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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

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Reviewer Name(s)	Denise Casey
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Established Name	Sonidegib
(Proposed) Trade Name	Odomzo
Therapeutic Class	Hedgehog Inhibitor
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	200 mg capsules
Dosing Regimen	200 mg once daily
Indication(s)	Basal Cell Carcinoma
Intended Population(s)	Adult patients with advanced basal cell carcinoma (BCC)

Labeling Recommendations

This review will focus on high-level labeling recommendations. The Applicant submitted an updated labeling proposal with the 120-day safety update on January 23, 2015 which included substantial content revisions based on the longer term follow-up of patients and a data cutoff date of July 11, 2014. Addendum 2 of the Summary of Clinical Safety provided the Applicant's 18-month data analysis, and datasets were included in the submission to support the proposed changes in the label. These data were reviewed to verify claims made in the label.

All sections of the proposed label were revised for clarity, brevity, and consistency. Only clinically-relevant, substantive content changes will be discussed in this review (sections pertaining to CMC, clinical pharmacology, or nonclinical issues are not included), with agreed upon wording for the key clinical sections of the product label for sonidegib (Odomzo) provided in italics.

Boxed Warning

The label originally proposed by the Applicant included a boxed warning for the risk of embryo-fetal toxicity with sonidegib. FDA recommended and provided rationale for longer term use of contraception (i.e. condom use for 8 months rather than (b) (4) months) following treatment with sonidegib based on preclinical studies, the 28 day half-life and pharmacokinetics (PK) of sonidegib. FDA and the Applicant agreed on the following text for the boxed warning:

- *ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. ODOMZO is embryotoxic, fetotoxic, and teratogenic in animals [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*
- *Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*
- *Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].*

Section 1: INDICATIONS AND USAGE

The label originally proposed by the Applicant included indications for the treatment of patients with locally advanced BCC (laBCC) who are not candidates for surgery or radiation therapy (b) (4)



FDA and the Applicant agreed on inclusion of the following indication in the final label:

ODOMZO (sonidegib) is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

Section 2: DOSAGE AND ADMINISTRATION

This section was extensively reorganized and reworded for clarity and readability. Substantial content changes were made to the dose modifications section.

- The originally proposed label included instructions (b) (4)

FDA removed these instructions because (b) (4)

- The Applicant originally proposed (b) (4)

FDA did not agree to the proposal (b) (4)

and prior dose-finding clinical studies of sonidegib suggested that 200 mg was the lowest dose at which antitumor effect was noted.

- The Applicant acknowledged that (b) (4) but proposed that patients who experienced Grade 3 (b) (4) CK elevation be rechallenged with sonidegib 200 mg daily (b) (4)

. FDA agreed to rechallenging after the first recurrence of Grade 3 serum CK elevation, (b) (4)

(b) (4)

- The Applicant proposed that [REDACTED] (b) (4)
[REDACTED] Given that patients tended to have muscle symptoms prior to experiencing laboratory evidence of serum CK elevation, FDA recommended that treatment be interrupted at the onset of muscle symptoms.

FDA and the Applicant agreed on inclusion of the following text in the DOSAGE AND ADMINISTRATION section of the label:

2.1 Recommended Dosing

The recommended dose of ODOMZO is 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal, administered until disease progression or unacceptable toxicity [see Clinical Pharmacology (12.3)].

Verify the pregnancy status of females of reproductive potential prior to initiating ODOMZO. Obtain serum creatine kinase (CK) levels and renal function tests prior to initiating ODOMZO in all patients [see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].

If a dose of ODOMZO is missed, resume dosing with the next scheduled dose.

2.2 Dose Modifications

Interrupt ODOMZO for

- *Severe or intolerable musculoskeletal adverse reactions.*
- *First occurrence of serum CK elevation between 2.5 and 10 times upper limit of normal (ULN).*
- *Recurrent serum CK elevation between 2.5 and 5 times ULN.*

Resume ODOMZO at 200 mg daily upon resolution of clinical signs and symptoms.

Permanently discontinue ODOMZO for

- *Serum CK elevation greater than 2.5 times ULN with worsening renal function.*
- *Serum CK elevation greater than 10 times ULN.*
- *Recurrent serum CK elevation greater than 5 times ULN.*
- *Recurrent severe or intolerable musculoskeletal adverse reactions.*

Section 4: CONTRAINDICATIONS

The label originally proposed by the Applicant included [REDACTED] (b) (4). FDA recommended this be removed because [REDACTED] (b) (4).

(b) (4)

. The Applicant agreed, and this contraindication was removed.

Section 5: WARNINGS AND PRECAUTIONS

The two warnings included in the label are for embryo-fetal toxicity and musculoskeletal adverse reactions. This section was reorganized and substantial content changes were made during labeling negotiations.

- In Section 5.1, consistent with the rest of the label, males are advised to use condoms for at least 8 months (rather than the originally proposed (b) (4) months) following treatment with sonidegib.
- Given that the warning for blood donation stems from the potential for blood products to be given to a female of reproductive potential, the originally proposed warning for “blood donation” was moved under Section 5.1.
- In Section 5.2, the Applicant proposed new language in the June 5, 2015 submission stating that (b) (4)

This addition was discussed at the late cycle meeting with the sponsor and internally. FDA and the Applicant agreed to the inclusion of modified text (see below).

- During the review, FDA requested that the Applicant provide a pooled safety analysis of all patients treated across the sonidegib development program specifically to address the safety signal of musculoskeletal adverse reactions including rhabdomyolysis. FDA also requested information on patients who required medical interventions for musculoskeletal adverse reactions. This data was requested because although the incidence of rhabdomyolysis across the development program was small, a relatively large proportion of the patients in Study A2201 experienced some muscle toxicity that resulted in a need for medical interventions (e.g., hospitalization, pain medications, intravenous hydration), treatment interruptions and discontinuations. Relevant information from these analyses were summarized in the final agreed upon label (see below).
- The Applicant proposed to include additional information describing the time to onset and resolution of serum CK elevations and additional text recommending prescribers advise patients of the risk for muscle-related adverse reactions and of the symptoms which should be reported promptly to providers when taking sonidegib.

FDA and the Applicant agreed on inclusion of the following text in the WARNINGS AND PRECAUTIONS section of the label:

5.1 Embryo-fetal Toxicity

ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, sonidegib was embryotoxic, fetotoxic,

and teratogenic at maternal exposures below the recommended human dose of 200 mg. Advise pregnant women of the potential risk to a fetus [see Use in Specific Populations (8.1)].

Females of Reproductive Potential

Verify pregnancy status of females of reproductive potential prior to initiating ODOMZO treatment. Advise females to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose [see Use in Specific Populations (8.3)].

Males

Advise male patients with female partners to use condoms, even after a vasectomy, during treatment with ODOMZO and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential [see Use in Specific Populations (8.3)].

Blood Donation

Advise patients not to donate blood or blood products while taking ODOMZO and for at least 20 months after the last dose of ODOMZO because their blood or blood products might be given to a female of reproductive potential.

5.2 Musculoskeletal Adverse Reactions

Musculoskeletal adverse reactions, which may be accompanied by serum creatine kinase (CK) elevations, occur with ODOMZO and other drugs which inhibit the hedgehog pathway.

In a pooled safety analysis of 12 clinical studies involving 571 patients with various advanced cancers treated with ODOMZO at doses ranging from 100 mg to 3000 mg, rhabdomyolysis (defined as serum CK increase of more than ten times the baseline value with a concurrent 1.5-fold or greater increase in serum creatinine above baseline value) occurred in one patient (0.2%) treated with sonidegib 800 mg.

In Study 1, musculoskeletal adverse reactions occurred in 68% (54/79) of patients treated with ODOMZO 200 mg daily with 9% (7/79) reported as Grade 3 or 4. The most frequent manifestations of musculoskeletal adverse reactions reported as an adverse event were muscle spasms (54%), musculoskeletal pain (32%), and myalgia (19%). Increased serum CK laboratory values occurred in 61% (48/79) of patients with 8% (6/79) of patients having Grade 3 or 4 serum CK elevations. Musculoskeletal pain and myalgia usually preceded serum CK elevation. Among patients with Grade 2 or higher CK elevations, the median time to onset was 12.9 weeks (range: 2 to 39 weeks) and the median time to resolution (to ≤ Grade 1) was 12 days (95% CI: 8 to 14 days). ODOMZO was temporarily interrupted in 8% of patients or permanently discontinued in 8% of patients for musculoskeletal adverse reactions. The incidence of musculoskeletal adverse reactions requiring medical intervention (magnesium supplementation, muscle

relaxants, and analgesics or narcotics) was 29%, including four patients (5%) who received intravenous hydration or were hospitalized.

Obtain baseline serum CK and creatinine levels prior to initiating ODOMZO, periodically during treatment, and as clinically indicated (e.g., if muscle symptoms are reported). Obtain serum creatinine and CK levels at least weekly in patients with musculoskeletal adverse reactions with concurrent serum CK elevation greater than 2.5 times ULN until resolution of clinical signs and symptoms. Depending on the severity of symptoms, temporary dose interruption or discontinuation may be required for musculoskeletal adverse reactions or serum CK elevation [see Dosage and Administration (2.2)]. Advise patients starting therapy with ODOMZO of the risk of muscle-related adverse reactions. Advise patients to report promptly any new unexplained muscle pain, tenderness or weakness occurring during treatment or that persists after discontinuing ODOMZO.

Section 6: ADVERSE REACTIONS

This section was reorganized and minor content changes were made during labeling negotiations. The adverse reactions table was reordered, the table of laboratory abnormalities was modified to show all grade abnormalities and grade 3-4 abnormalities, and additional information was added to describe the potential risk for amenorrhea. FDA and the Applicant agreed on inclusion of the following text in the ADVERSE REACTIONS section of the label:

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- *Musculoskeletal Adverse Reactions [see Warnings and Precautions (5.2)].*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ODOMZO was evaluated in Study 1, a randomized, double-blind, multiple cohort trial in which 229 patients received ODOMZO at either 200 mg (n=79) or 800 mg (n=150) daily. The frequency of common adverse reactions including muscle spasms, alopecia, dysgeusia, fatigue, nausea, decreased weight, decreased appetite, myalgia, pain, and vomiting was greater in patients treated with ODOMZO 800 mg as compared to 200 mg.

