) *[see Specific Populations (8.6)]*. Renal Impairment Based on the population PK analyses, mild (CLcr 60 to 89 mL/min, n=129) and moderate (CLcr 30 to 59 mL/min, n=60) renal impairment had no effect on the sonidegib steady-state exposure as compared to patients with normal renal function (CLcr ≥ 90 mL/min, n=161) *[see Specific Populations (8.7)]*. Age, (b) (4), and Race Based on population PK analyses, age, body weight, (b) (4) has no clinically meaningful effect on the systemic exposure of sonidegib. A cross study comparison suggests that geometric mean AUC_{inf} of sonidegib is 1.7-fold higher in Japanese healthy subjects compared to Western healthy subjects (Whites and Blacks) following a single 200 mg dose of ODOMZO.

2 APPLICANT'S ANALYSES

The Applicant performed population PK analyses to characterize sonidegib exposure at steady-state in cancer patients and identify significant factors affecting sonidegib steady-state exposure. The original NDA contained a study plan entitled, "Population pharmacokinetics of oral LDE225 in patients with advanced solid tumors and in healthy subjects: Analysis plan for basal cell cancer (BCC) submission" and a study report entitled "Population pharmacokinetics of sonidegib in cancer patients and healthy volunteers Modeling Report". An addendum entitled, "Full and Reduced Population Pharmacokinetic Models Modeling Report" was submitted on 6 February 2015 in response to the FDA clinical pharmacology information request (#11, 21 January 2015).

The Applicant performed E-R analyses using the available efficacy and safety data. Two separate reports entitled, "Exposure-creatine phosphokinase analysis of sonidegib in patients with advanced solid tumors" and "Exposure-efficacy analysis of sonidegib in patients with advanced basal cell carcinoma" were submitted. An additional report was submitted on 6 February 2015 that included E-R analyses using observed sonidegib C_{min} at week 17 and simulated average AUC adjusted by dose intensity before the event of best overall response (dose intensity: total dose up to an event divided by time) as a measure of sonidegib exposure in response to the FDA clinical pharmacology information request (#11, 21 January 2015).

The key findings from the Applicant' analyses are summarized below. The grey shaded areas highlight text, tables and figures taken directly from the study plan, reports and responses.

2.1 POPULATION PHARMACOKINETIC ANALYSIS

The primary objectives of the population analysis were to determine a structural PK model in cancer patients and healthy volunteers following sonidegib administration, quantify the variability in the PK of sonidegib and characterize the effects of covariates on the PK of sonidegib.

2.1.1 Datasets

This analysis included data from 5 trials: CLDE225A2201, CLDE225X2101, CLDE225X1101, CLDE225A2114, and CLDE225A1102. Only the Japanese subjects in Study X1101 and only subjects receiving the capsule formulation in Study A2114 were included. The study design, study population, and timing of blood samples are summarized in **Table 5**.

Table 5. Summary of studies included in population pharmacokinetic analysis

Study CLDE225	Description	Timing of PK collection (Protocol planned)	Number in popPK analysis dataset	Sonidegib doses (mg)
A2201	A phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma	*All patients:* *W1: 0 h* *W3: 0 h* *W5: 0 h* *W9: 0 h* *W13: 0 h* *W17: 0 h* *W21: 0 h* *W33: 0 h* *W45: 0 h* *W57: 0 h* *W69: 0 h* *Subset of approximately 60 patients:* *Additional PK* *W17: 1, 2, 4, 6 h*	[a]227	qd: 200, 800 capsule 2 hours after a light meal
X2101	A Phase I, multicenter, open-label, dose-escalation study of oral LDE225 in patients with advanced solid tumors.	*Escalation phase:* *PK run-in D1: 0, 0.5, 1, 2, 4, 6, 8 h* *PK run-in D2: 24 h* *PK run-in D3: 48 h* *PK run-in D4: 72 h* *PK run-in D5: 96 h* *C1D1: 0 h* *C1D8: 0 h* *C1D15: 0, 0.5, 1, 2, 4, 6, 8 h* *C1D16: 0 h* *C1D22: 0 h* *C2D1: 0 h* *C2D2: 0 h* *C2D8: 0 h* *C2D15: 0 h* *C2D16: 0 h* *C2D22: 0 h* *Subsequent cycles D1: 0 h* 1 cycle=28 days *Expansion phase:* *No patients in this phase*	103	qd: 100, 200, 400, 800, 1000, 1500, 3000 capsule bid: 250, 400, 750 capsule All 2 hours after a light meal

		No patients in this phase		
X1101	An East Asian phase I, multicenter, open-label, dose- escalation study of oral LDE225 in patients with advanced solid tumors. Only Japanese cohort is included. Chinese cohort has not been completed in time for BCC submission.	*PK run-in D1: 0, 0.5, 1, 2, 4, 6, 8 h* *PK run-in D2: 24 h* *PK run-in D3: 48 h* *PK run-in D4: 72 h* *PK run-in D5: 96 h* *C1D1: 0 h* *C1D8: 0 h* *C1D15: 0, 0.5, 1, 2, 4, 6, 8 h* *C1D16: 0 h* *C1D22: 0 h* *C2D1: 0 h* *C2D8: 0 h* *C2D15: 0 h* *C2D22: 0 h* *Subsequent cycles D1: 0 h* 1 cycle=28 days	[b]21	qd: 400, 600 capsule 2 hours after a light meal
A2114	A randomized, open label study to evaluate the relative bioavailability of three final market image (FMI) formulations of LDE225 compared with the clinical service formulation (CSF) capsule* formulation and the effect of food in healthy subjects. Only subjects taking capsule formulation were included. *CSF capsule is identical to the FMI capsule.	*D1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10,12 h* *D2: 24 h* *D3: 48 h* *D4: 72 h* *D5: 96 h* *D6: 120 h* *D8: 168 h* *D15: 336 h* *Stages 1&2 only:* *D22: 504 h* *D29: 672 h* *D43: 1008 h* *D57: 1344 h* *D71: 1680 h* *D85: 2016 h*	[c]49	Single Dose 200, 800, 1200 capsule after overnight fasting. Single dose 800 capsule after a high-fat meal
A1102	A phase I, open label, dose-escalation study to assess the pharmacokinetics of a single dose of LDE225 capsule in healthy Japanese subjects	*W1D1: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 h* *W1D2: 24 h* *W1D3: 48 h* *W1D4: 72 h* *W1D5: 96 h* *W1D6: 120 h* *W2D1: 168 h* *W3D1: 336 h* *W4D1: 504 h* *W5D1: 672 h* *W7D1: 1008 h* *W9D1: 1344 h* *W11D1: 1680 h* *W13D1: 2016 h*	36	Single Dose 200, 400, 800 capsule after overnight fasting

Note: W represents week, D day, C cycle, 0 h time of pre-dose measurement.

[a] In Study A2201, 227 patients had at least one post-dose PK assessment out of 229 patients that had at least one dose of sonidegib. Total number of randomized patients was 230.

[b] Number of Japanese patients in the study.

[c] In Study A2114, 49 out of 146 subjects received capsule formulation

Source: Population Pharmacokinetic Modelling Report, Table 3-1

2.1.2 Methods

The analysis was performed using the NONMEM software system, NONMEM 7.2.0 (Icon Development Solutions, Ellicott City, MD, USA), on the MODESIM high performance computing environment accessing data from GPSII. Perl-speaks-NONMEM 3.5.3 was used for run automation. All model building was performed using the first order conditional estimation with interaction (FOCEi) method.

Base Model Development

The base model is described by the structural model and the random effects model.

Structural Model

A two compartment model with first-order absorption (NONMEM subroutine ADVAN4) was fit to sonidegib concentrations. The disposition kinetics were modeled using a parameterization involving apparent oral clearance (CL/F), apparent central volume (Vc/F), apparent inter-compartment clearance (Q/F), and apparent peripheral volume (Vp/F) (NONMEM subroutine TRANS4). A first-order absorption rate constant (Ka) and a lag-time parameter (Tlag) were used to characterize the absorption process.

The bioavailability F was given by:

$F = Fi * (Dose/100mg)^p$, where $p < 0$; and

Fi = 1, for single or run-in dose in cancer patients,

q1, for multiple day dosing in cancer patients,

q2, for healthy volunteer with overnight fasting,

q3, for healthy volunteer on a high-fat meal diet

Random Effects Model

Between-subject variability in pharmacokinetic parameters (i.e., CL/F, Q/F, Vc/F, and Vp/F and Ka) was modeled using multiplicative exponential random effects of the form:

$$P_i = TVP \cdot e^{\eta}$$

In this example, Pi is the value of the pharmacokinetic parameter P in individual i. TVP is the population typical value of the parameter. ηi denotes the between subject random effect accounting for the i^{th} individual's deviation from the population typical value; ηi has a mean of zero and a variance of ω2. The percent coefficient of variation (%CV) will be reported as:

$$\%CV = \sqrt{\exp(\omega^2) - 1} \cdot 100$$

Residual variability was modeled using an additive plus proportional error model on the linear concentration domain:

$$Y_{ij} = F_{ij} + \varepsilon_{ij}\sqrt{\sigma^2_{add} + F^2_{ij} \cdot \sigma^2_{mult}}$$

Y_{ij} denotes the observed concentration for the i_{th} individual at time j. F_{ij} denotes the corresponding predicted concentration based on the pharmacokinetic model. εij denotes the random effect with mean zero and variance 1. The additive error component has standard deviation σadd and the multiplicative error component has standard deviation σmult.

Full Model Development

The full-covariate-model approach [(Gastonguay MR 2011)] was adopted. Relationships between covariates and model parameters were selected based on clinical relevance, mechanistic plausibility, and prior knowledge. Those relationships were included in a single model called the "full model".

For dichotomous covariates (coded 0 or 1), relationships were modeled as:

$$TVP = TVP_0 \times q^x$$

where TVP_0 denotes the typical population value of the pharmacokinetic parameter P for x = 0. The parameter q denotes the ratio of TVP when x = 1 relative to TVP_0. The dichotomous covariate included in the full model are the indicator for patient status, administration of high fat meal, significant use of PPI during PK assessment, significant use of H_2 receptor antagonists during PK assessment, gender, and ethnicity.

Continuous covariates were modeled as multiplicative effects of the form:

$$TVP = TVP_0 \times (x / x_{norm})^q$$

where TVP_0 denotes the population value of the pharmacokinetic parameter P when $x = x_{norm}$ (median of the continuous covariate, e.g., x_{norm} = 58 years for age and x_{norm} = 73 kg for weight). The parameter TVP denotes the population value conditional on the value of x, which is proportional to x raised to the power q. When q = 1, TVP is directly proportional to x.

The continuous covariates included in the final model are baseline weight, baseline creatinine clearance, baseline normalized ALT levels, baseline normalized albumin levels, baseline age, and planned dose level.

Table 4-1 Covariate parameter relations included in the full model

Covariate	Parameters	Reason for investigation
Dose (DOSE)	F	There was evidence of dose-dependent bioavailability.
Healthy subject vs. Cancer Patient (HV)	CL/F, F	CL/F differences may occur between healthy subjects and cancer patients. In addition, the meal protocols for healthy subjects and cancer patients were different, which may affect F.
High fat meal (FATM)	F, KA	High fat meal conditions may alter bioavailability.
Age (AGE)	CL/F	Clearance generally decreases with age.
Body weight (WT)	CL/F, Vc/F, Vp/F	Clearance and volume are often correlated with size. The impact of body weight was assumed to be same on Vp/F and Vc/F.
Sex (SEX)	CL/F	Sex can be correlated with differences in clearance.
Ethnicity (Western vs. Japanese) (RACE)	CL/F	Different ethnic populations may have differences in clearance.
Estimated creatinine clearance by Cockcroft-Gault formula [(Cockcroft DW)] (CRCL0)	CL/F	Renal function may affect clearance.
Albumin (ALB)	CL/F, Vc/F, Vp/F	Protein binding may affect clearance and volume
ALT (ALTN)	CL/F	Measures of liver function may be correlated with differences in clearance
Normalized -bilirubin (BILN)	CL/F	Measures of liver function may be correlated with differences in clearance
Multiple dosing in patients (FMDD)	F	Variable compliance with food restriction during the multiple dose phase may affect the bioavailability relative to the first dose.
Concurrent H2 receptor antagonists (H2)	F	As sonidegib solubility is pH dependent, medications that modify the gastric pH could affect the bioavailability.
Concurrent proton pump inhibitors (PPI)	F	As sonidegib solubility is pH dependent, medications that modify the gastric pH could affect the bioavailability

Revised Full Model

Several approaches were tested to achieve convergence of the original full model (run3.mod):

1) use of NONMEM 7.3 with option MCETA= 3;

2) fixing of the parameter ALAG1 to the final estimate from the original full model;

3) modifying the error structure to multiplicative error only.

Over-parameterization of the model was assessed by the condition number of the model which is defined as the ratio of the largest to the smallest eigenvalue of the parameter correlation matrix. Models with condition number less than 1000 are desirable, whereas those with condition number greater than 1000 are considered ill-conditioned, and therefore are not likely to be stable ([Montgomery and Peck 1982]).

Once a full model achieved convergence, it was subjected to backward elimination to retain only statistically significant covariates. The p-value for backward elimination was set at 0.01 corresponding to a difference in objective function value of 6.63 units for a single degree-of-freedom reduction in the model. Backward elimination steps were carried out using the SCM utility of PsN 3.5.3 with NONMEM 7.2. Once the reduced model was obtained, the tested parameter-covariate relationships were classified as clinically significant, potentially clinically significant, or statistically significant. Covariates that were not retained in the reduced model after backward elimination were classified as not statistically significant.

2.1.3 Results

Description of Observed Data

The analysis data from five studies consisted of 436 subjects (351 patients and 85 healthy volunteers). The dataset had 6510 sonidegib plasma concentrations that were above the lower limit of quantification (LLOQ), 97.5% of the 6680 total reported sonidegib plasma concentrations. Most of the PK observations in patients occurred within 5 months of time of the first dose.

Model Development

The sequence of modeling steps is described in Table 5-4.

Table 5-4 Steps undertaken during model building

Step	Description	NONMEM control stream
1	Fitting of the base model to the analysis dataset	run1.mod
2	Identification and removal of outlier from the analysis dataset	
3	Fitting of the base model to the analysis dataset without outliers	run2.mod
4	Fitting of the full model to the analysis dataset without outliers	run3.mod
5	Running the full model to the 500 bootstrapped dataset stratified by fat meal status, study, and planned dose regimen	run4.mod

The initial base model derived from prior exploratory analyses provided an acceptable fit to the data in Step 1, as judged by diagnostic plots.

However, three outlying observations were identified according to the criterion |CWRES|>6. Two observations were collected at 0.42 hours after the first dose at which time the population predictions were zero because of the time period being less than the estimated lag time, 0.47 h. One outlying observation was collected at 47.5 hours post first dose. These three outliers were

removed, and the base model was refitted to the reduced dataset in Step 2. The base model provided an acceptable fit to data after deletion of outlying observation, as judged by the plots.

The base model was a two-compartment disposition model with first order absorption with a lag. The parameters CL/F, V/F, and Ka had random effects that were independent of each other. The random effects for Vp/F and Q/F were mutually correlated.