The data described below reflect exposure to ODOMZO 200 mg daily in 79 patients with locally advanced BCC (laBCC; n=66) or metastatic BCC (mBCC; n=13) enrolled in Study 1. Patients were followed for at least 18 months unless discontinued earlier. The median duration of treatment with ODOMZO was 11.0 months (range 1.3 to 33.5

months). The study population characteristics were: median age of 67 years (range 25 to 92; 59% were ≥65 years), 61% male, and 90% white. The majority of patients had prior surgery (75%), radiotherapy (24%), systemic chemotherapy (4%), or topical or photodynamic therapies (18%) for treatment of BCC. No patient had prior exposure to a hedgehog pathway inhibitor.

ODOMZO was permanently discontinued in 34% of patients or temporarily interrupted in 20% of patients for adverse reactions. Adverse reactions reported in at least two patients that led to discontinuation of the drug were: muscle spasms and dysgeusia (each 5%), asthenia, increased lipase, and nausea (each 4%), fatigue, decreased appetite, alopecia, and decreased weight (each 3%). Serious adverse reactions occurred in 18% of patients.

The most common adverse reactions occurring in ≥10% of patients treated with ODOMZO 200 mg were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus (Table 1).

The most common laboratory abnormalities are described in Table 2.

Table 1: Adverse Reactions Occurring in ≥10% of Patients in Study 1

Adverse Reaction	ODOMZO 200 mg (N=79)	
	All Grades ^a %	Grade 3 %
Musculoskeletal and connective tissue disorders		
Muscle spasms	54	3
Musculoskeletal pain	32	1
Myalgia	19	0
Skin and subcutaneous tissue disorder		
Alopecia	53	0
Pruritus	10	0
Nervous system disorders		
Dysgeusia	46	0
Headache	15	1
General disorders and administration site conditions		
Fatigue	41	4
Pain	14	1
Gastrointestinal disorders		
Nausea	39	1
Diarrhea	32	1
Abdominal pain	18	0
Vomiting	11	1

Investigations		
Decreased weight	30	3
Metabolism and nutrition disorders		
Decreased appetite	23	1
^a No Grade 4 adverse reactions were reported.		

Table 2: Key Laboratory Abnormalities^a

Laboratory Test	ODOMZO 200 mg (N=79)	
	All grades %	Grades 3-4%
Chemistry		
Increased serum creatinine	92 ^b	0
Increased serum creatine kinase (CK)	61	8
Hyperglycemia	51	4
Increased lipase	43	13
Increased alanine aminotransferase	19	4
Increased aspartate aminotransferase	19	4
Increased amylase	16	1
Hematology		
Anemia	32	0
Lymphopenia	28	3
^a Based on worst post-treatment laboratory value regardless of baseline; grading by CTCAE v4.00.		
^b The serum creatinine level remained within normal range in 76% (60/79) of patients.		

Amenorrhea

Amenorrhea lasting for at least 18 months occurred in two of 14 pre-menopausal women treated with ODOMZO 200 mg or 800 mg once daily.

Section 8: USE IN SPECIFIC POPULATIONS

FDA recommended that additional information be included in Section 8.1 to provide a summary of risk for exposure during pregnancy and the findings from animal studies. The modification for the use of condoms for 8 months rather than (b) (4) months following the last dose of sonidegib was made to be consistent with the rest of the label. Additional information from the juvenile toxicology studies was included under Section 8.4. Additional information was included under Section 8.5 to describe clinically relevant trends noted in geriatric patients. FDA and the Applicant agreed on inclusion of the following text in the USE IN SPECIFIC POPULATIONS section of the label:

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of ODOMZO in pregnant women. In animal reproduction studies, oral administration of sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits [see Data]. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682. The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at ≥ 5 mg/kg/day (approximately 0.05 times the recommended human dose based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection.

8.2 Lactation

No data are available regarding the presence of sonidegib in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in breastfed infants from sonidegib, advise a nursing woman not to breastfeed during treatment with ODOMZO and for 20 months after the last dose.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action and animal data, ODOMZO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ODOMZO treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose.

Males

It is not known if sonidegib is present in semen. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose. Advise males not to donate semen during treatment with ODOMZO and for at least 8 months after the last dose.

Infertility

Based on findings from animal studies, female fertility may be compromised with ODOMZO [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of ODOMZO have not been established in pediatric patients.

Juvenile Animal Data

In a 5-week juvenile rat toxicology study, effects of sonidegib were observed in bone, teeth, reproductive tissues, and nerves at doses ≥ 10 mg/kg/day (approximately 1.2 times the recommended human dose based on AUC). Bone findings included thinning/closure of bone growth plate, decreased bone length and width, and hyperostosis. Findings in teeth included missing or fractured teeth, and atrophy. Reproductive tissue toxicity was evidenced by atrophy of testes, ovaries, and uterus, partial development of the prostate gland and seminal vesicles, and inflammation and aspermia of the epididymis. Nerve degeneration was also noted.

8.5 Geriatric Use

Of the 229 patients who received ODOMZO (79 patients receiving 200 mg daily and 150 patients receiving 800 mg daily) in Study 1, 54% were 65 years and older, while 28% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. There was a higher incidence of serious adverse events, Grade 3 and 4 adverse events, and adverse events requiring dose interruption or discontinuation in patients ≥ 65 years compared with younger patients; this was not attributable to an increase in any specific adverse event.

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin \leq 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

No dose adjustment is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)].

Section 14: CLINICAL STUDIES

This section was reorganized and substantial content changes were made during labeling negotiations.

- Information throughout the section was revised based on (b) (4) indication to patients with laBCC (b) (4)
- Additional information describing the modified RECIST guideline was added.
- A statement reporting the complete response (CR) rate based on a prespecified sensitivity analysis using response criteria that defined CR based on negative histology was added.
- The description of the duration of response data was revised to include information on ongoing responses.
- (b) (4) and text stating that there was no evidence of better antitumor activity among patients with laBCC randomized to receive 800 mg was added.
- Text describing the proportion of patients with Gorlin Syndrome in each treatment arm was added.
- The originally proposed (b) (4) were removed.

FDA and the Applicant agreed on inclusion of the following text in the CLINICAL STUDIES Section of the label:

The safety and effectiveness of ODOMZO were evaluated in a single, multicenter, double-blind, multiple cohort clinical trial conducted in patients with locally advanced basal cell carcinoma (laBCC) (n=194) or metastatic basal cell carcinoma (mBCC) (n=36) (Study 1). Patients were randomized (2:1) to receive either ODOMZO 800 mg or 200 mg orally, once daily, until disease progression or intolerable toxicity. Randomization was stratified by stage of disease (locally advanced or metastatic), laBCC disease histology (aggressive vs. non-aggressive), and geographic region. Patients with laBCC were required to have lesions for which radiotherapy was contraindicated or inappropriate (e.g., Gorlin syndrome or limitations because of location of tumor), that had recurred after radiotherapy, that were unresectable or for which surgical resection would result in substantial deformity, or that had recurred after prior surgical resection.

The major efficacy outcome measure of the trial was objective response rate (ORR) as determined by blinded central review according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC or RECIST version 1.1 for patients with mBCC. Duration of response (DoR), determined by blinded central review, was a key secondary outcome measure.

For patients with laBCC, the evaluation of tumor response was based on a composite assessment that integrated tumor measurements obtained by radiographic assessments of target lesions (per RECIST 1.1), digital clinical photography, and histopathology assessments (via punch biopsies). All modalities used must have demonstrated absence of tumor to achieve a composite assessment of complete response (CR). Response by digital clinical photography was evaluated by World Health Organization (WHO) adapted criteria [partial response (PR): $\geq 50\%$ decrease in the sum of the product of perpendicular diameters (SPD) of the lesions, CR: disappearance of all lesions, progressive disease (PD): $\geq 25\%$ increase in the SPD of the lesions]. Multiple punch biopsies of target lesions were performed to confirm a CR or when a response assessment was confounded by presence of lesion ulceration, cyst, and or scarring/fibrosis.

A total of 66 patients randomized to ODOMZO 200 mg daily had laBCC. Three of these patients had a diagnosis of Gorlin Syndrome. The demographic characteristics of the 66 patients with laBCC were: median age of 67 years (range: 25 to 92 years; 58% were ≥ 65 years); 58% male, 89% white, and ECOG performance status of 0 (67%). Seventy-six percent of patients had prior therapy for treatment of BCC; this included surgery (73%), radiotherapy (18%), and topical/photodynamic therapies (21%). Approximately half of these patients (56%) had aggressive histology.

Patients with laBCC randomized to receive ODOMZO 200 mg daily were followed for at least 12 months unless discontinued earlier. The ORR was 58% (95% confidence interval: 45, 70), consisting of 3 (5%) complete responses and 35 (53%) partial responses. A pre-specified sensitivity analysis using an alternative definition for complete response, defined as at least a PR according to MRI and/or photography and no evidence of tumor on biopsy of the residual lesion, yielded a CR rate of 20%. Among the 38 patients with an objective response, 7 (18%) patients experienced subsequent disease progression with 4 of these 7 patients having maintained a response of 6 months or longer. The remaining 31 patients (82%) have ongoing responses ranging from to 1.9+ to 18.6+ months and the median duration of response has not been reached.

A total of 128 patients randomized to ODOMZO 800 mg daily had laBCC. Twelve of these patients had a diagnosis of Gorlin Syndrome. There was no evidence of better antitumor activity (ORR) among patients with laBCC randomized to receive ODOMZO 800 mg daily and followed for at least 12 months unless discontinued earlier.

Section 17: PATIENT COUNSELING INFORMATION

FDA reorganized and reformatted this section for clarity and readability. FDA added a section on musculoskeletal adverse reactions. FDA and the Applicant agreed on inclusion of the following text in the PATIENT COUNSELING INFORMATION section of the label:

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

- *Advise female patients of the potential risk to a fetus.*
- *Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose.*
- *Advise males, even those with prior vasectomy, to use condoms, to avoid potential drug exposure in both pregnant partners and female partners of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose.*
- *Advise female patients and female partners of male patients to contact their healthcare provider with a known or suspected pregnancy.*
- *Advise females who may have been exposed to ODOMZO during pregnancy, either directly or through seminal fluid, to contact the Novartis Pharmaceuticals Corporation at 1-888-669-6682.*

Blood Donation

- *Advise patients not to donate blood or blood products while taking ODOMZO and for 20 months after stopping treatment.*

Musculoskeletal Adverse Reactions

Advise patients to contact their healthcare provider immediately for new or worsening signs or symptoms of muscle toxicity, dark urine, decreased urine output, or the inability to urinate [see Warnings and Precautions (5.2)].

Administration Instructions

Advise patients to take ODOMZO on an empty stomach, at least 1 hour before or 2 hours after a meal [see Dosage and Administration (2.1)].

Lactation

Advise women not to breastfeed during treatment with ODOMZO and for up to 20 months after the last dose [see Use in Specific Populations (8.2)].

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/s/

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07/23/2015

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07/23/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205266
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Submit Date(s)	September 26, 2014
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Denise Casey
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Established Name	Sonidegib
(Proposed) Trade Name	Odomzo
Therapeutic Class	Hedgehog Inhibitor
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	200 mg capsules
Dosing Regimen	200 mg once daily
Indication(s)	Basal Cell Carcinoma
Intended Population(s)	Adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy

(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewer recommends full approval of sonidegib at a dose of 200 mg daily for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy.

- The confirmed objective response rate for 66 patients with laBCC receiving 200 mg of sonidegib daily in Study LDE225A2201 was 58% (95% CI: 44.8, 69.7) based upon blinded central review. The median duration of response in this group of patients was non-estimable with 82% of patients who obtained a response maintaining that response at the efficacy data cut-off when all patients had received at least 12 months of treatment.

(b) (4)

-

(b) (4)

1.2 Risk Benefit Assessment

Data from one clinical trial were submitted as the primary support for this NDA. Study LDE225A2201 (Study A2201) was an international, multi-center, randomized, blinded trial of two doses of sonidegib administered to 230 patients with either metastatic basal cell carcinoma (mBCC, n=36) or locally advanced basal cell carcinoma (laBCC, n=194). Patients were randomized 2:1 to receive sonidegib 800 mg (n=151) or 200 mg (n=79) daily. The 200 mg dose was selected because it was the lowest dose at which antitumor activity was observed in the sonidegib dose-finding Study LDE225X2101 (Study X2101), while the 800 mg dose was determined to be the maximum tolerated dose in the same study. The results of Study X2101 suggested an exposure-dependent inhibition of Gli-1, an exploratory pharmacodynamic marker of sonidegib activity; therefore, Study A2201 included a 2:1 unbalanced allocation to the 800 mg treatment arm based on an anticipated exposure-response relationship. Patients were stratified by disease stage (laBCC or mBCC), histology (aggressive or nonaggressive), and geographic region (North America, Europe, or Australia). The subsets of patients with laBCC and mBCC in each treatment arm were analyzed

separately in the efficacy evaluation as these diseases, though similar in their molecular pathogenesis, are characterized by different natural histories, management principles and overall prognoses.

Unmet Medical Need

Basal cell carcinoma (BCC) is a common human cancer that is usually amenable to curative local therapy. Locally advanced aBCC that is not amenable to further local treatments and mBCC are rare conditions. As all BCCs are grouped within the non-melanoma skin cancer registry, accurate estimates of the prevalence and long term survival of patients with laBCC are difficult to obtain. For mBCC, the literature reports an incidence rate of 0.0028% to 0.55% of all BCCs and an average survival of 8-14 months for patients with disease that has spread to the lungs, bone, or liver [1]. For patients with laBCC no longer amenable to local treatment, progressive disease can result in substantial morbidity due to tissue invasion that can cause infection, bleeding, and severe disfigurement [2]. Vismodegib, a smoothed (Smo) inhibitor approved in 2012, is the only currently available systemic treatment for patients with laBCC not amenable to local treatment and for patients with mBCC [3, 4].

Assessment of Clinical Benefit

The assessment of benefit in this application is based on the endpoints of centrally reviewed objective response rate (ORR) and duration of response (DOR) determine (b) (4) according to a protocol-specific modified RECIST (mRECIST) for patients with laBCC. The mRECIST assessment involved a composite response based on integration of MRI, photographic and histopathologic results.

Study A2201 did not demonstrate an exposure-response relationship for the primary efficacy endpoint (b) (4). Both treatment arms met the prespecified primary endpoint requirement of ORR greater than or equal to 30% for patients with laBCC. (b) (4)

The following efficacy results confirm the results presented by the Applicant:

- In the group of patients with laBCC, the ORR for those treated in the 200 mg arm was 58% [95% confidence interval (CI): 44.8, 69.7], and the ORR for those treated in the 800 mg arm was 44% (95% CI: 35, 52.8). The median DOR for patients with laBCC was non-estimable (NE) in the 200 mg arm and 15.7 months (95% CI: NE) in the 800 mg arm.

- (b) (4)

(b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Assessment of Risk

The safety data supporting the application are primarily from Study A2201 and included 229 patients with advanced BCC exposed to sonidegib. The safety evaluation demonstrated an exposure-dependent relationship such that the majority of adverse events (AEs) occurred with increased frequency and severity in the 800 mg treatment arm as compared to the 200 mg arm. Patients in the 200 mg arm had a longer median duration of exposure and were more likely to discontinue treatment for progressive disease events while patients in the 800 mg arm were more likely to discontinue treatment for AEs. Serious adverse events (SAEs), grade 3 and 4 AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), and AEs leading to treatment discontinuation occurred more frequently in the 800 mg group. Common AEs that occurred in more than 20% of patients in either treatment arm were muscle spasms, alopecia, dysgeusia, nausea, fatigue, increased serum creatine kinase (CK), decreased weight, and diarrhea.

The primary safety risk with sonidegib treatment is for the occurrence of musculoskeletal adverse reactions including serum CK elevation and rhabdomyolysis. Musculoskeletal toxicity appears to be a hedgehog inhibitor drug class effect [6, 7]. Muscle spasms were the most frequently experienced AE and the AE that led to treatment discontinuation most often in both

treatment arms in Study A2201. Serum CK elevation occurred in over 60% of patients in both arms; however, grade 3 and 4 CK elevations were less common (8% in the 200 mg arm and 17% in the 800 mg arm). Rhabdomyolysis was the most commonly reported SAE (N=6). The rhabdomyolysis cases in Study A2201 were independently reviewed and none were adjudicated by an expert committee as rhabdomyolysis due to lack of evidence of concurrent renal impairment; however, in all cases, medical interventions including hospitalization, intravenous hydration, and analgesic administration were required. It is the reviewer's opinion that these interventions may have prevented the occurrence of impending renal failure and rhabdomyolysis for the patients at risk. At FDA's request, the Applicant provided additional data and an analysis from a pooled safety population from twelve clinical studies across the sonidegib development program to further evaluate the risk for musculoskeletal adverse reactions including rhabdomyolysis. The pooled data demonstrated a 0.2% incidence of rhabdomyolysis, defined as increased serum CK of more than ten times the baseline value with a concurrent 1.5 fold or greater increase in serum creatinine above baseline value, in 571 patients, with 27% of these patients requiring medical intervention(s) for musculoskeletal adverse reactions.

Similar to other adverse reactions, there was a dose-dependent relationship observed with musculoskeletal adverse reactions occurring in patients treated with sonidegib at a 200 mg daily dose as compared to patients receiving higher doses. At the final safety data cut-off for Study A2201, when all patients continuing in the study had received at least 18 months of treatment, in the cohort of patients receiving the 200 mg dose, 6% had experienced grade 3 or 4 serum CK elevation, 4% had experienced at least one musculoskeletal SAE, and 6% had discontinued sonidegib due to a musculoskeletal AE. Patients in the 800 mg arm experienced an increased frequency of all of these AE types. The reviewer does not believe the risk for musculoskeletal toxicity offsets the clinical benefit demonstrated by sonidegib in patients with laBCC treated at the 200 mg dose. The product label will include sufficient details regarding the musculoskeletal adverse reactions that occurred during clinical studies of sonidegib such that prescribers are adequately informed of this risk and the necessary monitoring involved in the treatment of patients with sonidegib.

An additional safety concern with sonidegib is the risk of fetal harm when administered during pregnancy. There are no available data on the use of sonidegib in pregnant women; however, animal studies demonstrated that sonidegib is embryotoxic, fetotoxic and causes teratogenic effects at maternal exposures below the recommended human dose of 200 mg. The sonidegib product label, which includes a Medication Guide, will effectively communicate this risk and provide precautionary measures to providers and patients.

Conclusion

In summary, ORR of sufficient magnitude and durability is an acceptable measure of tumor shrinkage and clinical benefit to patients with advanced BCC. Additionally, there is regulatory precedent for this primary endpoint to support full approval for sonidegib for patients with laBCC. The efficacy data from Study A2201 did not demonstrate an exposure-response relationship as similar antitumor activity was observed in both treatment arms. Patients with

laBCC experienced durable and clinically relevant response rates at the proposed 200 mg daily dose; [REDACTED] (b) (4)

[REDACTED] The safety data demonstrate a dose-dependent effect for the majority of adverse drug reactions including musculoskeletal toxicity. The safety profile of sonidegib at the 200 mg dose is acceptable in light of the demonstrated clinical benefit to patients with laBCC. The efficacy and safety data together support the approval of sonidegib at the proposed 200 mg daily dose in patients with laBCC not amenable to local treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The reviewer does not recommend any Postmarket Risk Evaluation and Mitigation Strategies for sonidegib.

1.4 Recommendations for Postmarket Requirements and Commitments

The following clinical Postmarket Requirement (PMR) is recommended to collect safety information on sonidegib exposure to developing fetuses and pregnancy outcomes:

Conduct a Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements:

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.
- Description of procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data. FDA recommends at least a ten year study duration.