The base model included covariate effects on bioavailability that had been identified as necessary during prior exploratory analyses. There appeared to be a dose effect on bioavailability. Also, a high-fat meal was seen to have led to higher exposures than fasting conditions. Patients were supposed to take their medication two hours after a light meal, but behavior of preliminary models suggested there might be a difference in compliance of cancer patients between the run-in dose and multiple-day-dosing. If the typical cancer patient occasionally took sonidegib with meals, this could lead to an increase in the average bioavailability during multiple-day dosing. So bioavailability was modeled.

In Step 3, the selected base model was augmented with a full covariate model. The goodness of fit plots of the full model show a satisfactory fit to the data (Figure 5-10).

In Step 4, the full covariate model was fitted to 500 datasets obtained by sampling with replacement from the original pharmacokinetic dataset stratified on the fat meal status, study, and planned dosing regimen.

The full sonidegib PK model (run3) was the same as the base model described in the previous section except that covariates were included in the PK parameters. In terms of those parameters, equations (1) through (7) give the apparent clearance (CL/F), apparent volume of the central compartment (Vc/F), apparent volume of the peripheral compartment (Vp/F), first order absorption rate constant (Ka), relative bioavailability (F), apparent inter-compartmental clearance (Q/F), and lag time of absorption (Tlag). The random effect model for individual pharmacokinetic parameters was modeled as a multivariate normal distribution with mean 0 and variance-covariance matrix W, given in equation (8).

$$\left(CL/F\right)_i = \theta_{CL/F} \cdot \left(AGE_i/58\right)^{\theta_{CL-AGE}} \cdot \left(WT_i/73\right)^{\theta_{CL-WT}} \cdot \left(\theta_{CL-SEX}\right)^{SEX_i} \cdot \left(CRCL_i/93.3\right)^{\theta_{CL-CRCL}} \cdot \left(ALB_i/43\right)^{\theta_{CL-ALB}} \cdot \left(ALTN_i/0.42\right)^{\theta_{CL-ALTN}} \cdot \left(BILN_i/0.38\right)^{\theta_{CL-BILN}} \cdot \left(\theta_{CL-JPN}\right)^{JPN_i} \cdot \left(\theta_{CL-HV}\right)^{HV_i} \cdot e^{\eta(CL/F)_i} \quad (1)$$

$$\left(Vc/F\right)_i = \theta_{Vc/F} \cdot \left(WT_i/73\right)^{\theta_{V-WT}} \cdot \left(ALB_i/43\right)^{\theta_{Vc-ALB}} \cdot e^{\eta(Vc/F)_i} \quad (2)$$

$$\left(Vp/F\right)_i = \theta_{Vp/F} \cdot \left(WT_i/73\right)^{\theta_{V-WT}} \cdot \left(ALB_i/43\right)^{\theta_{Vp-ALB}} \cdot e^{\eta(Vp/F)_i} \quad (3)$$

$$Ka_i = \theta_{ka} \cdot \left(\theta_{ka-FATM}\right)^{FATM_i} \cdot e^{\eta(ka)_i} \quad (4)$$

$$F_i = \left(\frac{Dose_i}{100}\right)^{\theta_{F-Dose}} \cdot (\theta_{F-HV.FATM})^{FATM_i} \cdot (\theta_{F-PPI})^{PPI_i} \cdot (\theta_{F-H2})^{H2_i} \cdot (\theta_{F-FMDD})^{FMDD_i} \cdot (\theta_{F-HV.Fasting})^{HV_i} \quad (5)$$

$$\left(\frac{Q}{F}\right)_i = \theta_{Q/F} \cdot e^{\eta_{(Q/F)_i}} \quad (6)$$

$$Tlag_i = \theta_{Tlag} \quad (7)$$

$$\begin{pmatrix} \eta_{(CL/F)} \\ \eta_{(Vc/F)} \\ \eta_{(Vp/F)} \\ \eta_{(Q/F)} \\ \eta_{(Ka)} \end{pmatrix}_i \sim MVN \left(\begin{matrix} \omega^2_{CL/F} & & & & \\ & \omega^2_{Vc/F} & & & \\ 0, & & \omega^2_{Vp/F} & & \\ & & \omega^2_{Vp/F,Q/F} & \omega^2_{Q/F} & \\ & & & & \omega^2_{ka} \end{matrix} \right) \quad (8)$$

Revised Model

The original full model with ALAG1 fixed to exp(-0.745), final parameter estimate from run3, provided successful convergence and was taken to be the new full model.

The original full model with fixed ALAG1 was first run using NONMEM Version 7.3 (run3new2) in order to take advantage of the MCETA option that became available in that version. It was also run using NONMEM Version 7.2 (testbase) to provide a direct comparison with the results of backward elimination, because PsN uses Version 7.2 in the validated Novartis implementation. The two runs gave similar results; the latter will be the basis of further considerations.

Fixing the value of ALAG1 had little impact on the objective function value and parameter estimates. The 95% confidence intervals of the parameter estimates from the new converged full model (testbase) and the 95% bootstrapped confidence intervals of the original full model that did not converge (run3) overlapped. No large differences, >25%, in mean values of parameter estimates were observed between run3 and testbase. The condition number of testbase was 3.31/0.0617 = 53.6, which is much less than 1000, the value suggested to be associated with over-parameterization. Thus, the new full model was not overparameterized.

Final Parameter Estimates

The final parameter estimates listed in Table 4-2 from the *Full and Reduced Population Pharmacokinetic Models Modeling Report* compares the final estimates generated by the original and revised full model. These estimates for the listed parameters were identified in equations (1) to (8).

Table 4-2 Parameter estimates from original un-converged and new converged full models

Parameters	run3[a], bootstrapped estimates	testbase[b], NONMEM final estimates
	Mean, (RSE), [95% CI]	Mean, (RSE), [95% CI]
OFV	63282	63283
Convergence	Not achieved	Achieved
CL/F (L/h)	10.2 (11.2%) [8.18, 12.6]	10.2 (6.8%) [8.92 11.7]
$\theta_{AGE-CL/F}$	-0.377 (43.4%) [-0.699, -0.063]	-0.366 (37.7%) [-0.636, -0.097]
$\theta_{WT-CL/F}$	-0.094 (226%) [-0.515, 0.320]	-0.094 (217%) [-0.503, 0.311]
$\theta_{Female-CL/F}$	0.845 (8.8%) [0.720, 0.995]	0.850 (7.60%) [0.730, 0.985]
$\theta_{CRCL0-CL/F}$	-0.047 (321%) [-0.341, 0.248]	-0.046 (311%) [-0.332, 0.249]
$\theta_{Alb-CL/F}$	-1.44 (23.9%) [-2.08, -0.782]	-1.42 (23.1%) [-2.07, -0.776]
$\theta_{ALT-CL/F}$	0.123 (60.3%) [-0.018, 0.266]	0.123 (56%) [-0.007, 0.259]
$\theta_{BIL-CL/F}$	0.060 (122%) [-0.082, 0.217]	0.065 (103%) [-0.067, 0.194]
$\theta_{JPN-CL/F}$	0.911 (9.5%) [0.762, 1.08]	0.925 (14.3%) [0.693, 1.20]
$\theta_{HV-CL/F}$	3.02 (11.4%) [2.40, 3.78]	3.11 (19.9%) [2.03, 4.52]
CL/F – IIV	64.5% (5.16%)	65.9% (4.8%)
Vc/F (L)	150.5 (13.3%) [117, 193]	150 (14.1%) [113, 194]
$\theta_{WT-Vc/F}$	0.734 (17.2%) [0.501, 0.975]	0.735 (20.2%) [0.433, 1.03]
$\theta_{ALB-Vc/F}$	-2.36 (28.9%) [-3.61, -0.977]	-2.40 (40.9%) [-4.31, -0.493]
Vc/F – IIV	219% (10.9%)	221% (15.5%)
Q/F (L/h)	218 (11.0%) [175, 265]	219 (8.0%) [186, 257]
Q/F – IIV	107% (7.86%)	109% (7.4%)
Vp/F (L)	8379 (10.1%) [6822, 10280]	8350 (5.8%) [7386, 9343]
$\theta_{ALB-Vp/F}$	-0.131 (240%) [-0.738, 0.470]	-0.157 (166%) [-0.649, 0.332]
Vp/F – IIV	77.5% (6.12%)	77.4% (4.9%)
KA (1/h)	0.226 (5.37%) [0.202, 0.251]	0.226 (4.8%) [0.207, 0.247]
$\theta_{FATM-KA}$	0.875 (143%) [0.662, 1.16]	0.932 (44.7%) [0.370, 1.90]
KA – IIV	42.0% (13.6%)	42.5% (11.3%)
ALAG (h)	0.474 (0.550%) [0.468, 0.478]	Fixed to exp(-0.745) = 0.475
F	1	
θ_{H2-F}	0.982 (15.0%) [0.713, 1.28]	0.980 (16.6%) [0.705, 1.34]
θ_{PPI-F}	0.694 (8.24%) [0.595, 0.814]	0.696 (6.0%) [0.622, 0.783]
$\theta_{HV-Fasting-F}$	0.858 (8.51%) [0.724, 1.01]	0.865 (11.7%) [0.681, 1.08]
$\theta_{HV-Fatmeal-F}$	5.29 (11.2%) [4.21, 6.59]	6.57 (41.9%) [2.78, 13.2]
θ_{DOSE-F}	-0.342 (13.0%) [-0.425, -0.251]	-0.340 (5.7%) [-0.377, -0.302]
$\theta_{MultDose-F}$	1.16 (6.55%) [1.01, 1.31]	1.16 (0.7%) [1.14, 1.17]
$Corr_{Vp-Q}$	0.683 (7.66%)	0.69 (12.7%)
σ_{add} (ng/L)	0.623 (50.4%) [0.455E-06, 1.087]	0.737 (1.7%) [0.712, 0.762]
σ_{mult} (%CV)	31.5% (1.9%) [30.3%, 32.6%]	31.5% (0.6%) [31.2%, 31.9%]

[a]run3: The summary of parameter estimates are obtained from bootstrapping. Source: /RScripts/CIFromBootstrap_2.R -> .Rout, [Table 5-5, Population Pharmacokinetic Report]

[b]testbase: The model converged after fixing ALAG1 to exp(-0.745) h. The 95% CI are obtained by parametric bootstrap of the final estimates and respective standard errors. Source: /RScripts/CIfromlst-base.R -> .Rout

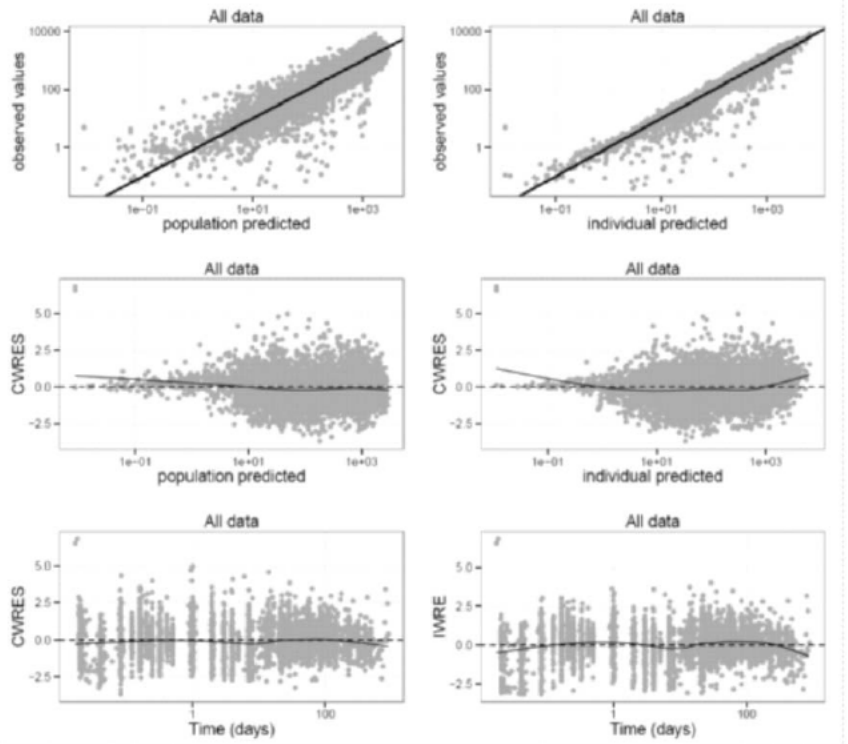
Evaluation of Full Model

Goodness of fit evaluation of the full sonidegib model for the pooled data, data from healthy volunteers, data from the run-in phase in cancer patients, and data from the multiple dosing phase in cancer patients are shown in Figure 5-10.

Figure 5-10 reveals no major inadequacies when the model is assessed on all of the data spanning four orders of magnitude in concentration. The plot of individual weighted residuals versus time does show some over-prediction early during the first profile likely due to difficulty

in capturing early absorption phase.

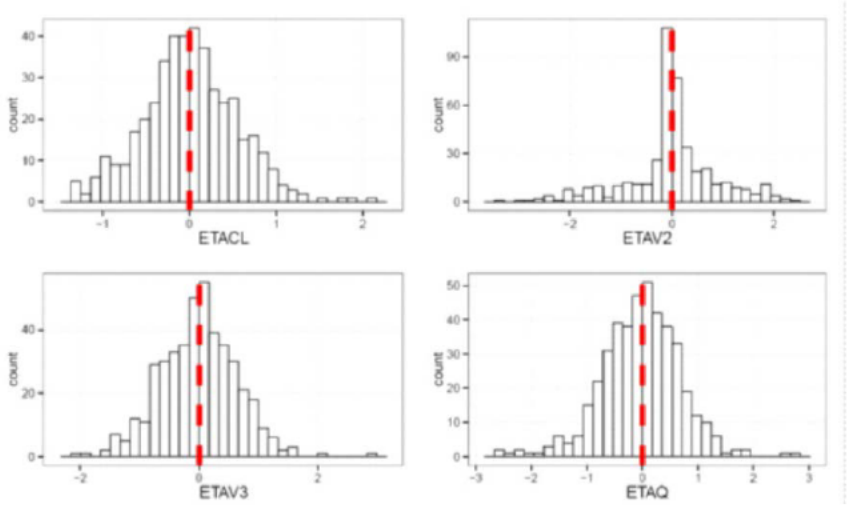
Figure 5-10 Goodness-of-fit plots for the full model, all subjects

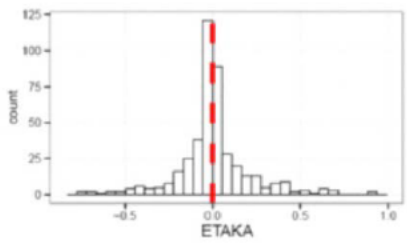


/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

The median values of the random effects appear close to zero with no striking outlying values, Figure 5-14. The histogram of random effects of Vc/F and Ka show peaked distributions and signs of shrinkage of the posthoc values. The shrinkages of random effects on Vc/F and Ka were estimated to be 32.7% and 48.5%, respectively. The covariance distribution of the posthoc estimates of the random effects shows that correlations >0.3 are observed between CL/F and Vp/F (corr: 0.347), between Vp/F and Q/F (corr: 0.789). The random effects on Vp/F and Q/F were modeled as correlated.