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

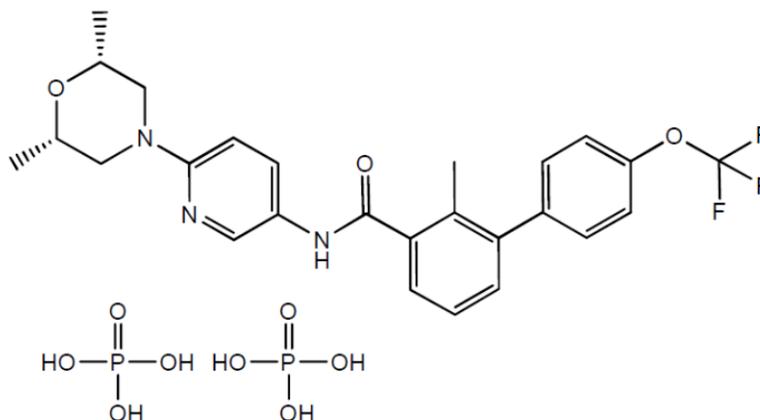
2 Introduction and Regulatory Background

The Applicant seeks approval for the following indication: “Sonidegib is for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4).” The application was submitted on September 26, 2014, and the PDUFA goal date is September 26, 2015. This review will describe the efficacy and safety data supporting sonidegib for the treatment of laBCC [REDACTED] (b) (4) and the recommendation of the clinical reviewer.

2.1 Product Information

Sonidegib (LDE225) is an oral small molecule inhibitor that binds and inhibits smoothed (SMO), a G-protein-coupled receptor in the hedgehog (Hh) signaling pathway. It is derived from a novel structural class. Sonidegib diphosphate is the active drug substance, and the chemical name for the drug substance is N-[6-(cis-2,6-Dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy) [1,1'-biphenyl]-3-carboxamide diphosphate. The molecular weight is 681.49. The drug product submitted for marketing authorization is a 200 mg hard capsule formulation. The structural formula of sonidegib is shown in Figure 1 (copied from submission).

Figure 1: Chemical structure of sonidegib



2.2 Currently Available Treatments for Proposed Indications

The National Comprehensive Cancer Network (NCCN) guidelines and the medical literature agree that the goal of treatment for patients with BCC is to cure the tumor while preserving function and decreasing or eliminating disfigurement. In general, surgical resection is the treatment of choice for the vast majority of patients. The three surgical procedures used for BCC lesions are curettage and electrodesiccation (C&E), excision with postoperative margin assessment (POMA) and Mohs surgery. Mohs surgery incorporates an intraoperative analysis

of 100% of the excision margin and is generally preferred for patients with high risk disease. These techniques have been reported to achieve five-year disease free rates of between 92% and 99% [8, 9]. Recurrence rate after resection is higher for BCCs with aggressive histology and for BCCs located in the head and neck region [10].

The literature suggests a lower recurrence rate in patients with BCC receiving surgery versus radiation; however, if a surgical resection is likely to cause disfigurement or loss of function, or if the patient prefers to not undergo surgery, radiation therapy may be used as a primary treatment. A five-year recurrence rate of 8.7% was reported in a meta-analysis of primary BCC treated with radiation therapy[11].

In patients with superficial BCC, when surgery or radiation is contraindicated, topical therapies including 5-fluorouracil 5% cream, imiquimod, photodynamic therapies (aminolevulinic acid [ALA], porfimer sodium), and cryotherapy have been used, though only 5- fluorouracil 5% cream and imiquimod are FDA-approved for a BCC indication.

Vismodegib (Erivedge®), a first-in-class Hedgehog (Hh) pathway inhibitor, is the only approved systemic drug for the treatment of BCC. It was approved on January 30, 2012 for the treatment of adults with mBCC, or with laBCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. The vismodegib application was supported by a multicenter, international, single-arm trial of vismodegib 150 mg daily in patients with mBCC and those with laBCC who had inoperable disease or for whom surgery was inappropriate. The primary end point was independently assessed objective response rate (ORR). The study prespecified that patients treated with vismodegib for laBCC would achieve a response rate greater than 20% and that patients with mBCC would achieve a response rate greater than 10%. At the time of the primary analysis, in 33 patients with mBCC, the independently assessed ORR was 30% (95% CI, 16 to 48). In 63 patients with laBCC, the ORR was 43% (95% CI, 31 to 56), with complete responses observed in 13 patients (21%). The median duration of response was 7.6 months in both cohorts [12].

In the present application, sonidegib is proposed as an additional systemic drug for the treatment of inoperable laBCC not amenable to radiation (b) (4). Table 1 lists treatment options for patients with BCC supported by the NCCN guidelines and the literature. Except for vismodegib, none are approved by FDA for the intended indication for sonidegib.

Table 1: Currently available treatments for basal cell carcinoma

Drug	Formulation	Labeled indication
Vismodegib (Erivedge®)	Oral	Indication: “For the treatment of adults with mBCC, or with laBCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for

Drug	Formulation	Labeled indication
		radiation.
Fluorouracil Cream 5% strength (Efudex®)	Topical	Indication: “The 5% strength is useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites...The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred.”
Imiquimod Cream (Aldara®)	Topical	Indication: “Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of sBCC should be established prior to treatment, since safety and efficacy of Aldara Cream have not been established for other types of BCCs, including nodular and morpheaform (fibrosing or sclerosing) types.”
Porfimer (Photofrin®)	Intravenous	Photosensitizing agent; does not have a labeled indication for BCC
ALA (Levulan® kerastick®)	Topical	Photosensitizing agent; does not have a labeled indication for BCC

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

Vismodegib was approved in 2012 and is a first-in-class Hh pathway inhibitor. The vismodegib label includes a boxed warning for embryo-fetal death and severe birth defects. Similarly, the vismodegib Medication Guide provided for patients states, “ERIVEDGE can cause your baby to die before it is born (be stillborn) or cause your baby to have severe birth defects”[4]. This

precaution is based on the mechanism of action. Vismodegib was observed to be embryotoxic, fetotoxic, and teratogenic in rats at maternal exposures lower than human exposures at the recommended dose. In rats, malformations included craniofacial anomalies, open perineum and absent or fused digits. Fetal retardation and variations were also observed.

The risk for teratogenicity associated with sonidegib treatment is discussed in Section 4.3 of the review.

Another apparent drug class effect associated with Hh pathway interference is musculoskeletal toxicity including serum creatinine kinase (CK) elevation and risk for rhabdomyolysis [6, 7]. The occurrence of muscle spasms is a commonly reported adverse event in patients exposed to vismodegib [3]. Over 70 % of patients experienced muscle spasms during the trial that supported approval; however, routine CK levels were not collected during the study, and the risk for developing rhabdomyolysis during treatment with vismodegib is not clear. Additional risk determinations involving vismodegib are ongoing.

The risk for musculoskeletal toxicity associated with sonidegib treatment is discussed in detail in Section 7 of this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following timeline summarizes the key presubmission regulatory activity for sonidegib:

- November 17, 2008: IND 102961 for LDE225 (sonidegib) submitted.
- June 9, 2011: End of Phase 1 meeting. Novartis sought FDA agreement that the proposed design for Study A2201, a multi-center, double-blind study of 120 patients with mBCC or laBCC randomized 2:1 to receive either 800 mg or 200 mg of LDE225, could support submission of an NDA.
- The Applicant's rationale for a study design which randomized patients to one of two doses of sonidegib was based on a dose-finding study of sonidegib in patients with advanced solid tumors (StudyX2101) demonstrating evidence of antitumor activity at doses of sonidegib > 200 mg daily in patients with BCC. (b) (4)

The Applicant considered this design to be a reasonable alternative to an internally controlled trial to provide a robust evaluation of the efficacy and safety of sonidegib because at the time of designing the study, there was no approved systemic treatment to consider as a comparator control. Additionally, the Applicant did not believe that a placebo arm would be feasible given the evidence of antitumor activity demonstrated in the dose-finding study in patients with BCC and in considering the morbidities associated with the disease.

- FDA encouraged Novartis to select an appropriate dose prior to embarking on a registration study. FDA expressed concern that the chosen doses of 200 mg and 800 mg may have similar activity and less of the dose response effect [REDACTED] (b) (4). FDA stated that if the trial demonstrated a similar response rate in both arms, these results could pose regulatory issues. Therefore, FDA recommended that Novartis conduct a single arm study at a dose level known to be active in a sample size of more than 120 patients such that the lower limit of the 95% confidence interval exceeded 20%, assuming the true ORR is 30%. Novartis prepared a slide presentation to provide further rationale for the proposed two arm study design. [REDACTED] (b) (4)
[REDACTED]
- FDA commented that the proposed sample size was small, and that it was preferable to have at least 100 patients in the 800 mg arm to provide data on drug safety and activity.
- FDA stated that the eligible patient population needed to be well-defined regarding prior therapy and disease stage. FDA told Novartis to specifically collect information on reasons why patients with laBCC were not considered amenable to surgery, local therapies or radiation.
- FDA stated that all patients who enroll on study should have central histopathologic review of the most recent biopsy of the lesion by a dermatopathologist to assure that the lesions are basal cell carcinoma without other malignant components.
- FDA agreed that the primary endpoint of ORR is acceptable provided that the responses are of clinically meaningful magnitude and duration and the safety profile is acceptable. FDA recommended the first secondary endpoint be duration of response rather than time to response, and Novartis agreed.
- FDA noted that in a single-arm trial, all statistical analyses would be considered as descriptive and that analyses for time to event endpoints (PFS and OS) are not interpretable in a single-arm study.
- FDA recommended that an independent review board confirm the investigator determination of response.
- FDA requested that Novartis propose a modified RECIST criteria for defining response and progression in laBCC specifically addressing issues of ulceration and measurement of scar or fibrosis formation.
- FDA recommended that all patients considered to have a complete response be biopsied with central review of pathology to confirm absence of tumor.
- FDA agreed to the safety monitoring plan within the protocol.

- FDA additionally recommended that Novartis conduct *in vitro* studies with sonidegib to assess whether it is an inducer of any CYP isozymes.
- September 27, 2011: Novartis submitted the modified RECIST guidelines for FDA review. FDA provided comments regarding the proposed criteria in a letter issued on December 22, 2011, and Novartis responded on February 3, 2012. The following list summarizes key discussion points regarding the modified RECIST that was used to assess response in patients with laBCC during Study A2201.
- FDA disagreed with [REDACTED] (b) (4)
[REDACTED]
[REDACTED] FDA recommended that clinical signs suggestive of residual tumor in photographs or on MRI preclude a composite overall response of "complete response." FDA stated that the Applicant's "complete response" definition of complete disappearance of all target lesions should be used in the setting of ulcerations and cyst formation also, with subsequent confirmation by negative histology on punch biopsies. Novartis agreed to these recommendations.
- FDA did not agree to Novartis' proposal that [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] Novartis agreed to stipulate the use of only annotated photographs and MRI scans (if lesions were deemed measurable) for tumor response assessment by central reviewers in patients with laBCC.
- FDA stated that all tumor responses characterized as complete response with positive histology (CRih) be regarded as partial responses. Novartis agreed.
- FDA stated that the photographic equipment and techniques used to obtain photographs of lesions must be standardized to afford the best image possible. Novartis stated that guidance for standardization of photograph acquisition would be included in the imaging manual developed by the imaging vendor.
- FDA asked Novartis to provide a proposal regarding how the scope of the clinical assessment of lesions might be expanded for the trial. Novartis stated that the clinical assessment of lesions involves palpation to delineate indurations and palpable components of lesions that is captured via photograph annotations.

Reviewer: The mRECIST criteria were implemented in protocol amendment 2 submitted on November 17, 2011. The majority of patients with laBCC enrolled prior to this amendment were not evaluable for response according to mRECIST due to lack of baseline MRI or annotated photography; therefore, protocol amendment 4 introduced the primary efficacy analysis subset (pEAS), a subset of the full analysis set (FAS) or the intent-to-treat population. All patients in the pEAS were evaluable using mRECIST. The Applicant performed the primary endpoint efficacy analyses based on both the pEAS and the FAS.

- June 5, 2012: Teleconference between FDA and Novartis to discuss the proposed drug substance starting materials and the control strategy for impurities in LDE225 drug substance.
 - FDA stated that the selection of (b) (4) as starting materials in the synthesis of LDE225 seemed reasonable but that the adequacy would be determined at the time of NDA review. FDA stated that risk assessment should be performed for any potential change of vendor, method of manufacturing, or quality of raw materials used for the preparation of the proposed starting materials during the life cycle of the product.
 - Regarding genotoxic impurities assessments and the proposed limit for mutagenic compounds, FDA stated that Novartis would need to provide adequate scientific justification for each exposure, consistent with ICH S9.
 - FDA stated that Novartis should propose an (b) (4) and that the adequacy of the proposal would be determined at the time of NDA review. FDA additionally recommended that Novartis perform (b) (4) studies to demonstrate (b) (4) in the manufacturing process and that the results of these studies be submitted with the NDA.
- February 13, 2013: Novartis requested a Type C meeting to discuss the planned analyses from the sonidegib development program in preparation for an NDA submission. FDA denied this meeting because the request was considered premature. FDA recommended Novartis resubmit a meeting request as a Type B End-of-phase2/pre-NDA meeting when more high-level data was available.
- April 3, 2013: Novartis submitted a briefing package with questions and requested FDA written responses in lieu of the Type C meeting that was denied. Novartis again requested input from FDA on the planned analyses from the sonidegib development program in preparation for an NDA submission. FDA issued written responses on July 8, 2013.
 - FDA stated that there was insufficient information provided in the briefing package to determine whether Study CLDE225A2201 had demonstrated substantial evidence of a

treatment effect on a surrogate endpoint or of an effect that is a measure of direct clinical benefit, sufficient to support filing of the proposed NDA.

- FDA noted that there was inadequate information to determine whether there was sufficient data for either the 200 mg or the 800 mg doses of sonidegib to determine whether the safety database would be adequate to characterize serious risks and describe the adverse reaction profile in sufficient detail in product labeling.
- FDA agreed with the proposal to submit studies LDE225X2101, LDE225B2209, and LDE225A2201 to support clinical safety and efficacy, but recommended not including study LDE225X1101 as it was ongoing and would have possibly incomplete data.
- FDA agreed to the proposed clinical pharmacology studies to be submitted in support of an NDA, but had the following additional recommended that Novartis:
 - a. Include the final study report from the food effect study (A2114) in the NDA.
 - b. Conduct a drug-drug interaction study with a gastric pH elevating drug.
 - c. Conduct a drug-drug interaction study with a known BCRP substrate as coadministration of a BCRP substrate may potentially result in a clinically important drug-drug interaction and increased risk for rhabdomyolysis or other muscle related adverse events.
 - d. Evaluate the in vitro ability of sonidegib to act as an inhibitor of OATP to determine the need for a drug-drug interaction study as coadministration of sonidegib and statins (OATP substrate) may potentially result in an increased risk for rhabdomyolysis or other muscle related adverse events.
 - e. Evaluate the in vitro ability of sonidegib to act as a potential inducer of CYP1A2 and CYP2B6 or a potential substrate of BCRP.

With regard to the proposed analysis methods for the primary and secondary endpoints for the pivotal study, FDA recommended that the primary analysis of ORR and key secondary analyses of PFS and OS be performed in the intent to treat population, while the analysis of ORR in the pEAS should be considered a supportive analysis. FDA noted that if there were substantial differences between the two analyses, the most appropriate analysis for establishing efficacy and to support labeling claims would be determined during the review of the NDA.

- FDA did not agree to the proposed pooling strategies and plan for the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS), and emphasized that safety and efficacy data should be provided by subgroups based on dose administered.
- FDA stated [REDACTED] (b) (4) based on information in the Investigator's Brochure, it seemed possible to achieve therapeutic and supratherapeutic exposures in a thorough QT study when a single dose is administered with a high fat meal in healthy volunteers.

- FDA stated that Novartis' proposal for providing CRFs and Patient Narratives would fulfill the NDA requirements under 21 CFR 314.50.
- With regard to Novartis' request for a full waiver of the requirement to submit pediatric assessments for sonidegib in BCC, FDA stated that Novartis should submit a request for a waiver of pediatric studies that is disease-specific with the NDA and that the request should contain the proposed indication for which the waiver is sought, what pediatric age groups are included, a rationale and justification for requesting the waiver, and a certification statement indicating that sonidegib qualifies for a disease-specific waiver.
- June 12, 2013: Novartis submitted a fifth amendment of Protocol CLDE225A2201. This amendment allowed for ORR according to RECIST 1.1 to be derived for central review data by MRI and photography [REDACTED] (b) (4)
- FDA issued a written response on August 2, 2013, and informed Novartis that the proposed revisions to the response criteria were not acceptable and may alter the acceptability of these data to support labeling claims.
- A teleconference took place on August 8, 2013, between FDA and Novartis to further discuss the provisions for central review of response according to amendment 5 of protocol CLDE225A2201. FDA informed Novartis that [REDACTED] (b) (4) was not acceptable and that response assessments should be harmonized to include evaluation of the same target lesions by each modality included in the composite assessment plan. FDA emphasized that a composite overall response assessment for each target lesion should incorporate photographic, MRI and histological evaluation as described in Appendix 2 of the protocol.
 - a. Novartis agreed to clarify that for patients with laBCC assessed with all modalities (photo, MRI and histology) the same lesion would be evaluated to assess the surface component (by photo and biopsy), and sub-dermal component (by MRI and biopsy, where practicable) of the lesion.
 - b. Novartis agreed to update Appendix 2, table 3-1 (mRECIST guidelines) to capture all possible assessment scenarios.
 - c. Novartis agreed to submit Amendment 6 to provide clarity and propose a plan for integrated evaluation of lesions using the three modalities.
- August 19, 2013: FDA issued a letter informing Novartis that their proposed proprietary name "ODOMZO" was conditionally acceptable.
- October 2, 2013: Initial Pediatric Study Plan (iPSP) submission to FDA with intent to request a waiver for BCC pediatric studies.

- November 7, 2013: FDA issued comments in response to Novartis' request for input regarding the draft protocol amendment 6 and the proposed IRC charter submitted on October 1, 2013. FDA made the following key comments:
 - In the presence of a lesion on MRI, lesions having negative photographs and histology should be considered a PR and not a CR considering the potential for sampling error with punch biopsy assessments.
 - FDA reiterated that the primary analysis of ORR and key secondary analyses of PFS and OS be performed in the intent to treat population while the analysis of ORR in the pEAS should be considered a supportive analysis.
 - Whether the observed ORR of 30% can be considered an adequate measure of effectiveness will be based on the overall risk benefit assessment, and FDA will also evaluate the lower bound of the 95% confidence interval of the observed ORR.
- April 15, 2014: Pre-NDA meeting held.
 - FDA stated that the findings from Study A2201 provided in the meeting package would not support the filing of an NDA because an efficacy estimation based on ORR needs to be supported by adequate magnitude and duration with an acceptable risk/benefit ratio. FDA noted that since a majority of the data on duration of response was not available, an NDA submission based on the data proposed would not be acceptable. FDA additionally stated that the data provided on the proportion of patients without disease progression or death at 9 months and at 12 months is not interpretable in this trial because, although there is a dose-comparison, there is no information on the natural history in the absence of sonidegib in order to determine whether sonidegib treatment improves progression-free survival rates at 9 and 12 months. FDA stated that this data cannot substitute for duration of response in responding patients. Novartis presented several slides at the meeting to address FDA's concerns. The key discussion points regarding efficacy assessment are as follows:
 - a. Novartis showed in the slide presentation that the pre-specified endpoint of ORR measured at 24 weeks post-treatment in all patients was greater than or equal to 30% and the 95% lower Confidence Level (CL) was greater than or equal to 20% demonstrating efficacy for both doses based on the FAS.
 - b. Novartis stated that among the responders, the minimum duration of response was 1.9 months and that responses were ongoing.
 - c. FDA requested that Novartis provide individual patient listings for the duration of response in the NDA submission and Novartis agreed.
 - FDA noted the small number of patients available for safety evaluation at the proposed dose; therefore, FDA stated that the safety information obtained at the 800 mg dose for this patient population as well as all available safety information in the development program would be considered during the review.