Figure 5-14 Histograms of estimated random effects from the full model

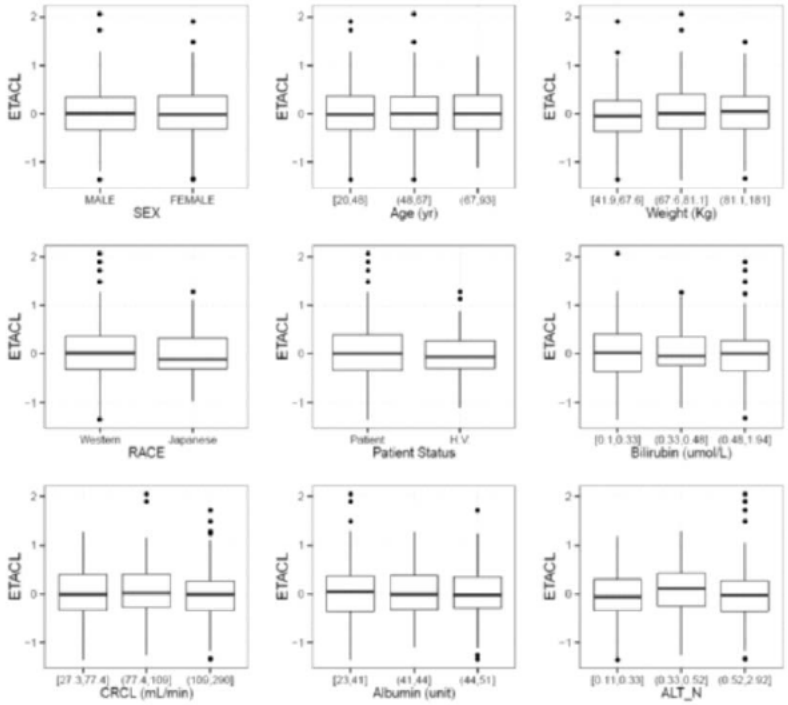




/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

The relationships between random effects and covariates are shown in Figure 5-16 through Figure 5-20. The random effects on CL/F, Vp/F, and Q/F do not show any trends. There is a trend of the ethnicity effect on Vc/F suggesting Japanese patients may have low apparent volume of distribution, Figure 5-17. However, since a large value of shrinkage is estimated for random effects of Vc/F the evidence of large ethnicity effect is unreliable. It should be noted that the ethnicity effect on Vc/F was not assessed as part of the full covariate model. There is a trend that Ka is lower in patients taking a high fat meal, Figure 5-20. This relationship did not reach statistical significance in the covariate model.

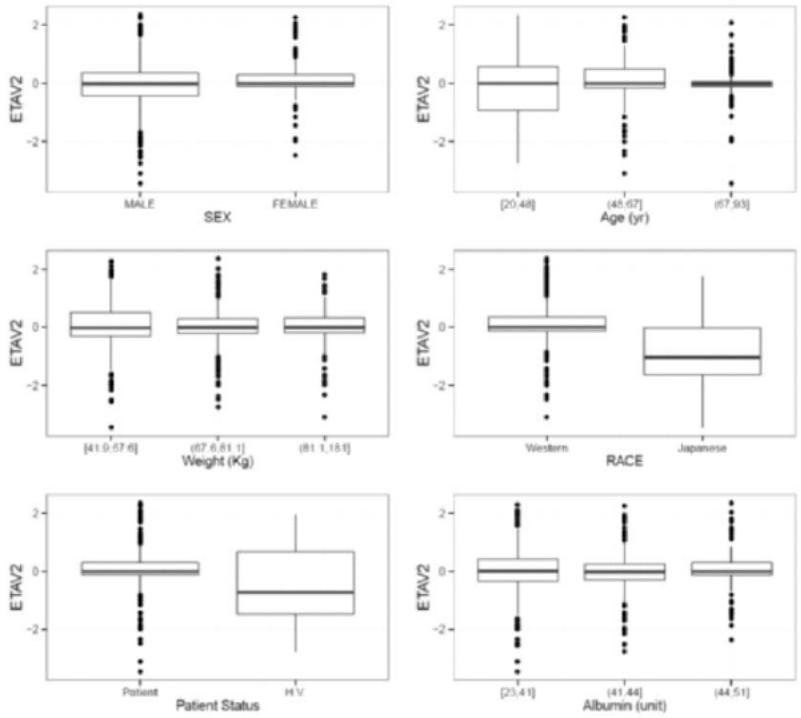
Figure 5-16 Estimated random effects on CL/F from the full model versus covariates



Note: The continuous covariates are binned into tertiles

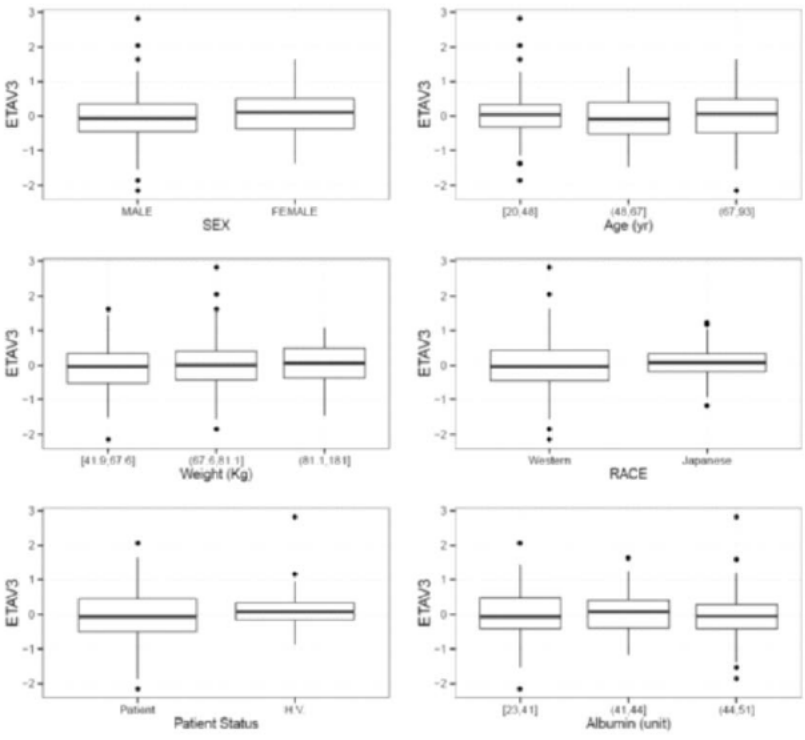
/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

Figure 5-17 Estimated random effects on Vc/F from the full model versus covariates



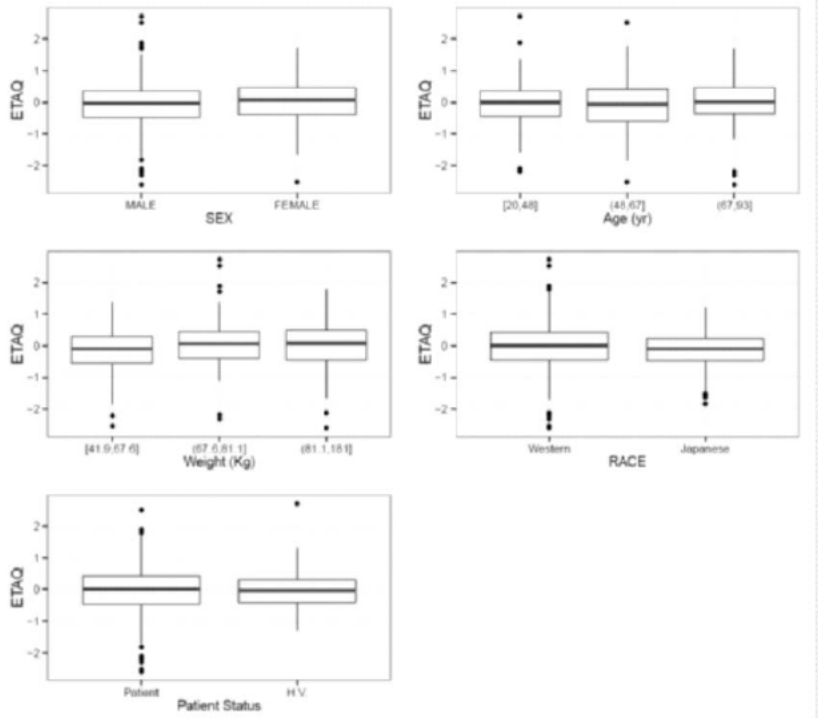
Note: The continuous covariates are binned into tertiles
/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

Figure 5-18 Estimated random effects on Vp/F from the full model versus covariates



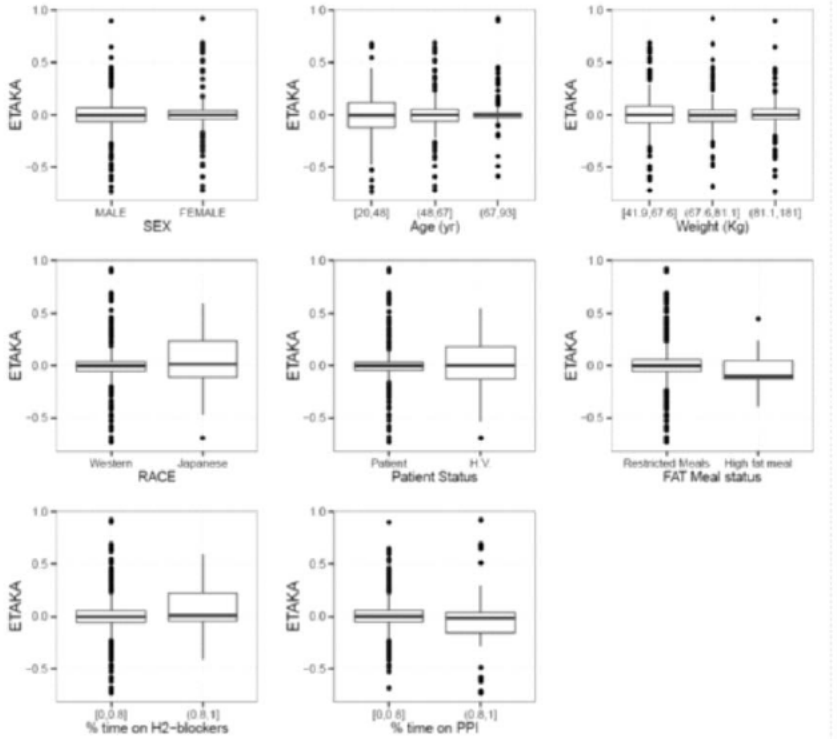
Note: The continuous covariates are binned into tertiles
/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

Figure 5-19 Estimated random effects on Q/F from the full model versus covariates



/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

Figure 5-20 Estimated random effects on Ka from the full model versus covariates



/vob/CLDE225X/pool/pkpd_002/pgm_01/POPPK_Submission_1/Rscripts/NonmemDiagnostics_2.R

Reviewer's comment: *The population PK analysis followed a reasonable model selection and optimization process with the revised full model. The Applicant's population PK analysis is acceptable.*

2.2 EXPOSURE-RESPONSE ANALYSES

The Applicant submitted two study reports. The exposure-efficacy report summarizes the analysis of the relationship between sonidegib plasma concentrations and occurrence of confirmed best overall response of CR or PR, progression-free survival (PFS), and time to tumor response (TTR). The addendum to this report summarizes the analysis of the relationship between sonidegib plasma concentration at week 17 and simulated average AUC. The exposure-safety report summarizes the analysis of the relationship between sonidegib plasma exposure and occurrence of grade 3 or 4 CK elevation.

2.2.1 Methods

Exposure-Safety Relationship

The endpoint used for the model based analyses is the occurrence of a CK elevation of grade ≥ 3 (using CTCAE v4.03) over the course of the study, defined as yes or no. Therefore, each patient had only one endpoint for this analysis. CK elevations for this analysis were determined only from the lab test, not from reported adverse events. Occurrence of CK elevation of grade ≥ 3 was utilized as a categorical variable via logistic regression to explore the association between PK and grade 3 or 4 CK elevations.

The following three PK parameters were used as explanatory variables for the analysis: C (cycle) 1D (day) 15 AUC, C1D15 C_{max}, and C2D1 C_{min}. These measures of exposure were chosen based on the fact that most CK elevations of grade ≥ 3 occurred within the first 6 weeks of treatment. In addition, C2D1 C_{min} was chosen because it is a common measure of exposure collected across all studies included in the pool.

A logistic regression model was used for the analysis. The assumption of this model is that the PK exposure at a given timepoint is predictive of a grade 3 or 4 CK elevation regardless of when the CK elevation occurred with respect to when the PK was assessed. In addition, no grade 3 or 4 CK elevations have occurred prior to C1D15. If a patient does not undergo dose changes prior to the occurrence of CK elevation, the PK exposure measure on C1D15 or C2D1 will be correlated with the PK exposure at the time of CK elevation. In the rare case the grade 3 or 4 CK elevation occurs prior to the C2D1 C_{min} collection, this observation was excluded from the analysis as the concentration was likely low due to interruption or reduction, and may introduce bias into the analysis.

Exposure-Efficacy Relationship

The primary analysis data from Study A2201 with data cut-off of 28-Jun-2013 was used for this analysis. This is most appropriate given the limited number of locally advanced or metastatic basal cell carcinoma (BCC) patients in other studies included in this submission, and because of different response criteria used.

Responses for all analyses were determined by central review according to:

- For la(locally advanced)BCC patients: Modified RECIST (mRECIST) using an integrated composite response based on MRI, digital clinical photography, and histopathology. MRI tumor response was evaluated by RECIST 1.1. Clinical photographs were evaluated in

accordance with World Health Organization (WHO) criteria.

- For m(metastatic)BCC patients: RECIST 1.1 based on CT or MRI scans (and/or color photography for skin lesions, if any).

For the analyses, W(week)5 C_{min} was used as the explanatory variable. W5 was chosen as the measure of exposure for the analyses because this corresponds to the timing of the first efficacy assessment, and the exposure level is expected to be approximately 70% of the steady state exposure. Later timepoints closer to or at steady state (e.g. W9, W17) were not chosen for the primary analyses due to the concern that non-responders may have discontinued at this time, and some of the responders may have attained a response prior to the respective C_{min} collection, biasing the analyses. However, the correlation was assessed between W5 and W9, and W5 and W17 C_{min} to evaluate if the measure of exposure used for the model based analyses is predictive of the exposure at later timepoints, justifying the use of W5 C_{min} for the analyses. The PK dataset used for the analyses contained W5 C_{min} and (if available) W9 and W17 C_{min} for each patient.

Logistic regression of occurrence of CR or PR vs. W5 C_{min} for all patients and for each level of any identified subgroup was used for this analysis. The assumptions of this model are that the W5 C_{min} exposure is predictive of the occurrence of a CR or PR on or after the W5 C_{min} is collected, regardless of how long after W5 the CR/PR occurs.

The FAS (Full Analysis Set; defined in CLDE225A2201 RAP M3) includes all patients who are assigned study treatment (regardless of receiving the treatment). The PK/FAS includes all patients included in the CLDE225A2201 FAS with a Week 5 (W5) evaluable trough concentration (C_{min}). A concentration is evaluable if the patient took the same sonidegib dose for at least 15 consecutive days prior to the PK sample, did not vomit within 4 hours of drug administration on the day prior to the PK sample, and the concentration is not flagged via the concentration exclusion flags. If available, evaluable W9 and/or W17 C_{min} were also to be used for the analyses in case the correlation coefficient between W9 and W5 C_{min} or W17 and W5 C_{min} was less than 0.7, but were not required for a patient to be included in this analysis set.

The Applicant completed additional analyses following FDA information request. Exposure-response analysis by logistic regression modeling in patients with advanced basal cell carcinoma for probability of best overall response (BOR) being CR or PR (responders) using sonidegib minimal concentrations (C_{min}) measured at Week 17 (W17) as well as using simulated average AUC derived from the individual patient posthoc clearances which were derived from the reduced and converged population PK model after backward elimination (run16).

Simulated average AUC was calculated using the DI (dose intensity) divided by the individual post-hoc clearance (CL) from the pop PK model, i.e.:

Simulated average AUC (ng*hr/mL per day) = (DI (mg/day) / CL (L/hr))*1,000,000 (ng/mg)*0.001 (L/mL)

For this analysis, the DI period considered was:

- For responders with first CR/PR assessed while on treatment, from first dose to the first CR/PR.
- For responders with first CR/PR assessed after treatment discontinuation and for nonresponders, from the first dose to the minimum of (cutoff date, last dose date), i.e. the entire duration while they are on treatment.

DI for patients with non-zero DI period was calculated as follows:

DI (mg /day) = Cumulative dose (mg) received over the DI period / DI period (days).

2.2.2 Results

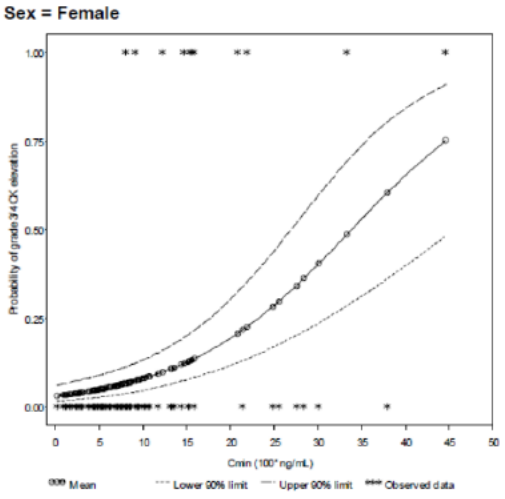
Exposure-Safety Relationship

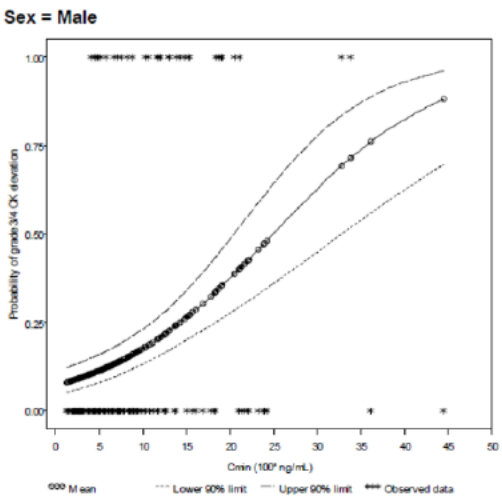
The logistic regression models of grade 3 or 4 CK elevation vs. C2D1 C_{min}, C1D15 C_{max}, and C1D15 AUC all showed a significant relationship between the measure of sonidegib exposure and grade 3 or 4 CK elevation, indicating that increasing exposure increases the risk of grade 3 or 4 CK elevation. The model for C2D1 C_{min} included the largest number of patients among the PK-CK models (N=306 after excluding one patient with grade 4 CK occurring before C2D1 C_{min} PK collection), the majority coming from Study A2201; the model for C1D15 C_{max} (N=102) and C1D15 AUC (N=72) did not include Study A2201. In the model for C2D1 C_{min}, sex was identified as a risk factor for grade 3 or 4 CK elevation with a lower risk for female patients than for males.

Reviewer's Comment: *Only the analyses for C2D1 will be discussed below, as this dataset included patients from the registration trial Study A2201.*

The final model of grade 3 or 4 CK elevation vs. C2D1 C_{min} included C2D1 C_{min} and sex. The odds ratio for C_{min} was 1.1 (p-value <0.0001), indicating higher sonidegib exposure poses a higher risk for grade 3 or 4 CK elevation (Figure 3-2). The odds ratio for female relative to male was 0.40 (90% CI 0.20, 0.77; p-value = 0.02), indicating a lower risk of grade 3 or 4 CK elevation for female vs. male patients.

Figure 3-2 **Estimated mean probability of grade 3 or 4 CK elevation and 90% CI vs. C2D1 Cmin (PK/CK set)**





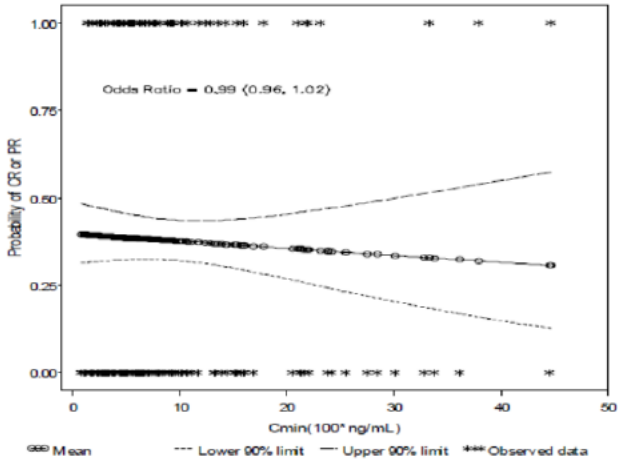
The model was log(p/(1-p)) = Cmin + sex, where p is the probability of a Grade 3 or 4 CK elevation.
Source: CREDI Figure 2-6
/report/pgm_saf/f_reg_cmin.sas@@/main/4 11MAR14:02:56 Final Version

Exposure-Efficacy Relationship

Reviewer's Comment: *Only the analyses for ORR will be discussed below, as Study A2201was an uncontrolled clinical trial.*

The logistic regression model of W5 C_{min} vs. ORR for PK/FAS indicated no relationship between sonidegib exposure resulting from 200 mg and 800 mg qd (once daily) and the probability of CR/PR, i.e. the response rate is robust across the observed levels of exposure. The odds ratio (corresponding to a 100 ng/mL change in C_{min}) from the logistic regression model for W5 C_{min} vs. ORR was 0.991 (90% CI 0.961, 1.022; p-value = 0.630) (Figure 3-3).

Figure 3-3 Estimated mean (90% CI) probability of CR/PR vs. W5 Cmin (PK/FAS)

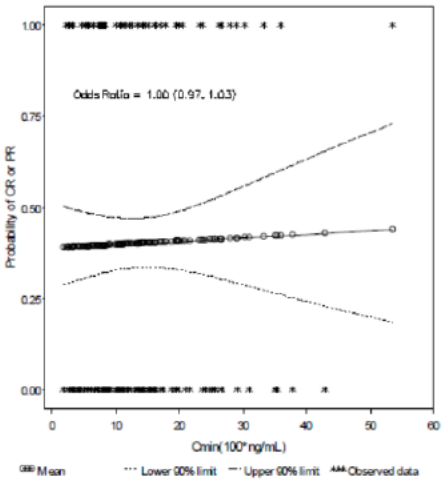


The model was log(p/(1-p)) = Cmin, where p is the probability of a CR or PR.
Using this model, the p-value for W5 Cmin was 0.63 (Table 3-4).
Source: CREDI Figure 2-10a
/report/pgm_eff/f_prob_w5.sas@@/main/3 07MAR14:05:42 Final Version

Reviewer's Comments: *The following text and figures were taken from the response to FDA Information Request dated 6 February 2015.*

Similar to what is observed in the original Exposure Efficacy Report using W5 C_{min}, the W17 PK/FAS2 analysis shows a flat exposure-response relationship (Figure 2-1).

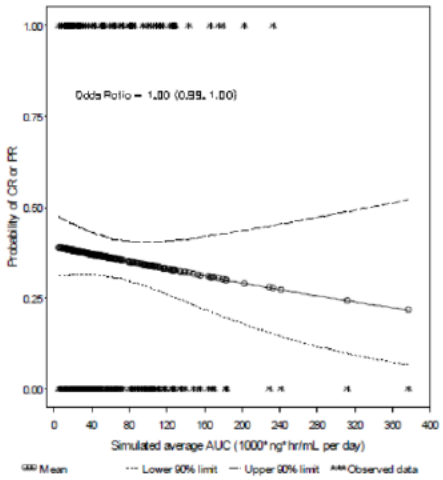
Figure 2-1 **Estimated mean (90% CI) probability of BOR being CR or PR vs. W17 Cmin (PK/FAS2)**



The model was log(p/(1-p)) = Cmin, where p is the probability of BOR being CR or PR.
Source: Figure HAQ_2-10a_W17.

Although a negative trend was observed in the logistic regression using DI (dose intensity)/FAS (full analysis set) (Figure 2-3), there is no statistically significant effect (p=0.393, Table 2-4) of AUC on the probability of CR/PR. In addition, the odds ratio (90% CI) is 0.998 (0.993, 1.002) for every 1,000 ng*hr/mL per day increase in AUC.

Figure 2-3 **Estimated mean (90% CI) probability of BOR being CR or PR vs. simulated average AUC (DI/FAS)**



The model was log(p/(1-p)) = simulated average AUC, where p is the probability of BOR being CR or PR.
Source: Figure HAQ_2-10a_AUC.

2.3 APPLICANT'S CONCLUSIONS

The logistic regression analysis of grade 3 or 4 CK elevations vs. C1D15 AUC, C1D15 C_{max}, and C2D1 C_{min} showed a positive relationship between all three measures of sonidegib exposure and grade 3 or 4 CK elevation. In addition to C2D1 C_{min}, sex was identified as a risk factor for grade 3 or 4 CK elevation with a lower risk for female patients than for males.

Efficacy of sonidegib in advanced BCC has been shown for both 200 mg qd and 800 mg qd in the pivotal Phase-II study A2201. The ORR (95% CI) was similar between the two dose groups:

41.8% (30.8, 53.4%) for 200 mg and 32.5% (25.1, 40.5%) for 800 mg based on FAS. The logistic regression analysis of objective response (CR or PR) vs. W5 Cmin…did not show a relationship between exposure and efficacy. This indicates a robust response rate across the observed levels of exposure. The logistic regression results using exposure from W17 Cmin and simulated average AUC have shown no relationship between exposure and efficacy. These results are consistent with the conclusion of robust and comparable response rates across the observed range of exposure based on several pharmacokinetic metrics, and with the similar overall response rate between sonidegib doses of 200 mg qd and 800 mg qd in Study A2201.

Given the similar efficacy of sonidegib 200 mg qd and 800 mg qd and the lack of exposure efficacy relationship resulting from these two doses (i.e. robust efficacy across the exposure), and an association of higher risk of a grade 3 or 4 CK elevation with higher sonidegib exposure, 200 mg qd is the recommended dose for the treatment of advanced BCC.

Reviewer's Comment: *The Applicant's analyses and interpretations are acceptable.*

2 REVIEWER'S ANALYSES

3.1 INTRODUCTION

The Applicant conducted a population PK analysis that produced a full model that did not converge and that was overparameterized. An information request (#11, 21 January 2015) was sent to the Applicant to provide a population PK model of successful convergence, which can be potentially achieved by using a simplified error structure, for the assessment of covariate effects on drug exposure. Alternatively, the Applicant could use a stepwise approach including procedures of forward selection and backward elimination for the development of a final population PK model.

The Applicant also conducted exploratory E-R analyses between the observed sonidegib minimal concentrations measured at week 5 and the primary endpoint of ORR in the registration trial and the development of grade 3 or 4 CK elevation in the safety dataset. An information request (#11, 21 January 2015) was sent to the Applicant to provide similar analyses for probability of best overall response using week 17 minimal concentrations and simulated average AUC adjusted by dose intensity before the event of best overall response (dose intensity: total dose up to an event divided by time).

3.2 OBJECTIVES

The objectives of the reviewer's analyses were:

- To explore the E-R relationships for the primary endpoint of ORR at two different time points in the registration trial for the proposed patient population;
- To explore E-R relationships for grade 3 or 4 CK elevation in the safety population; and
- To evaluate the population PK model for successful convergence.

3.3 METHODS

Exposure-Safety Relationships

E-R analyses were conducted, using the observed sonidegib C_{min} measured on Week 5 as a measure of sonidegib systemic exposure, to determine the mean probability of grade 3 or 4 CK elevation in 310 patients enrolled into Study A2201 (n=218), X2101 (n=73) and X1101 (n=19).

Logistic regression analyses were conducted using this data. A generalized linear model was fit to identify the effects of baseline age, baseline weight, sex and race on the E-R relationship. No covariates affected exposure-safety relationship, but sex was identified as a significant covariate. Subsequent E-R analyses were conducted using the observed sonidegib C_{min} measured on Week 5 as a measure of sonidegib systemic exposure, to determine the mean probability of grade 3 or CK elevation in men and women separately. Men appear to have higher baseline mean probability of grade 3 or 4 CK elevation compared to women

Exposure-Efficacy Relationships

E-R analyses were conducted, using the observed minimal sonidegib concentrations measured on Week 5 (n=218) and Week 17 (steady-state, n=183) as a measure of sonidegib systemic exposure, for ORR in patients with BCC randomized to a dose of 200 mg or 800 mg in Study A2101. Logistic regression method was also applied to analyze these relationships. A generalized linear model was fit to identify the effects of baseline age, baseline weight, sex, ECOG performance status and race on the exposure-efficacy relationship. Only ECOG performance status was identified as a significant covariate. Subsequent E-R analyses were conducted using the observed sonidegib C_{min} measured on Week 5 and Week 17 as a measure of sonidegib systemic exposure, to determine the mean probability of an overall response in subjects with an ECOG performance of 0 and in subjects with an ECOG performance status of 1 or 2 separately. Patients with a poorer performance status (ECOG 1 or 2) have a lower baseline probability of an objective response compared to patients with good performance status (ECOG 0).

Population Pharmacokinetic

The population dataset and revised control stream (run16.mod) provided by the Applicant were run using NONMEM 7.2. FDA made changes to the time variable, the table block and the theta block to make these items compatible with xpose library in R. The output generated by NONMEM was subsequently run in R to generate the diagnostic plots and tabular summaries of the eta, parameters and covariates.

3.3.1 Datasets

The datasets used in these analyses are summarized in **Table 6**.

Table 6. Analysis datasets

Dataset description	Name	Link to EDR
Population Pharmacokinetic	Poppksubmission2csv	\\cdsesub1\evsprod\nda205266\0018\m5\datasets\lde225a-poppk\analysis\poppksubmission2csv.txt
Exposure – Safety	adpkck	\\cdsesub1\evsprod\nda205266\0000\m5\datasets\lde225ptscppkck\analysis\adam\datasets\adpkck.xpt
Exposure - Efficacy	adpkeff	\\cdsesub1\evsprod\nda205266\0000\m5\datasets\lde225ptscppkeff\analysis\adam\datasets\adpkeff.xpt

3.3.2 Software

R Version 2.14.0 and NONMEM 7.2

3.4 RESULTS

Refer to Key Review Questions for results from population and E-R analyses.