- FDA agreed to the proposed submission plan for clinical pharmacology studies. FDA stated that the NDA submission should contain justification for not including the additional ongoing clinical pharmacology studies and a description of the proposed post marketing requirements, including proposed timelines for completion of the studies and submission of the final study reports.
- FDA stated that the adequacy of the proposed risk mitigation strategies (b) (4) could only be determined upon review of the application. FDA recommended that Novartis submit a proposed risk management plan (b) (4) and other serious risks that would include additional activities such as a pregnancy registry and evaluation of drug interactions with oral contraceptives. FDA referred Novartis to the approval letter for NDA 203388 (visomodegib) that outlined such a plan.
- Novartis proposed inclusion of updated efficacy data for ORR and duration of response in addition to the updated safety data in the 120-day safety update. Novartis presented slides to support this proposal. FDA stated that the proposal was acceptable.
- Novartis presented slides to justify the proposed (b) (4). FDA agreed that a (b) (4) could be provided in the NDA and that the specific labeling would be agreed upon during labeling negotiations.
- FDA stated that primary MRI images would not be reviewed (b) (4). FDA told Novartis to submit the data in PDF format within the NDA.
- Agreement was reached on the proposal for submission of electronic datasets.
- FDA agreed with Novartis's proposal not to include a Risk Evaluation and Mitigation Strategy (REMS) in the initial NDA submission. FDA advised that during the review of the NDA, additional safety information that would require Novartis to prepare a REMS may be identified, to ensure that the benefits of the drug outweigh the risks.
- In general, the proposed contents for the NDA were acceptable; however, FDA noted that agreements could not be reached on what would constitute a complete application for an NDA under PDUFA V program because the pre-NDA meeting for discussion of Quality component of the NDA had not yet been held.
- June 18, 2014: Pre-NDA CMC meeting held.
 - Regarding the content of Quality Module 3, FDA agreed that the listed eCTD sections were acceptable in that all sections which provided CMC information were included.

FDA provided several additional comments describing the CMC information to be included in specific sections and the background information (See FDA Quality review for details).

- Novartis agreed to summarize the stability data that would be provided at submission and the stability data that could be provided by mid-cycle review, so that agreement could be reached as to the stability data that may be submitted during review.
- August 14, 2014: Novartis issued a request for agreement to submit the A2201 50 week updated safety and efficacy data (data cut-off Dec 31, 2013) with the NDA instead of at day 120 post-NDA filing. This request was based on an unanticipated delay in filing the NDA which allowed for 50 week data to be available at the time of the NDA submission. Additionally, Novartis proposed that the composition of the Day 120 Safety update include 78 week updated data (data cut-off July 11, 2014).
- FDA agreed that this proposal was acceptable and confirmed that the A2201 clinical study report (CSR) would include the primary analysis of 24 week data (data cut-off date June 28, 2013) and that the 50 week updated data would be provided as addenda to the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS). FDA agreed that the 120 day safety update would include listings of new SAEs, deaths on study, and adverse events of special interest occurring from December 31, 2013, through July 11, 2014 for A2201 or since August 31, 2014 through December 2014, approximately 3 months after planned submission of the NDA) for all other ongoing studies.
- September 26, 2014: NDA 205266 for sonidegib was submitted.

2.6 Other Relevant Background Information

Disease Background

BCC is the most common human cancer and accounts for approximately 80% of non-melanoma skin cancers [13]. Abnormal activation of the hedgehog (Hh) pathway is a key driver in BCC pathophysiology. The majority of mutations in BCC occur in *PTCH1*, a protein that inhibits Smoothed (Smo) in this signaling pathway [13]. Risk factors for the development of BCC include fair skin pigmentation, radiation (ultraviolet and/or ionizing), exposure to arsenic or aromatic hydrocarbons, immunosuppression, and underlying genetic syndromes, such as nevoid BCC syndrome (NBCCS). NBCCS is also known as Gorlin syndrome, and is a hereditary condition caused by mutations in the *PTCH1* gene. It is characterized by a wide range of developmental abnormalities and a predisposition to developing cancers including medulloblastoma and BCC [20]. BCC tends to develop in patients over the age of 40; however, patients with Gorlin syndrome tend to develop BCCs in their teen years. The vast majority of BCC cases are amenable to local therapy including surgical resection, and in some cases, radiation. The recurrence rate is estimated to be 5% after local treatment [14].

Despite BCC being a relatively common cancer, locally advanced and metastatic BCC are rare diseases. Accurate estimates of the incidence and longterm survival of patients with advanced BCC are difficult to obtain because all BCCs are grouped together within the non-melanoma skin cancer registry. The literature estimates that advanced BCCs, including laBCC and mBCC, account for approximately 1-10% of all BCCs, with mBCCs accounting for 0.0028% to 0.55% of all BCC cases [15].

There are no formal criteria to define laBCC; this population generally includes multiply recurrent patients in which repeat resections would not be curative or could be disfiguring or cause a major functional deficit (e.g., facial, periorbital, cranial nerve tumors). Standard therapy for laBCC includes surgical resection or radiation or both. In patients where surgery would cause unacceptable morbidity or is unlikely to be curative, and in patients who have disease that is refractory to radiation or in cases where radiation is contraindicated, the recommendation is for patients to be treated with a smoothed (Smo) inhibitor [14]. The only currently available Smo inhibitor is vismodegib.

In patients with mBCC, the most common locations for metastatic growths are regional lymph nodes, followed by the lungs, liver and bone. The prognosis for mBCC is poor with an estimated survival of 8-14 months from diagnosis [15]. The role of local therapy in patients with metastatic disease is decided on an individual basis. Vismodegib is the only currently available systemic treatment for mBCC [4].

Response criteria in skin cancers

The divisions in the Office of Hematology and Oncology Products have accepted durable response rates, or the reduction in the size of a tumor in cancers with significant skin involvement, as a measure of direct clinical benefit in patients with various primary skin cancers. Standard solid tumor response criteria such as RECIST may not be a reliable or feasible assessment of clinically meaningful responses in patients with cutaneous malignancies. There is regulatory precedent for the use of alternative tumor assessment criteria as a means of determining clinically relevant responses in patients with skin cancers. One example is the Severity Weighted Assessment Tool (SWAT) which was established for determining response in patients with cutaneous T-cell lymphomas [16]. Another example that is more relevant to the present application is the modified RECIST assessment used in the study supporting the approval of vismodegib for patients with advanced BCC. The modified RECIST used in the vismodegib study was based on a composite endpoint derived from integrating radiologic, photographic and histologic response data, similar to that used in the sonidegib study [12].

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

The submission contained all of the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication.

Multiple hyperlinks were not initially accessible (e.g. the define file, the Independent Adjudication Committee assessment forms); however, the Applicant corrected the files to include functional hyperlinks soon after submission.

Numerous information requests were sent to the Applicant during the review cycle. Examples of these were requests to clarify the location of specific components in the application, to clarify the definitions of specific flagged populations in the datasets, to investigate potential errors noted in the case report forms (CRFs), and to explain and categorize the protocol violations that occurred during the registration trial (see Section 6.1.3). The Applicant was also asked to conduct additional safety analyses to allow further characterization of identified signals (e.g., musculoskeletal adverse reactions and lipase elevation) and to conduct additional subgroup analyses (e.g. patients with nevoid basal cell carcinoma syndrome, patients over the age of 75). Finally, the Applicant was asked to submit the datasets for a larger pooled safety population of patients treated across twelve clinical studies in the sonidegib development program. The additional safety data was requested for the purpose of evaluating specific identified safety concerns in a larger population and with the intent to adequately describe the risk:benefit profile of sonidegib in the product label.

Reviewer: The Applicant was able to provide responses to satisfy all FDA information requests.

Please refer Section 3.2 of this review and to the review conducted by FDA's Office of Scientific Investigations for a discussion of the inspections conducted at specific study sites.

3.2 Compliance with Good Clinical Practices

The Applicant stated the following: "All studies in the sonidegib BCC clinical development program were conducted in full compliance with Good Clinical Practice (GCP)". Additionally, all studies were "monitored by Novartis personnel or a contract research organization for compliance to the protocol, Novartis standard operating procedures (SOPs), and applicable regulatory guidance." (Module 2.5, *Clinical Overview in Advanced Basal Cell Carcinoma*).

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) on November 24, 2014 to perform an audit of select clinical sites. Sites were selected based on the number of patients enrolled, the relative number of protocol violations recorded,

and specific efficacy results determined from data collected at the site. Two sites were chosen for inspection: Site 1513 and 1503. Additionally, two study Contract Research Organizations (CROs) were inspected: (b) (4) were inspected because they played a major role in the conduct of medical image analyses (i.e., radiology and photography) that contributed to the determination of the primary efficacy endpoint for the registration study. The inspections conducted by OSI did not identify issues that could affect the quality and interpretation of the data submitted in the application. See the FDA Clinical Inspection review for details.

3.3 Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes copies of the financial disclosures and FDA forms 3454 and 3455 for investigators with disclosed interests.

The Applicant noted that no clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Between 93% and 100% of investigators across all “covered studies” in the sonidegib development program responded to the Applicant’s requests for financial disclosure information. For Study A2201, 243 of a total of 253 (96%) of clinical investigators responded. Of the 243 investigators for whom disclosures were collected, one investigator disclosed a financial interest, and a total of (b) (6) patients were enrolled at his center (Site (b) (6)). A total of two investigators who participated in the conduct of clinical studies of sonidegib supporting this application disclosed financial arrangements. Table 2 lists the investigators and their respective disclosures.

Table 2 Investigators with disclosed financial interests

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
(b) (6)	(b) (6)	(b) (6)	>\$25,000	Study grants from Novartis to study Imatinib
	LDE225A2201		\$2,500	Speaker Bureau

Source: Module 1.3.4, “Financial Disclosure by Clinical Investigators” (page 3)

The Applicant stated that potential bias was minimized by independent data monitoring by Novartis; multiple investigators used in the studies, and the double-blind design of the registration trial.