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
run2.mod	Population pharmacokinetic control stream	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER Safety.R	R code for logistic regression for grade 3 or 4 CK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER Safety_Covariates.R	R code for logistic regression for grade 3 or 4 CK for men and women	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER W17ORR	R code for logistic regression for ORR at week 17	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER W17ORR_Covariates.R	R code for logistic regression for ORR at week 17 for ECOG 0 vs ECOG 1 or 2	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER W5ORR	R code for logistic regression for ORR at week 5	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS
Sonidegib ER W5ORR_Covariates.R	R code for logistic regression for ORR at week 5 for ECOG 0 vs ECOG 1 or 2	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Sonidegib_NDA205266_SSS

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205266
Drug Name	Sonidegib (LDE255)
Proposed Indication	Treatment locally advanced (b) (4) basal cell carcinoma
Clinical Division	DOP2
PBPK Consult request	Stacy S. Shord, PharmD
Primary PBPK Reviewer	Ping Zhao, PhD
Secondary PBPK Reviewer	Yaning Wang, PhD
Sponsor	Novartis

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1. Objectives

The main objectives of this review are to 1) evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the drug-drug interaction (DDI) potential of sonidegib as a victim of the CYP3A metabolic pathway, and 2) understand factors that impact sonidegib oral absorption using PBPK.

To support its conclusions the sponsor provided the following PBPK modeling and simulation reports and updates:

1. Simcyp predictions of the interaction of sonidegib with ketoconazole or rifampin [1]
2. Response to FDA Information Request 1 (Clinical Pharmacology) received 07-Nov-2014 [2]
3. Simcyp predictions of the interaction of sonidegib with erythromycin, rifampin, or efavirenz using the cancer patient Simcyp model for sonidegib [3]

2. Background

2.1. Regulatory History on PBPK Submission

Smoothened (Smo) is a G protein-coupled receptor-like molecule that positively regulates Hedgehog (Hh) signal transduction pathway. Sonidegib (LDE225) is a potent, selective, and orally bioavailable small molecule inhibitor of the Hh signaling pathway, which acts by binding to Smo. The intended dosing regimen for sonidegib is 200 mg once daily (q.d.) [4].

A PBPK model of sonidegib was developed by the sponsor to simulate the drug-drug interaction (DDI) trials of sonidegib, given a single 800 mg dose on day 5, with multiple dosing of cytochrome P450 (CYP) 3A modulators in healthy subjects [5]. The modulators used were a strong CYP3A inhibitor ketoconazole 200 mg twice daily, b.i.d., or a strong CYP3A inducer rifampin 600 mg q.d. for 14 days. The predicted DDI magnitude of sonidegib (800 mg dose) was similar to the observed magnitude in the presence of ketoconazole (e.g., predicted vs observed fold increase in sonidegib area under the curve (AUC) 2.4 vs 2.3, respectively) or rifampin (e.g., predicted vs observed percent decrease of sonidegib AUC 66% vs 72%, respectively) [5]. Sponsor conducted additional simulations to predict the same DDI magnitude of sonidegib when the drug is dosed at clinical dose of 200 mg in healthy subjects. Therefore, sponsor stated that DDI study A2108 [5] was "expected to provide adequate information on the need for dose adjustment in patients concomitantly taking strong CYP3A inhibitors or inducers with the recommended dose of 200 mg", and administration of sonidegib with agents that are strong CYP3A4 inhibitors or strong CYP3A inducers should be avoided.

On Nov 7, 2014, the FDA requested sponsor to consider PK difference between healthy subjects and cancer patients in their PBPK modeling and to simulate the effect of ketoconazole on steady state sonidegib exposure when sonidegib is administered at 200 mg q.d. or 200 mg once every other day (q.o.d.) in cancer patients (11072014IR, Appendix 6.2.1). On March 6, 2015, a second PBPK information request was sent to the sponsor to conduct additional simulations of untested DDI scenarios (03062015IR, Appendix 6.2.2). Sponsor submitted model files and response to these information requests on Nov 19, 2014 [2] and March 13, 2015 [3], respectively.

This review evaluates the adequacy of sponsor's sonidegib PBPK model to predict the effect of CYP3A modulators on steady state PK of sonidegib. Additional modeling and simulations were conducted to understand the factors that impact sonidegib oral absorption, which may significantly contribute to high intersubject variability in sonidegib exposure in cancer patients.

3. Methods

3.1. Model Development

A population based PBPK software Simcyp® (V13, release 1, release 2, or V14 release 1, Sheffield, UK) [6,7] was used by the sponsor to develop a PBPK model for sonidegib. Parameters and their sources for sonidegib are summarized in **Appendix Tables 1 -3**. Unless otherwise stated, all simulations were conducted in Software's built-in "Sim-Healthy volunteer" population and ten trials of 10 subjects were simulated for each dosing regimen (age range 20-50 years, female ratio 0.5).

Perpetrator models for ketoconazole "Sim-Ketoconazole 200 mg BID.cmp" and rifampin "Sim-Rifampicin.cmp" from the software's drug model library (v13.1) were directly used in original PBPK report [1]. Models for ketoconazole "Sim-Ketoconazole 200 mg BID.cmp" (V13.1), erythromycin "Sim-Erythromycin.cmp" (V13.2), and efavirenz "Sim-Efavirenz.cmp" (V14.1) were directly used in additional simulations in cancer patients [2,3]. To simulate the effect of rifampin on sonidegib PK in cancer patients [3], sponsor used both the default rifampin model "Sim-rifampicin.cmp" (V13.2, with CYP3A maximal induction effect $I_{nd,max}$=8) and a modified model with a higher $I_{nd,max}$ of 16, which was requested by the FDA in 03062015IR (Section 6.2.2). Simulated sonidegib PK parameters across different software versions under the same condition are consistent (data not shown).

Simulations were conducted for the following clinical trials:

Study X2101: Dose-escalation study of oral sonidegib in patients with advanced solid tumors (200 and 800 mg single and multiple doses) [8]

Study A2114: Relative bioavailability study and effect of food in healthy subjects (fasted data from 200 and 800 mg single doses of CSF formulation) [9]

Study A2110: Radiolabeled human mass balance study in healthy subjects (800 mg single oral dose) [10]

Study A2108: Clinical drug-drug interaction studies of the effect of strong CYP3A inhibitor or inducer (ketoconazole and rifampin) on single oral dose of 800 mg sonidegib [5].

Of note, study A2108 is considered an independent verification data set, because the effect of CYP modulators was not considered during model development process. In the model, value of fractional metabolism by CYP3A ($f_{m,CYP3A}$) was set at 0.75 according to human mass balance study and in vitro CYP phenotyping study (% hepatic clearance, CL, **Appendix Table 2**). Results from mass balance study show that sonidegib is primarily metabolized in humans, with 25% of metabolism via amide hydrolysis (non CYP pathway) [1, 10]. In human liver microsomes, CYP3A inhibitor ketoconazole or azamulin inhibited total sonidegib metabolism to 89-96% [1].

In response to FDA's 11072014IR [2], sponsor refined the PBPK model (referred below as PBPK model for healthy subjects) by reducing hepatic intrinsic clearance (CL_{int}) without changing the contribution of CYP3A (**Appendix Table 2**, second values of $CL_{int,CYP3A4}$ and liver microsomal CL_{int}) to account for lower apparent clearance of sonidegib observed in cancer patients (referred below as PBPK model for patients).

3.2. Model Application

Sponsor used sonidegib models to predict the effect of CYP3A modulators for scenarios that have not been tested through clinical trials (**Table 1**).

Table 1. Simulation study design for drug-drug interaction scenarios with sonidegib as CYP3A substrate

Simulation	Modulator name (type)	Sonidegib dosing	Modulator dosing	Reference
Model for healthy subjects				
1	Ketoconazole (strong inhibitor)	200 mg single dose on day 5	200 mg b.i.d. for 14 days	[1]
2	Rifampin (strong inducer)	200 mg single dose on day 5	600 mg q.d. for 14 days	[1]
Model for patients				
3	Ketoconazole (strong inhibitor)	800 mg single dose on day 5	200 mg b.i.d. for 14 days	[2]
4	Rifampin (strong inducer)	800 mg single dose on day 5	600 mg q.d. for 14 days	[2]
5	Ketoconazole (strong inhibitor)	200 mg q.d., 120 days	200 mg q.d., 120 days	[2]
6	Ketoconazole (strong inhibitor)	200 mg q.o.d., 120 days	200 mg q.d., 120 days	[2]
7	Ketoconazole (strong inhibitor)	200 mg q.d., 133 days	200 mg q.d., 14 days, starting on day 120	[2]
8	Ketoconazole (strong inhibitor)	200 mg q.o.d., 133 days	200 mg q.d., 14 days, starting on day 120	[2]
9	Erythromycin (moderate inhibitor) [a]	200 mg single dose on day 5	500 mg four times a day (q.i.d.) for 14 days	[3]
10	Erythromycin (moderate inhibitor) [a]	200 mg q.d., 120 days	500 mg q.i.d. for 120 days	[3]
11	Erythromycin (moderate inhibitor) [a]	200 mg q.d., 133 days	500 mg q.i.d., 14 days, starting on day 120	[3]
12	Rifampin (strong CYP3A inducer) [a,b]	200 mg single dose on day 5	600 mg q.d. for 14 days	[3]
13	Rifampin (strong CYP3A inducer) [a,b]	200 mg q.d., 120 days	600 mg q.d. for 120 days	[3]
14	Efavirenz (moderate CYP3A inducer) [c]	200 mg single dose on day 5	600 mg q.d. for 14 days	[3]
15	Efavirenz (moderate CYP3A inducer) [c]	200 mg q.d., 120 days	600 mg q.d. for 120 days	[3]
16	Efavirenz (moderate CYP3A inducer) [c]	200 mg q.d., 133 days	600 mg q.d., 14 days, starting on day 120	[3]

[a] Simcyp version 13 release 2.

[b] Simulations using induction of CYP3A4 $I_{nd,max}$ of 8 (default) and 16 (updated in Simcyp version 14) for rifampin were separately conducted

[c] Simcyp Version 14.1 (Appendix Table 3)

3.3. Modeling of Oral Absorption of Sonidegib

Sponsor's PBPK models assumed first-order absorption for sonidegib (**Appendix Table 2**). The FDA reviewer expanded the model for healthy subjects by using the software's "Advanced Dissolution, Absorption, and Metabolism (ADAM)" model (version 13.2). Input parameters describing various processes responsible for oral absorption are summarized in **Appendix Table 3**, including an intrinsic water solubility of (b) (4) mg/mL [11]. The following scenarios were explored using this "ADAM model for healthy subjects":

1. Single oral dose of sonidegib at 200, 800, or 1200 mg in fasted healthy subjects.

2. Single oral dose of sonidegib at 800 mg in fed healthy subjects. Software's "Sim-Healthy Volunteers" population model under "fed" condition was used. Gastric emptying time of 1 hour (default, vs 0.5 hr under fasted) and 4 hours were simulated.

The simulation duration was 2106 hours (84 days) or 336 hours (14 days).

4. Results

4.1. Can the Sonidegib PBPK Model Predict the Effect of CYP3A Modulation on Sonidegib Exposure in Healthy Subjects?

Yes. Two factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for sonidegib) and capability of the model to predict the PK profile under different dosing regimens.

In sonidegib PBPK model, organ intrinsic clearance was optimized using single dose sonidegib PK data in healthy subjects (Retrograde analysis, **Appendix Table 2**). The model reasonably describes the observed PK profiles of a single dose of sonidegib in healthy subjects (**Appendix Figure 1**, Study A2114, A2108 (control arm of the DDI trial)). The simulated mean PK profile for a single 800 mg dose of sonidegib appears to over-predict the observed data in mass balance study in healthy subjects (Study A2110). The observed differences in sonidegib PK between A2110 and other studies in healthy subjects were due to differences in capsule formulations [4].

The $f_{m,CYP3A}$ in the sonidegib PBPK model is 0.75 (**Appendix Table 2**). This is verified by clinical DDI data using ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) [5]. The PBPK model reasonably predicts mean AUC ratio (AUCR) and maximal concentration (C_{max}) ratio ($C_{max}R$) by ketoconazole and rifampin (**Table 2**).

Table 2. Comparison of observed and PBPK simulated PK parameters of sonidegib (800 mg single oral dose) in the presence or absence of ketoconazole or rifampin in healthy subjects

	Sonidegib alone		**Sonidegib with ketoconazole**		**Sonidegib with rifampin**	
Geometric mean values	Observed	Simulated	Observed	Simulated	Observed	Simulated
AUC $_{0\text{-}240hr}$ (ng/ml h)	5620	5863	12700	13827	1550	1982
Cmax (ng/mL)	212	239	316	356	98	136
AUCR (90% confidence interval)	NA	NA	2.25 (1.78, 2.86)	2.37 (2.26, 2.50)	0.28 (0.22, 0.35)	0.34 (0.32, 0.37)
CmaxR (90% confidence interval)	NA	NA	1.49 (1.11, 1.99)	1.49 (1.45, 1.53)	0.46 (0.35, 0.61)	0.57 (0.54, 0.60)

NA, not applicable. Source: Table 6-4 of [1]. Observed and PBPK simulated PK profiles can be found in ***Appendix Figure 2***

4.2. Can the PBPK Predictions be Used to Support Dose Recommendations of Sonidegib in Cancer Patients Concomitantly Taking a CYP3A Modulator?

Yes. Both the PBPK model for healthy subjects and the PBPK model for cancer patients are considered adequate in predicting the effect of CYP3A modulators on sonidegib PK.

The simulated PK profiles using the PBPK model for healthy subjects tend to under predict the observed data in cancer patients, especially after multiple dosing (**Appendix Figures 1 and 3**, with observed data

in patients from Study X2101 in **Appendix Figure 3**). Simulations using the PBPK model for cancer patients better predicted the observed data in cancer patients (**Appendix Figures 4-5**).

The PBPK model for cancer patients was modified by reducing total hepatic CL (Methods and **Appendix Table 2**). As shown in **Table 3**, the predicted DDI magnitudes using the model for cancer patients are smaller than the predictions using the PBPK model for healthy subjects.

Table 3. PBPK predicted geometric mean ratios (AUC and C_{max}) of sonidegib using models for healthy subjects and cancer patients.

	Sonidegib with ketoconazole		**Sonidegib with rifampin**	
	Model for healthy subjects[a]	Model for cancer patients[a]	Model for healthy subjects[a]	Model for cancer patients[a]
Geometric AUCR	2.37	1.85 [b]	0.34	0.41 [b]
Geometric C_{max}R	1.49	1.29 [b]	0.57	0.67 [b]

[a] *See Methods and **Appendix Table 2**.* [b] *Simulation number 3 and 4, **Table 1**. Source: ref [2]*

Of note, alternative model structures for patients could also account for the observed sonidegib PK differences between healthy subjects and cancer patients. One alternative is the model with increased fraction absorbed (f_a) in patients without a decrease in hepatic CL. Sonidegib PK is sensitive to f_a. Both formulation and food intake can significantly affect sonidegib exposure [4] (More discussion in **4.5** below). Difference in fa between patients and healthy subjects may exist. However, ascribing PK differences between healthy subjects and patients to hepatic CL appears plausible. If volume of distribution does not differ between healthy subjects and cancer patients, a decreased hepatic CL in cancer patients results in increased elimination half-life. In healthy subjects, elimination half-life was approximately 10-days [9], whereas elimination half-life in cancer patients was estimated to be 28 days (see Question based review document).

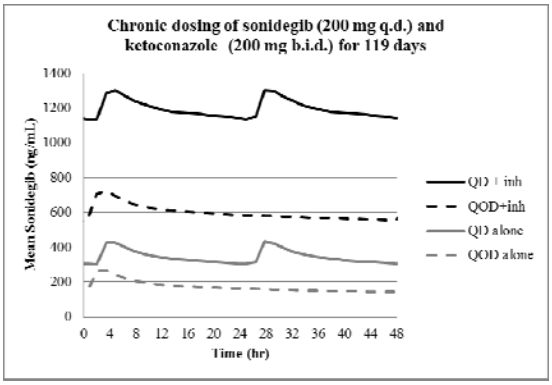
4.3. What Are the Effects of CYP3A Inhibitors on Steady State Sonidegib in Cancer Patients?

Sponsor used the PBPK model for cancer patients to predict the effect of a strong or a moderate CYP3A inhibitor (ketoconazole and erythromycin, respectively) on steady state exposure of sonidegib (Simulation #5-11, **Table 1**).

Under the condition that sonidegib (200 mg q.d.) and ketoconazole (200 mg b.i.d.) are co-administered chronically (119 days, **Figure 1**), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) are 3.0 and 3.5-fold higher, respectively, than those for sonidegib alone. When sonidegib is dosed less frequently (200 mg q.o.d.), the predicted mean steady state sonidegib C_{max} and AUC (0-48 hour) are 2.6- and 3.5-fold higher, respectively, than those for sonidegib q.o.d. alone. The predicted mean steady-state C_{max} and AUC (0-48 hours) values for 200 mg q.o.d. sonidegib and 200 mg b.i.d. ketoconazole are approximately 70% higher than those for 200 mg q.d. sonidegib alone (Ratios of 1.67 and 1.74 for Cmax and AUC, respectively, reviewer's calculation on file[1]).

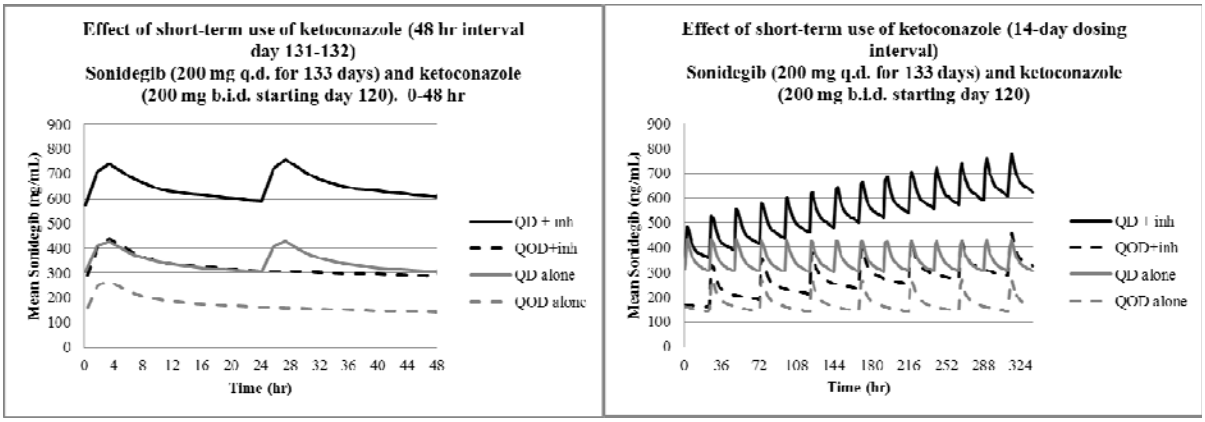
[1] AUC (0-48 hours) was calculated for 200 mg q.d. sonidegib alone by multiplying AUC (0-24 hours) by 2.

Figure 1. PBPK simulation of the effect of chronic use of ketoconazole on steady-state sonidegib exposure.



Under the condition that ketoconazole is introduced for a shorter duration (14-days, starting on day 120) when sonidegib has reached steady state after 200 mg q.d. (total 133 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) on day 133 are 1.8- and 2.0-fold higher, respectively, than those for sonidegib alone. When sonidegib is dosed less frequently (200 mg q.o.d. for 133 days), the predicted mean steady state sonidegib C_{max} and AUC (0-48 hour) are 1.6- and 1.9-fold higher, respectively, than those for sonidegib alone. The predicted mean steady-state sonidegib C_{max} and AUC (0-48 hours) values for 200 mg q.o.d. sonidegib coadministered with 200 mg b.i.d. ketoconazole were similar to those for 200 mg q.d. sonidegib alone (Ratio of 1.02 and 0.94 Cmax and AUC, respectively, reviewer's calculation on file).

Figure 2. PBPK simulation of the effect of short-term ketoconazole on steady state sonidegib exposure.



Under the condition that sonidegib (200 mg q.d.) and erythromycin (500 mg four times a day, q.i.d.) are co-administered chronically (119 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) are 2.4- and 2.8-fold higher, respectively, than those for sonidegib alone. Under the condition that erythromycin is introduced for a shorter duration (14-days, starting on day 120) when sonidegib has reached steady state after 200 mg q.d. (total 133 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) on day 133 are 1.6- and 1.8-fold higher, respectively, than those for sonidegib alone (Trials 2-3, **Appendix Table 4**).

4.4. What Are the Effects of CYP3A Inducers on Steady State Sonidegib in Cancer Patients?

Sponsor used the PBPK model for cancer patients to predict the effect of a strong or a moderate CYP3A inducers (rifampin or efavirenz, respectively) on steady-state exposure of sonidegib in patients taking sonidegib 200 mg q.d. (Simulation numbers #12-16, **Table 1**).

Under the condition that sonidegib and rifampin (600 mg q.d.) are co-administered chronically (119 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) are 64% and 74% lower (C_{max} and AUC ratios of 0.36 and 0.26), respectively, than those for sonidegib alone (Trial 5, **Appendix Table 4**). To address the concern of potential under prediction of the effect of rifampin using default rifampin model, Xu et al proposed the use of a higher CYP3A $I_{nd,max}$ (11.5, versus the default value of 8) in rifampin model [15]. The FDA reviewer also requested sponsor to simulate the effect of rifampin on sonidegib PK using a rifampin model with a 2-fold higher $I_{nd,max}$ of 16, a value suggested recently by the software provider, to explore the "worst case scenario". The predicted C_{max} and AUC ratios using rifampin model with 2-fold higher $I_{nd,max}$ are 0.20 and 0.12, respectively (Trial 7, **Appendix Table 4**). Additional research may be needed to optimize $I_{nd,max}$ of default rifampin model in SimCYP V13.2.

Under the condition that sonidegib and efavirenz (600 mg q.d.) are co-administered chronically (119 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) are 60% and 69% lower (C_{max} and AUC ratios of 0.40 and 0.31), respectively, than those for sonidegib alone (Trial 9, **Appendix Table 4**). Under the condition that efavirenz is introduced for a shorter duration (14-days, starting on day 120) when sonidegib has reached steady state after 200 mg q.d. (total 133 days), the predicted mean steady state sonidegib C_{max} and AUC (0-24 hour) are 49% and 56% lower (C_{max} and AUC ratios of 0.51 and 0.44), respectively, than those for sonidegib alone (Trial 10, **Appendix Table 4**).

4.5. Additional Modeling and Simulations to Evaluate Sonidegib Oral Absorption

The observed sonidegib plasma concentrations in cancer patients at steady state are highly variable (**Appendix Figure 6**, [16]). (b) (4) oral absorption (b) (4) may be significantly influenced by factors including formulation, changes in gastrointestinal physiology, and food intake. In healthy subjects taking a single dose of sonidegib under fasted condition, sonidegib exposure increased less than dose proportional (**Appendix Table 5**, [9]). At single dose of 800 mg, sonidegib exposure in healthy subjects taking a high fat meal was approximately 7-fold higher than that in subjects under fasting condition [9].

To gain insight into the effect of low solubility and moderate permeability on oral drug absorption of sonidegib in humans, the FDA reviewer expanded sponsor's PBPK model for healthy subjects by considering mechanistic oral drug absorption processes (Software V13.2, ADAM parameters in **Appendix Table 3**). The mechanistic absorption model included a relatively low aqueous solubility (intrinsic solubility of (b) (4) mg/mL, [11]). Permeability parameters and other software default ADAM parameters were kept the same.

The reviewer used the PBPK model with mechanistic absorption (ADAM model for healthy subjects) to simulate single dose sonidegib PK in healthy subjects according to Study 2114 [9]. **Table 4** shows that the ADAM model for healthy subjects predicts nonlinear PK of sonidegib from 200 mg to 1200 mg. (b) (4) Using the ADAM model for healthy subjects, the predicted mean apparent f_a values are 0.3, 0.13, and 0.10 for 200 mg, 800 mg, and 1200 mg, respectively. The values for 200 mg and 800 mg are comparable to those used by sponsor assuming first order absorption (**Appendix Table 2**). Limited sensitivity analyses were conducted. The model appears to be sensitive to apparent permeability and precipitation rate constant across the three single doses. The

model does not seem to be sensitive to super-saturation ratio or particle radius (data not shown). Therefore, the set of ADAM parameters in **Appendix Table 3** appears to be reasonable in describing the dose-dependent oral absorption of sonidegib, and sonidegib PK is considered to be sensitive to fa.

The reviewer used the ADAM model for healthy subjects to simulate effect of food on sonidegib exposure (**Table 4**). Two virtual healthy volunteer populations under fed conditions were tested. The difference between the two populations was gastric emptying time. One simulation used 1 hour gastric emptying time (default, Sim (1) in **Table 4**) and the other simulation used a 4-hour gastric emptying time to approximate physiology under a high fat meal[2] (Sim (2) in **Table 4**). Other parameters remain the same. When gastric emptying time increases from fasted condition (0.4 hour) to 1 hour and to 4 hours, the predicted magnitudes of exposure increase from fasted condition are 2.7 and 3.6-fold for Sim (1) and Sim (2), respectively; whereas the observed increase was 6.9-fold [9] (ratios calculated using AUC 85d data in **Table 4**). The predicted time to reach C_{max} (T_{max}) increases from 1.1 (fasted) to 1.9 (Sim (1)) and 7.0 (Sim (2)) hours; whereas the observed T_{max} values are 2.1 and 5.0 for fasted and fed conditions, respectively (**Table 4**).

The additional simulations using the ADAM model for healthy subjects suggest that oral absorption of sonidegib may be highly sensitive to changes in gastrointestinal physiology caused by food intake, (b) (4) Given the short review timeline and the lack of established confidence in using PBPK to quantitatively predict formulation effect or food effect, the reviewer did not further optimize mechanistic absorption model of sonidegib. These additional analyses of the factors affecting oral absorption of sonidegib should be considered exploratory.

[2] Personal communications with Dr. Christian Wagner

Table 4. PBPK predicted and observed AUC and C_{max} of sonidegib in healthy subjects using ADAM model for healthy subjects

Source data in **Appendix Tables 5 and 6**

		Mean PK Parameters				Ratio (Sim/Obs)		
Treatment		AUC 85d (ng*hr/mL)	AUC 14d (ng*h/mL)	Cmax (ng/mL)	Tmax [a] (hr)	AUC 85d (ng*hr/mL)	AUC 14d (ng*h/mL)	Cmax (ng/mL)
Fasted condition								
200 mg	Sim	5291	4157	136	1.1	1.6	1.6	1.3
	Obs	3327	2614	104	2.0			
800 mg	Sim	9066	7165	283	1.1	0.7	1.0	1.1
	Obs	12088	7299	258	2.1			
1200 mg	Sim	NA	7981	318	1.1	NC	1.0	1.2
	Obs	NA	7778	270	2.0			
Fed condition								
800 mg	Sim (1)	24459	NI	533	1.9	0.3		0.3
	Sim (2)	32973	NI	478	7.0	0.4		0.3
	Obs	83363	49785	1726	5.0			

Sim, simulated; Obs, observed; NC, not calculated; NI, not included.

5. Conclusion

Sponsor's PBPK model of sonidegib is considered sufficient to predict steady state sonidegib PK in patients co-administered CYP3A modulators with sonidegib. The effects of chronic use and short-term use of a strong inhibitor ketoconazole were predicted to increase sonidegib exposure by approximately 3.5-fold and 2.0-fold, respectively; the effects of chronic use and short-term use of moderate inhibitor erythromycin were predicted to increase sonidegib exposure by approximately 2.8-fold and 1.8-fold, respectively; the effects of chronic use of strong inducer rifampin were predicted to decrease sonidegib exposure by more than 74%; and the effects of chronic use and short-term use of moderate inducer efavirenz were predicted to decrease sonidegib exposure by approximately 69% and 56%, respectively.

The reviewer acknowledges scientific discussions with Dr. Masanobu Sato and Dr. Christian Wagner.

6. Appendices

6.1. Abbreviations

ADAM, Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; b.i.d., twice daily dosing; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; F, bioavailability; f_a, fraction absorbed; Fg, fraction that escapes intestinal metabolism; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; f_{up}, fraction unbound in plasma; $f_{u,gut}$, apparent unbound fraction in enterocytes; GI: gastrointestinal; Hh, Hedgehog; γ, Hill coefficient; $I_{nd,max}$, maximal fold induction; $I_{nd,50}$, concentration causing half-maximal fold induction; k_a, first order absorption rate constant; K_i, reversible inhibition constant; $LogP_{o:w}$, logarithm of the octanol-water partition coefficient; NA, not applicable; ND, not determined; NDA: new drug application; NI: Not included; P_{app}, apparent passive permeability; $P_{eff,man}$, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; q.i.d., four times a day dosing; q.o.d., once every other day; Q_{gut}, a hypothetical flow term for the intestine absorption model; Smo, Smoothened; T_{max}: time at maximal concentration in plasma; T_{LAG}: lag time; $V_{d,ss}$, volume of distribution at steady state.

6.2. Information Request

6.2.1. Clinical Pharmacology Nov 07, 2014 (11072014IR)

We conducted an initial review of the physiologically based pharmacokinetic (PBPK) study report (Study 1400133) entitled "Simcyp predictions of the interaction of LDE225 with ketoconazole or rifampin". It appears that sonidegib exposure is generally higher in cancer patients as compared to healthy subjects and that the sonidegib PBPK model has been developed primarily using pharmacokinetic (PK) data of healthy subjects. Figures 7-2 and 7-4 found in this study report show that the model is not able to describe sonidegib PK profiles in cancer patients on day 15.

a. Submit your justification formally to the NDA whether the current data and the PBPK model allow prediction of the magnitude of sonidegib exposure change by concomitant use of strong CYP3A modulators in cancer patients, especially if higher sonidegib exposure observed in cancer patients is primarily due to lower hepatic metabolism.

b. Submit the following simulations, including the study reports, model files and other related excel files as listed below, formally to the NDA.

Simulate the effect of strong CYP3A inhibitor ketoconazole administered at a dose of 200 mg twice daily (b.i.d.) on steady state sonidegib PK (C_{max} and AUC within dosing interval) when sonidegib is administered at a dose of

i. 200 mg once daily (q.d.)

ii. 200 mg once every other day (q.o.d.)

Provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

6.2.2. Clinical Pharmacology March 06, 2015 (03062015IR)

Submit the following simulations, including the study report or summary, model files and other related excel files as listed below, formally to the NDA.

i. Simulate the effect of a moderate CYP3A inhibitor (such as aprepitant or erythromycin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Effects of both chronic use and short term use of a moderate inhibitor on steady state sonidegib pharmacokinetics should be simulated. Novartis can apply the strategy for the effect of ketoconazole presented in your response to FDA's information request (Response to FDA Information Request 1 (Clinical Pharmacology) received 07-Nov-2014).

ii. Simulate the effect of a strong CYP3A inducer (such as rifampin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Use both the library rifampin model and a modified rifampin model according to Simcyp's recent update on the drug's induction potency. Update your simulation in Study 1400133 using the modified rifampin model.

iii. Simulate the effect of a moderate CYP3A inducer (such as efavirenz) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose.

Provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

6.3. Appendix Tables and Figures

Appendix Table 1. Physicochemical parameters of sonidegib PBPK model (Source: Table 6-1 of ref [1])

Parameter	Value
Physical chemistry	
Molecular Weight (g/mol)	485.5
$logP_{o\,w}$	4.26
pKa	4.2
Compound type	Monoprotic base

Appendix Table 2. ADME parameters of sonidegib PBPK model (Source: Table 6-1 of ref [1])

Parameter	Value	Reference/comments
Absorption		
Model used	First order absorption	
f_a	0.3 (200 mg) 0.15 (800 mg)	*Two values of fa were based on fitting of the actual clinical pharmacokinetic data of the two doses*
k_a (h^{-1})	0.57	*User defined*
Lag time (h)	1	*User defined*
Q_{gut} (L/h)	*9.086*	*Simcyp predicted*
$f_{u,gut}$	1	default
Peff,man (x 10^{-4} cm/s)	*2.00*	*Simcyp predicted*
Papp Caco-2 (10^{-6} cm/s)	4.58	A:B (passive+active) [12]
Papp Caco-2 reference (10^{-6} cm/s)	15.7	Ref compound: propranolol, A:B (passive+active) [12]
Distribution		
Model used	Full PBPK	
$V_{d,ss}$ (L/kg)	*22.6*	Predicted according to [13] (Software Method 2)
B/P	0.55	1-hematocrit, "little or no affinity to blood cells"[5]
f_{up}	0.025	[5]
Elimination		
Model used	Enzyme kinetics/ Retrograde model	
% hepatic CL	75% CYP3A4	See discussion in Methods. First value in healthy volunteers, second value in cancer patients assuming the same % hepatic CL by CYP3A [2]
Resultant $CL_{int,\,CYP3A4}$ (µL/min/pmol CYP)	0.687, 0.417	
Resultant HLM CL_{int} (µL/min/mg protein)	31.38, 19.06	
CLR(L/h)	0	[10]
Interaction		
CYP2B6		
$K_{i,u}$ (µM)	0.007	[14]
CYP2C9		
$K_{i,u}$ (µM)	0.237	[14]

Abbreviations used in this table can be found in 5.1 above.

Appendix Table 3. Mechanistic absorption parameters of sonidegib PBPK model (FDA analysis)

Parameter	Value	Reference/comments
Model used	ADAM model	
$f_{u,gut}$	(b) (4)	Default[a]
Papp Caco-2 (10^{-6} cm/s)		Apical:Basal (A:B) (passive+active) [11] pH 7.4/7.4
Papp Caco-2 reference (10^{-6} cm/s)		Ref compound: propranolol, A:B (passive+active) [12]
Input form	Solid formulation immediate release	
Intrinsic solubility (mg/mL)	(b) (4)	Water solubility [11]
Precipitation rate constant (1/h)		Default[a]
Maximum supersaturation ratio		Default[a]
Dispersion type		Default[a]
Radius (micrometer)		Default[a]
Particle density (g/mL)		Default[a]
Ionized Diffusion coefficient (10^{-4} cm^2/min)		Software predicted
Micelle Diffusion coefficient (10^{-4} cm^2/min)		Software predicted
Diffusion coefficient (10^{-4} cm^2/min)		Software predicted
Effective diffusion layer thickness (micrometer)		Default[a]
Bile Micelle mediated solubilisation		Default[a]
Bile Micelle Partition: Slope		Software predicted
Bile Micelle Partition: Offset		Software predicted

[a] Software default value were kept

Appendix Table 4. Additional PBPK simulated effects of CYP3A modulators on sonidegib (LDE225) PK in patients (Table 3-1, ref [3])

Trial #	Substrate/ Perpetrator	Substrate Dose/Regimen	Perpetrator Dose/Regimen	Substrate PK measurement	Results from Simulation Geometric mean ratio for AUC and Cmax
1	LDE225/ERY	200 mg single dose on day 5	500 mg QID, day 1-14	Day 5, 0-24h (and 0-240h)	1.36, 1.26 (1.70, 1.26)
2	LDE225/ERY	200 mg QD, day 1-120	500 mg QID, day 1-120	Day 120, 0-24h	2.79, 2.43
3	LDE225/ERY	200 mg QD, day 1-133	500 mg QID, day 120-133 (14 days)	Day 133, 0-24h	1.79, 1.64
4	LDE225/RIF (Emax of 8)	200 mg single dose on day 5	600 mg QD, day 1-14	Day 5, 0-24h and 0-240h)	0.57, 0.67 (0.41, 0.67)
5	LDE225/RIF (Emax of 8)	200 mg QD, day 1-120	600 mg QD, day 1-120	Day 120, 0-24h	0.26, 0.36
6	LDE225/RIF (Emax of 16)	200 mg single dose on day 5	600 mg QD, day 1-14	Day 5, 0-24h (and 0-240h)	0.34, 0.46 (0.21, 0.46)
7	LDE225/RIF (Emax of 16)	200 mg QD, day 1-120	600 mg QD, day 1-120	Day 120, 0-24h	0.12, 0.20
8	LDE225/EFV	200 mg single dose on day 5	600 mg QD, day 1-14	Day 5, 0-24h (and 0-240h)	0.63, 0.71 (0.48, 0.71)
9	LDE225/EFV	200 mg QD, day 1-120	600 mg QD, day 1-120	Day 120, 0-24h	0.31, 0.40
10	LDE225/EFV	200 mg QD, day 1-133	600 mg QD, day 120-133	Day 120, 0-24h	0.44, 0.51

Appendix Table 5. Summary of PK parameters for variant C formulation in healthy volunteers [9]

Treatment	Parameter	AUCinf (ng*h/mL)	AUC 85d (ng*hr/mL)	AUC 14d (ng*h/mL)	Cmax (ng/mL)	Tmax (hr)
200 mg fasted	N	11	10	11	12	12
	Mean	3410	3327	2614	104	NA
	Geo-Mean	2627	2481	2056	87	NA
	Median (min, max)	3926 (171, 6241)	3402 (159, 6190)	2782 (159, 5108)	102 (7, 204)	2.0 (1.0, 5.0)
800 mg fasted	N	12	11	12	13	13
	Mean	12545	12088	7299	258	NA
	Geo-Mean	10739	10348	6682	216	NA
	Median (min, max)	8933 (5657, 32498)	8809 (5607, 29677)	6491 (3660, 13708)	204 (71, 575)	2.1 (1.0, 5.0)
800 mg fed	N	12	12	12	12	12
	Mean	86472	83363	49785	1726	NA
	Geo-Mean	79296	77692	47742	1685	NA
	Median (min, max)	75260 (42704, 205378)	74963 (42690, 173890)	46718 (28501, 90734)	1625 (1220, 2390)	5.0 (3.0, 12.0)
1200 mg fasted	N	NA	NA	11	12	12
	Mean	NA	NA	7778	270	NA

	Geo-Mean	NA	NA	7126	251	NA
	Median (min, max)	NA	NA	7021 (3975, 14780)	271 (157, 454)	2.0 (1.1, 3.0)

NA. Not available [9]

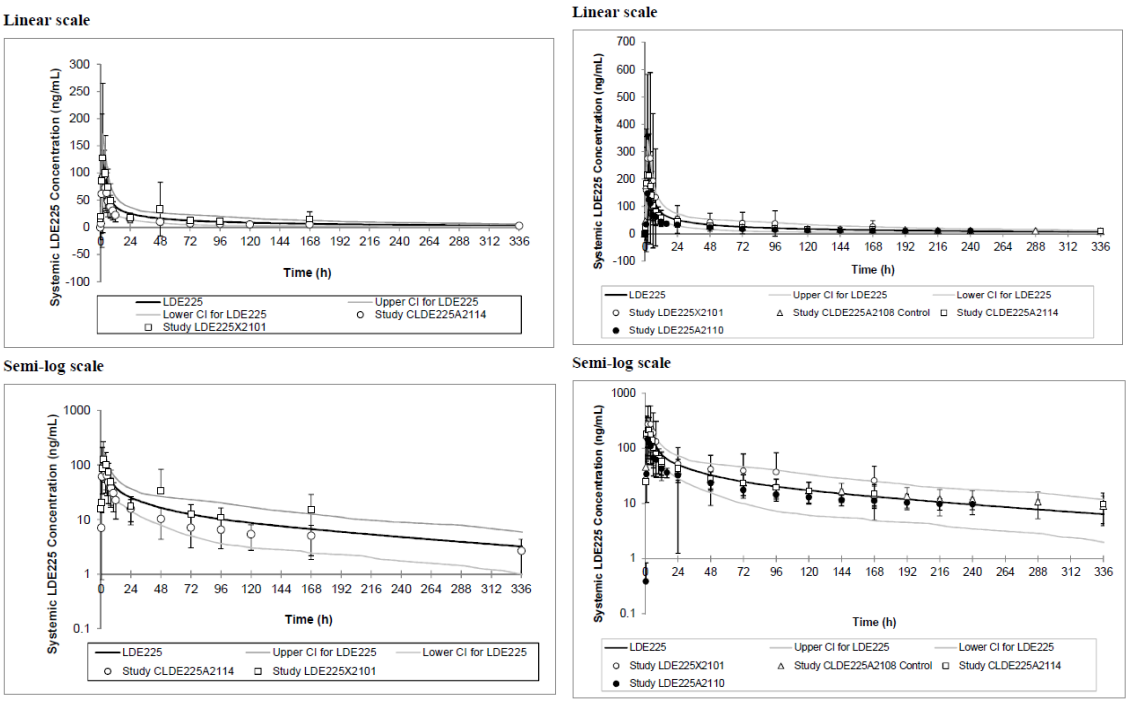
Appendix Table 6. Summary of simulated mean PK parameters using ADAM model for healthy subjects

Treatment	Parameter	AUC 85d (ng*hr/mL)	AUC 14d (ng*h/mL)	Cmax (ng/mL)	Tmax (hr)
200 mg fasted	Mean	5291	4157	136	NA
	Geo-Mean	4648	3675	125	NA
	Median	4598	3493	130	1.1
800 mg fasted	Mean	9066	7165	283	NA
	Geo-Mean	7794	6162	237	NA
	Median	8109	6538	281	1.1
800 mg fed 1[a]	Mean	24459	NI	533	NI
	Geo-Mean	21682	NI	495	NI
	Median	22668	NI	491	1.9
800 mg fed 2[b]	Mean	32973	NI	478	NI
	Geo-Mean	29565	NI	454	NI
	Median	31152	NI	455	7.0
1200 mg fasted	Mean	NA	7981	318	NI
	Geo-Mean	NA	6802	259	NI
	Median	NA	7165	302	1.1

[a] Simulation using default gut physiology parameters under fed condition; [b] Simulation using gastric emptying time of 4 hours (default 1 hr) under fed condition (See Methods); NA. Not available [9]; NI. Not included.

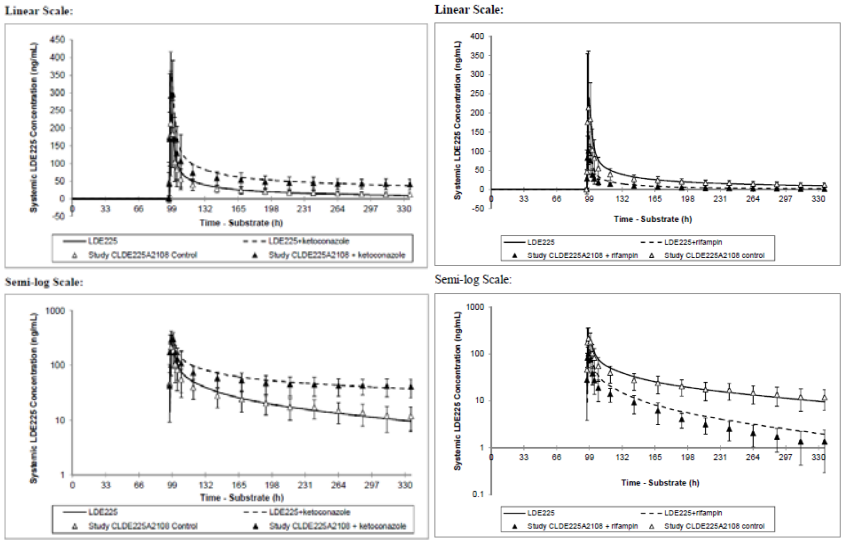
Appendix Figure 1. PBPK simulated concentration-time profiles of sonidegib in healthy subjects after a single dose. (Left, 200 mg; right 800 mg)

The bold line is the mean **simulated** concentration-time profile and the light gray lines below and above the mean are the lower 10th and upper 90th confidence intervals, respectively. The points on the lines are the observed mean data and the error bars **are the standard deviation** (Figure 7-1 and 7-3, reference [1])**.**



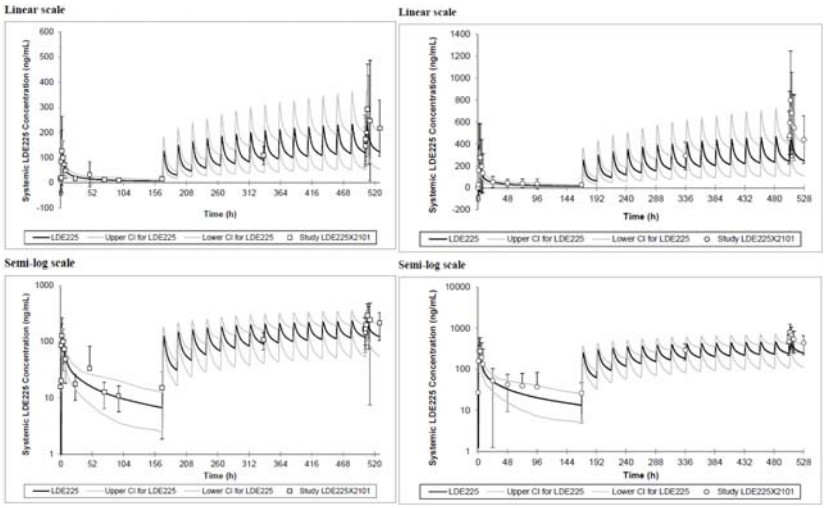
Appendix Figure 2. PBPK simulated concentration-time profiles of sonidegib (800 mg) in healthy subjects with and without co-administration of ketoconazole (200 mg b.i.d., left) or rifampicin (600 mg q.d., right)

Lines are the mean simulated concentration-time profiles (solid, sonidegib alone; dashed, sonidegib with CYP modulator). The points are the observed mean data and the error bars are the standard deviation. (Figures 7-5 and 7-6, reference [1])