The reviewer does not believe that the reported disclosures compromise the integrity of the results of Study A2201.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of New Drugs Quality Assessment (ONDQA) team reviewed the data relevant to the manufacture of sonidegib drug substance and drug product and has recommended approval of the application. An “approval” recommendation has also been received from the facilities reviewer. Refer to the FDA ONDQA review and the facilities inspection report for details. The following key summary points were adapted from the ONDQA review:

Drug substance:

- Sonidegib phosphate is the active drug substance, and the chemical name is *N*-{6-[(2*R*, 6*S*)-2, 6-dimethylmorpholin-4-yl] pyridin-3-yl}-2-methyl-4'-(trifluoromethoxy)-[1, 1' - biphenyl]-3-carboxamide diphosphate (C₂₆H₂₆F₃N₃O₃·2H₃O₄P, Molecular Weight = 681.50).

- [REDACTED] (b) (4)

- The sonidegib phosphate drug substance release specifications and impurity limits were acceptable.

Drug product

- Sonidegib will be supplied as pink [REDACTED] (b) (4) opaque, hard, gelatin, immediate release capsules packaged in two configurations: a 30-count high density polyethylene (HDPE) bottle and a 30-count blister pack. [REDACTED] (b) (4)

- The sites for manufacture and control have been found to meet cGMP requirements. The manufacturing process and process parameters are acceptable.
- The proposed specifications for release and stability are acceptable.
- The proposed packaging systems are acceptable.
- Registration and supportive stability studies were adequate to address the proposed commercial presentations from the drug substance and drug product manufacturing sites.
- The study data supports the proposed shelf life for the commercial product.

4.2 Clinical Microbiology

According to the Product Quality Microbiology reviewer, the microbial limits specification for sonidegib capsules is acceptable. See FDA ONDQA review for details.

4.3 Preclinical Pharmacology/Toxicology

The FDA nonclinical review team reviewed the pharmacology and toxicology data submitted with the application and have recommended approval of sonidegib. Refer to the FDA nonclinical review for details of the preclinical data supporting the application. The following summary was derived from the FDA nonclinical review and from the Applicant's "Toxicology Written Summary" found in module 2.6.6 of the application.

Preclinical Pharmacology

Pharmacology studies demonstrated that sonidegib interferes with the hedgehog signaling pathway through inhibition of the transmembrane protein Smo. Various in vitro assays showed that Sonidegib inhibited Gli-dependent transcription with IC50s of between 4 and 13 nM.

Toxicology

Toxicology studies were conducted in Sprague Dawley rats and Beagle dogs. Major target organs identified in both species included the bone (growth plate closure), gastrointestinal tract, and hair follicles. The teeth were an additional target in rats, and findings included atrophy of the root, malocclusion, and tooth loss. In repeat dose toxicology studies, continuous or intermittent full body tremors occurred at the highest dose level in each species as well as in the juvenile rats though there were no pathologic signs of muscle toxicity. Transient increases of greater than 100% in serum creatine kinase (CK) occurred in rats. Sonidegib was also observed to have off target activity on the rat sodium brain channel type II which may have contributed to rat tremors at high dose levels.

Sonidegib was negative in assays for genotoxicity. Carcinogenicity studies were not conducted; however, given the potential for chronic sonidegib treatment in patients with laBCC who are likely to survive for years with this disease, carcinogenicity studies in rats and mice are recommended as postmarketing requirements.

Dedicated fertility and embryofetal development studies were conducted in rats. Treatment with sonidegib resulted in a lack of fertility in female rats at doses resulting in exposures approximately 1.3 times the recommended dose in humans. Embryotoxicity and fetal toxicity were observed at exposures as low as 0.12 times the clinical exposure. In a study conducted in rabbits, sonidegib administration caused embryofetal toxicity and demonstrated severe teratogenicity with occurrences of vertebral, limb and digit malformations and severe craniofacial defects, at exposures below the recommended human dose. Skeletal variations were also observed when maternal exposure to sonidegib was below the limit of detection for the drug.

Reviewer: A black box warning for embryofetal risk will be included in the product label based on the nonclinical data.

4.4 Clinical Pharmacology

The FDA clinical pharmacology review team concluded that the clinical pharmacology data submitted with the application support the approval of sonidegib. Refer to the FDA clinical pharmacology review for details.

The following summary is derived from the clinical pharmacology review, the product label and the Applicant's "Pharmacokinetics Written Summary" submitted in module 2.6.4 of the application.

4.4.1 Mechanism of Action

Sonidegib inhibits Smo, a transmembrane protein that activates the Hh signal transduction pathway. In the resting state, the activity of Smo is blocked by Patched (Ptch), a Hh ligand-specific cell surface receptor. Aberrant mutations in Smo or Ptch are thought to drive proliferation in specific cancers including BCC. Hh pathway activation by Smo leads to activation and nuclear localization of Glioma-Associated Oncogene (Gli) transcription factors. Sonidegib binds Smo and causes downstream inhibition of Gli proteins.

4.4.2 Pharmacodynamics

In vitro and in vivo pharmacology studies demonstrated affinity of sonidegib for human Smo with IC50s between 4 and 11 nM observed in cell based assays. Sonidegib specificity for Smo and the ability to induce Gli-1 expression inhibition was demonstrated in cellular assays.

Study LDE225X2101 (Study X2101) was a dose-finding study of sonidegib in patients with advanced solid tumors. The primary measure of the pharmacodynamics effects of sonidegib was the change in Gli-1 mRNA expression as measured by real time quantitative PCR. According to the Applicant's analysis in the Study X2101 study report, increased doses of sonidegib were generally associated with increased Gli-1 inhibition. In Study A2201, Gli-1 inhibition was also demonstrated in biopsy specimens taken during sonidegib treatment; however, the data did not show a substantial difference in the level of Gli-1 expression between the 200 mg and 800 mg dosing cohorts.

4.4.3 Pharmacokinetics (PK)

Sonidegib exhibited nonlinear PK at doses higher than 400 mg daily and has an approximate half-life of 28 days. Dose interruption or an alternative sonidegib dose or schedule in the setting of toxicity with the intent of providing similar sonidegib exposure to the 200 mg dose is not feasible, because of the non-linear PK and long elimination half-life.

Absorption: Doses between 100 and 3000 mg have been administered to cancer patients. Less than 10% of the oral dose of sonidegib is absorbed. The median time to peak concentration after oral administration is 2-4 hours. Sonidegib exhibited dose-proportional

increases in the area under the curve (AUC) and the maximal concentration (C_{max}) over the dose range of 100 mg to 400 mg, but less than dose-proportional increases at doses greater than 400 mg. Steady-state was reached approximately 4 months after starting treatment. Sonidegib should be taken under fasting conditions because studies demonstrated that a high-fat meal increased exposure to sonidegib by 7.4- to 7.8-fold.

Distribution: Sonidegib is predominantly distributed to plasma and is greater than 97% bound to human plasma proteins independent of sonidegib concentrations. The population estimated central volume of distribution (V_{ss/F}) of sonidegib was 9,166 L based on the original full population PK model.

Elimination: Sonidegib and its metabolites are eliminated primarily by the hepatic route. Studies demonstrated that approximately 70% of the drug was eliminated in the feces and 30% was eliminated in the urine. The half-life of sonidegib estimated from population PK modeling was approximately 28 days.

Special populations: There are no dosing recommendations specific to patients with hepatic or renal impairment. There will be a PMR to complete an ongoing PK study in patients with hepatic impairment. Based on population PK analyses, age, body weight, or gender have no clinically meaningful effect on sonidegib exposure.

Drug-drug Interactions:

- CYP3A4 modulators: Sonidegib is metabolized by CYP3A4 to several inactive metabolites. It is recommended that patients avoid taking strong and moderate CYP3A modulators with sonidegib.
- Acid-reducing agents: The population PK analysis indicates that sonidegib steady-state exposure is 34% lower in cancer patients concurrently taking an acid-reducing agent with a 200 mg sonidegib dose compared to patients not concurrently taking the acid reducing agent. A dedicated study in healthy subjects is ongoing to determine an appropriate dose regimen for patients concurrently taking an ARA.

Reviewer: The clinical pharmacology reviewer also evaluated the feasibility of alternative day dosing in the setting of grade 3 and 4 serum CK elevation and other musculoskeletal AEs (b) (4)

(b) (4) Multiple clinical and clinical pharmacology IRs were sent to the Applicant to collect information on sonidegib levels that may have been obtained at the time of muscle-related AEs, the duration of CK elevations per patient and the recurrence rate of muscle toxicity following treatment interruptions and dose reductions. The team recommended permanent discontinuation of sonidegib for serious toxicity (b) (4) (b) (4) given the long half-life, the recurrence rate of musculoskeletal AEs after dose reductions observed in the 800 mg arm, some evidence of durable responses after discontinuation and because the antitumor activity at doses less than 200 mg has not been established. The clinical team agrees with this recommendation. See Section 7.3.5 for a detailed discussion of musculoskeletal toxicity.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 lists the clinical studies for which there is efficacy or safety data in the NDA submission. The evidence to support the clinical efficacy of sonidegib at a dose of 200 mg daily in patients with laBCC who are not amenable to local therapies is derived solely from Study 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.”

The safety data used to characterize the safety profile of sonidegib for patients with BCC is primarily from Study A2201. A pooled safety population including patients in Study A2201 pooled with 43 patients treated in study X2101 with doses equal to or less than 800 mg daily was reviewed and considered as supportive information. The clinical study report (CSR) submitted for Study X1101 was not reviewed as the study is small, ongoing, and unlikely to provide additional substantive safety information.

The Applicant also submitted a report entitled, “Independent Safety Review and Adjudication Committee for Muscular Events Report” in Module 5.3.5.3. This report includes summary safety data and patient narratives derived from a safety pooling performed by the Applicant in response to the occurrence of a case of rhabdomyolysis in a patient treated with sonidegib. The pooled data was from 505 patients in the safety and clinical databases across the sonidegib development program who experienced musculoskeletal adverse events (data cut-of date August 15, 2013). This report was reviewed and is discussed in Section 7.3.5 of this review.