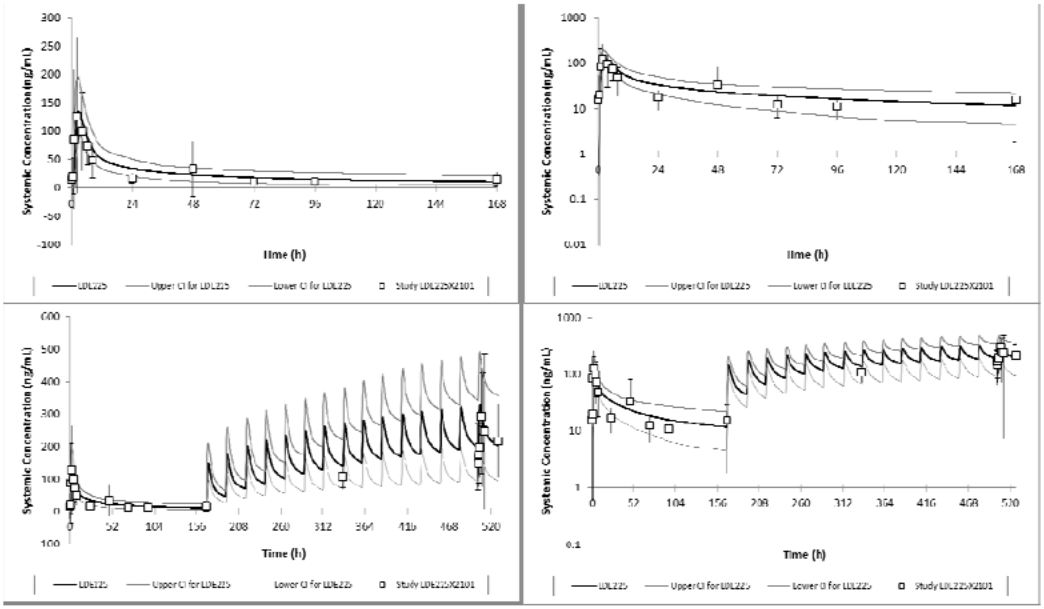
Appendix Figure 3. PBPK simulated concentration-time profiles of sonidegib in healthy subjects after multiple dosing. Left, 200 mg; right 800 mg

The bold line is the mean **simulated** concentration-time profile and the light gray lines below and above the mean are the lower 10th and upper 90th confidence intervals, respectively. The points on the lines are the observed mean data (in patients) and the error bars **are the standard deviation** (Figure 7-2 and 7-4, reference [1])



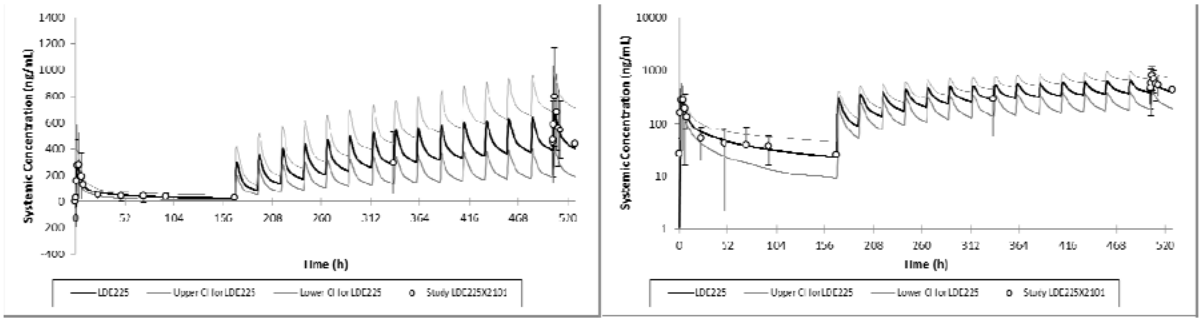
Appendix Figure 4. PBPK simulated concentration-time profiles of sonidegib in patients. Upper: 200 mg single dose; lower: 200 mg q.d.

The bold line is the mean simulated concentration-time profile and the light gray lines below and above the mean are the lower 10th and upper 90th confidence intervals, respectively. The points on the lines are the observed mean data and the error bars are the standard deviation. (File source: 200 mg LDE225 SD patient PK 0-168h.xls and 200 mg MD patient day 15 0-24h with observed data FOR PICTURE.xls)



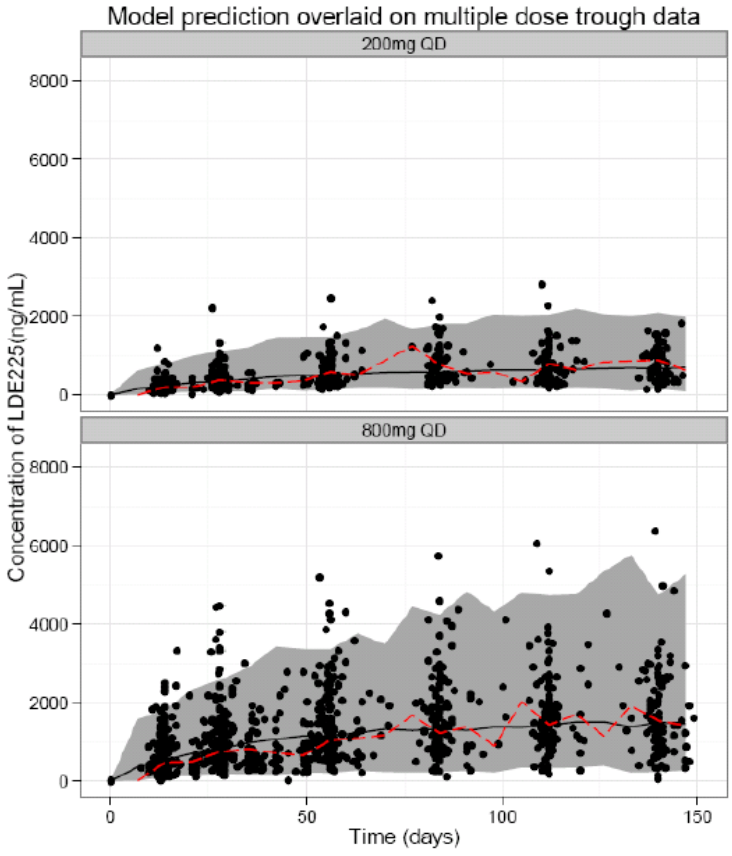
Appendix Figure 5. PBPK simulated concentration-time profiles of sonidegib in patients (800 mg q.d.).

The bold line is the mean simulated concentration-time profile and the light gray lines below and above the mean are the lower 10th and upper 90th confidence intervals, respectively. The points on the lines are the observed mean data and the error bars are the standard deviation. (File source: 800 mg MD patient day 15 0-24h with observed data FOR PICTURE and PK on last day xls)



Appendix Figure 6. Observed sonidegib plasma concentration in cancer patients taking once daily dosing for 5 months

Source data: Figure 5-25, reference [16]



References

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2. Novartis. Response to Health Authority Request Document: (b) (6) Response to FDA Information Request 1 (Clinical Pharmacology) received 07-Nov-2014
3. Novartis. Study DMPK R1400133b: (b) (6) Simcyp predictions of the interaction of LDE225 with erythromycin, rifampin, or efavirenz using the cancer patient Simcyp model for LDE225
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5. Novartis: Clinical Study Report CLDE225A2108. A Phase I, single center, parallel group, open label, randomized, drug-drug interaction study to assess the effect of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of LDE225 in healthy volunteers
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8. Novartis. Study CLDE225X2101. (b) (6) A Phase I, multicenter, open-label, dose-escalation study of oral LDE225 in patients with advanced solid tumors
9. Novartis. Study CLDE225A2114. (b) (6) A randomized, open-label study to evaluate the relative bioavailability of three FMI formulations of LDE225 compared with the CSF formulation and the effect of food in healthy subjects
10. Novartis. Study LDE225A2110. (b) (6) . An open-label, single center study to determine the absorption, distribution, metabolism, and excretion (ADME) of a single oral dose of [14C]LDE225 (74 kBq) to healthy male subjects
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12. Novartis. Study DMPK R0700984. (b) (6) In vitro permeability and transporter interaction assessment of [14C]LDE225 across Caco-2 cell monolayers
13. Rodgers T, Leahy D, Rowland M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. J Pharm Sci. 2005 Jun;94(6):1259-76

14. Study DMPK R0700986. (b) (6) In vitro assessment of cytochrome P450 enzyme inhibition by LDE225

15. Xu Y, Zhou YH, Hayashi M, Shou M, Skiles G. Simulation of Clinical Drug-Drug Interactions from Hepatocyte CYP3A4 Induction Data and Its Potential Utility in Trial Designs. DMD 39:1139–1148, 2011.

16. Novartis. Modeling Report. (b) (6) Population pharmacokinetics of sonidegib in cancer patients and healthy volunteers. 31-Mar-2014

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

/s/

STACY S SHORD
05/26/2015

PING ZHAO
05/27/2015

YANING WANG
05/27/2015

HONG ZHAO
05/27/2015
I concur.

NAM ATIQUR RAHMAN
05/27/2015
I concur with the recommendation.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

Office of Clinical Pharmacology

NDA or BLA Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205-266	**Brand Name**	Odomzo
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Sonidegib
Medical Division	DOP2	**Drug Class**	Hedgehog inhibitor
OCP Reviewer	Stacy S. Shord, Pharm.D.	**Indication(s)**	Basal Cell Carcinoma
OCP Team Leader	Hong Zhao, Ph.D.	**Dosage Form**	Oral capsules
Pharmacometrics Reviewer	Stacy S. Shord, Pharm.D. Liang Zhao, Ph.D. Ping Zhao, Ph.D.	**Dosing Regimen**	200 mg once daily
Date of Submission	September 26, 2014	**Route of Administration**	By mouth
Estimated Due Date of OCP Review	May 29, 2015	**Sponsor**	Novartis
Medical Division Due Date	May 29, 2015	**Priority Classification**	Standard
PDUFA Due Date	July 24, 2015	\\CDSESUB1\evsprod\NDA205266\205266.enx	

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments
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	4		DMPK-R1300055 DMPK-R1000477 DMPK-R700658-02 DMPK-RCLDE225A1102
I. Clinical Pharmacology				
Mass balance:	x	1		LDE225A2110
Isozyme characterization:	x	1		DMPK-R0800034
Blood/plasma ratio:	x	1		DMPK-R0700955-03
Plasma protein binding:	x	1		DMPK-R1100368
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		LDE225A1102 – Japanese LDE225A2108 – DDI LDE225A2110 – ADME LDE-225A2114 – RBA, Food
multiple dose:				
Patients-				
single dose:	x	2		LDE225X1101 – East Asian LDE225X2101 – U.S., Europe
multiple dose:	x			LDE225X1101 – East Asian LDE225X2101 – U.S., Europe
Dose proportionality -				
fasting / non-fasting single dose:	x			LDE225X2101 – U.S., Europe
fasting / non-fasting multiple dose:	x			LDE225X2101 – U.S., Europe
Drug-drug interaction studies -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

In-vivo effects on primary drug:	x	1		LDE225A2108 (3A4) LDE225A-POPPK (PPI, H2RA) (b) (4) Planned
In-vivo effects of primary drug:				LDE225A2112 (2B6, 2C9), Started Apr 2013
In-vitro:	x	13		DMPK-R0700986 (Inhibit CYP) DMPK-R1200636 (Induce CYP) DMPK-R0800482 (PXR) DMPK-R0700988 (Inhibit Pgp) DMPK-R080032301 (Inhibit BCRP) DMPK-R1200553 (Inhibit OATP) DMPK-R1200564 (Inhibit OAT) DMPK-R1200565 (Inhibit OCT) DMPK-R0800540 (Inhibit MRP2) DMPK-R1300665 (BCRP substrate) DMPK-R1200562 (Transport substrate) DMPK-R0700984 (Transport substrate) DMPK-R1400133 (SIMCYP DDI)
Subpopulation studies -				
ethnicity:	x	2		PK Ethnicity Sensitivity Report (A1102, A2114) LDE225A-POPPK (A1102, A2114, A2201, X2101, X1101)
gender:	x			LDE225A-POPPK
pediatrics:		Waiver		
geriatrics:	x			LDE225A-POPPK
renal impairment:	x			LDE225A-POPPK
hepatic impairment:	x	1		LDE225A-POPPK DMPK-R1400132 (SIMCYP HI) – LDE225A2113, Started Mar 2013
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	3		LDE225A-PKCK (A2201, X2101, X1101, B2209) PK-QTc Pooled Analysis (A2201, X2101, X1101, B2209, A1102, A2108, A2110, A2114) LDE225A-PKEFF (A2201)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			LDE225A-POPPK
Data sparse:	x			LDE225A-POPPK
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		LDE225A2114
Bioequivalence studies -				FMI identical to 200-mg capsule in registration trial
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x			LDE225A2114 LDE225A-POPPK
Bio-waiver request based on BCS				
BCS class	x			(b) (4)
III. Other CPB Studies				
Genotype/phenotype studies				
Pediatric development plan	x			Waiver Requested
Literature References	x			
Total Number of Studies		32		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

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

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	The 200-mg capsule given in the registration trial is identical to FMI.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			An IR was placed for the datasets for the PBPK analyses.
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			An IR was placed for the datasets for the PBPK analyses.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	x			
4	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			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	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			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

During the pre-NDA meeting held on April 15, 2014, Novartis agreed to provide the following clinical pharmacology information in the NDA submission. These reports and the associated datasets, text files and models if appropriate have been included in the NDA.

- Clinical Study Report: Studies A1102 (dose escalation), A2108 (drug interaction), A2110 (mass balance) and A2114 (food effect).
- Analyses Across Multiple Studies:
  - PK-QTc analysis (A1102, A2114, A2108, A2110, A2201, X2101, X1101, B2209)
  - PK-efficacy analysis (A2201)
  - PK-CPK analysis (A2201, X2101, X1101, B2209)
  - Population PK analysis (A1102, A2114, A2201, X2101, X1101) and
  - Ethnic Sensitivity Report (A1102, A2114)

It was agreed that the study report for [redacted] (b) (4) would not be included in the NDA. Novartis was asked to provide a description and timeline for post marketing requirements related to these studies during the pre-NDA meeting. The requested information was not included in the NDA. An information request (stated below) was sent to Novartis for this information.

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

Not applicable.

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

An information request was formally submitted to Novartis on November 7, 2014. We requested a response by November 19, 2014.

1. Submit to the NDA a description of the proposed post marketing studies, including your proposed timelines for completion of these studies and submission of the final study reports, for the hepatic impairment study and two drug interaction studies with a cytochrome P450 substrates and a proton pump inhibitor as requested during the pre-NDA meeting held in April 15, 2014.
2. We conducted an initial review of the physiologically based pharmacokinetic (PBPK) study report (Study 1400133) entitled "Simcyp predictions of the interaction of LDE225 with ketoconazole or rifampin". It appears that sonidegib exposure is generally higher in cancer patients as compared to healthy subjects and the sonidegib PBPK model has been developed primarily using pharmacokinetic (PK) data of healthy subjects. Figures 7-2 and 7-4 in this study report show that the model is not able to describe sonidegib PK profiles in cancer patients on day 15.
   a. Submit justification to the NDA whether the current data and the PBPK model allow prediction of the magnitude of sonidegib exposure change by concomitant use of strong CYP3A modulators in cancer patients, especially if higher sonidegib exposure observed in cancer patients is primarily due to lower hepatic metabolism.
   b. Submit the following simulations, including the study reports, model files and other related excel files as listed below, formally to the NDA.

      Simulate the effect of strong CYP3A inhibitor ketoconazole administered at a dose of 200 mg twice daily (b.i.d.) on steady state sonidegib PK (C_{max} and AUC within dosing interval) when sonidegib is administered at a dose of

i. 200 mg once daily (q.d.)
ii. 200 mg once every other day (q.o.d.)

Provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

Signatures:

Stacy S. Shord

Reviewing Clinical Pharmacologist Date

Hong Zhao

Team Leader/Supervisor Date

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

/s/

STACY S SHORD
11/12/2014

PING ZHAO
11/12/2014

LIANG ZHAO
11/12/2014

HONG ZHAO
11/12/2014
I concur.