Table 3: Summary of clinical studies supporting the sonidegib application

Study	Design	Disease	Dose (mg)	Sample Size	Status
A2201	Randomized double-blind study of two dose levels	laBCC and mBCC	200 and 800 daily	230	Enrollment complete
X2101	Dose escalation	Advanced solid tumors	<i>Daily:</i> 100, 200, 400, 800, 1000, 1500, 3000 <i>Twice daily:</i> 250, 400, 750	103 (43 treated at doses ≤ 800 mg)	Enrollment complete
X1101	Dose finding	Advanced solid tumors;	400 and 600 daily	21	Ongoing

Study	Design	Disease	Dose (mg)	Sample Size	Status
		Japanese patients			
Independent Adjudication Committee for Muscular Events Report	Blinded review of pooled safety data from sonidegib clinical studies	Patients with investigator-reported rhabdomyolysis or CK elevation $\geq 10x$ ULN	Range of doses from 100 to 3000	53 patient narratives included in the report	Complete

5.2 Review Strategy

The primary safety and efficacy data from Study A2201 (data cutoff June 28, 2013; 6 month analysis) was reviewed including the CSR, datasets, case report forms (CRFs), line listings, and patient narratives of serious adverse events, deaths and adverse events of special interest. Safety and efficacy data submitted as addenda to the Summary of Clinical Safety (SCS) and the Summary of Clinical Efficacy (SCE) based on longer follow-up of patients (data cutoff December 31, 2013; 12 month analysis) was also reviewed.

Medical photographic data for patients who experienced an objective response with sonidegib treatment was submitted in the original NDA. As part of the efficacy evaluation, serial photographic images for patients receiving sonidegib at the intended dose of 200 mg daily were reviewed in the context of the centrally determined ORR, time to response and duration of response.

A separate report entitled, “Independent Safety Review and Adjudication Committee for Muscular Events Report” contained an analysis of a safety population pooled from the sonidegib development program in which all patients were reported to have musculoskeletal adverse reactions. The summary statement as well as patient narratives and the adjudication assessment forms from this report were reviewed.

The Applicant submitted additional safety data with the 120-day safety update as a second addendum to the SCS (data cut-off July 11, 2014; 18 month analysis). Select analyses were performed by the reviewer using the 18 month data to ensure that there were no major differences in the safety profile with longer term use of sonidegib and for the purpose of informing in the product label.

At FDA’s request, the Applicant submitted additional pooled safety analyses during the review cycle to address specific safety signals, and these are discussed in the review.

Recent medical literature on BCC and the Applicant's orientation materials were reviewed. Consultation reports from the Interdisciplinary Review Team for QT Studies (QT IRT), Office of Scientific Investigation (OSI), Office of Prescription Drug Promotion (OPDP), Patient Labeling Team (PLT), Study Endpoints and Labeling Development (SEALD), and Pediatric and Maternal Health Staff (PMHS) were reviewed. Specific questions regarding the application and the proposed labeling were discussed with two Special Government Employees (SGEs) and a patient advocate. See Section 9.4 of the review for a summary of the discussion with SGEs.

5.3 Discussion of Study CLDE225A2201

The results from one clinical study supported this application: Study LDE225A2201, “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.” The most recent version of the protocol (Amendment 6.0, November 14, 2013) was reviewed and is summarized below. Changes in the protocol between versions are summarized in Table 6.

At the time the study was designed and initiated, there was no approved therapy for the treatment of the subset of patients with BCC with inoperable locally advanced or metastatic disease. Without an available active comparator for a control arm and not wanting to randomize patients to a placebo arm, the Applicant designed the protocol to evaluate two doses of sonidegib: 200mg and 800 mg. The 200 mg dose was the lowest dose to demonstrate preliminary antitumor effects in the dose-finding Study X2101, and the 800 mg dose was the maximum tolerated dose in the same study.

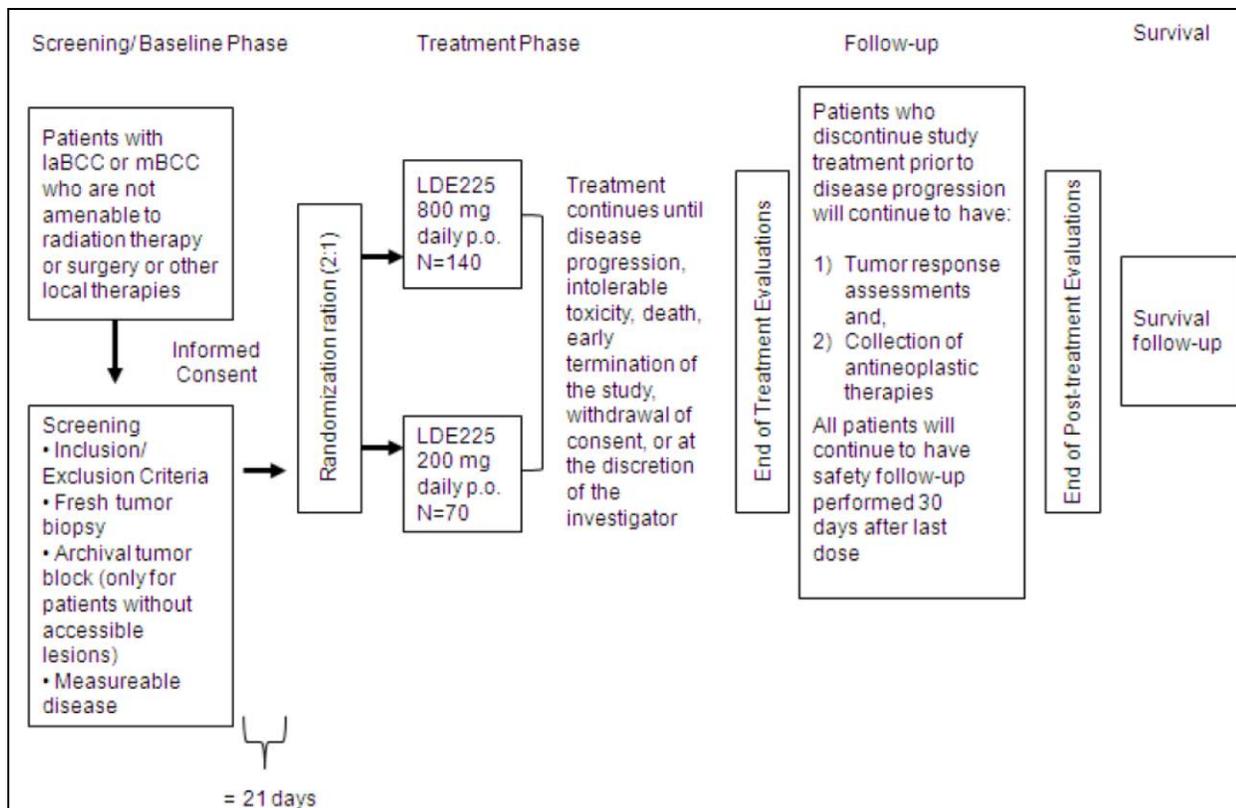
Study Design

Study A2201 was a multi-center, randomized double-blind study of sonidegib in patients with laBCC or mBCC. Patients were randomized 2:1 to receive sonidegib at either 800 mg or 200 mg on a continuous once daily dosing schedule. Patients were stratified according to stage of disease (locally advanced or metastatic), aggressive or non-aggressive histology, and geographic region (Australia, Europe, and North America). The design called for accrual of approximately 210 patients, and 230 patients were randomized, 79 to treatment with sonidegib 200 mg and 151 to treatment with sonidegib 800 mg. Patients continued treatment until disease progression, intolerable toxicity, withdrawal of consent, or death.

The primary endpoint for the study was ORR defined as the proportion of patients with a centrally reviewed and confirmed objective response according to modified RECIST (mRECIST) in patients with laBCC and RECIST 1.1 in patients with mBCC. Centrally reviewed duration of response (DOR), was a key secondary endpoint. The primary analysis was conducted when all patients had been treated for 24 weeks or discontinued treatment. A final analysis of safety and efficacy was performed at 78 weeks following enrollment of the last patient. After the final analysis, the study was closed; however, patients who had not experienced disease progression were able to continue to receive sonidegib if they were deriving clinical benefit.

Efficacy assessments were conducted at week 5, week 9, week 17, and then once every eight weeks during the first year of treatment and once every twelve weeks thereafter. See Figure 2 for a schematic of the study design.

Figure 2: LDE225A2201 Study Design



Source: LDE225A2201 clinical protocol, version 6, submitted November 2013

Study Objectives

Primary Objective: To assess the efficacy of sonidegib as measured by ORR as determined by central review, according to mRECIST in patients with laBCC and RECIST 1.1 in patients with mBCC.

Key Secondary Objectives:

- To assess DOR, as determined by central review
- To assess the rate of complete response (CR) as determined by central review
- To assess the effect of sonidegib on PFS
- To assess the effect of sonidegib on OS
- To assess time to tumor response (TTR)
- To assess ORR, DOR, PFS, and TTR, as determined by site investigator

- To evaluate safety including changes in QT/QTc intervals from baseline as determined by central review of ECG and their correlation with systemic drug exposure
- To further characterize pharmacokinetics of sonidegib

Study Population (modified from protocol for brevity)

Inclusion Criteria

- Age 18 years or older.
- Patient with locally advanced BCC or metastatic BCC:
 - Patients with a histologically confirmed diagnosis of laBCC that is not amenable to radiation therapy, curative surgery, or other local therapies. Histological confirmation of diagnosis must be based on the fresh tumor biopsy obtained at screening. Patients who do not have accessible BCC lesion(s) must provide an archival tumor specimen for this purpose. Patients with laBCC must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension as ≥ 10 mm with MRI scan or on color photographs.
 - Patients with a histologically confirmed diagnosis of mBCC. Histological confirmation of diagnosis must be based on the screening fresh tumor biopsy (if feasible) or archival tumor specimen. Patients with mBCC must have measurable disease, defined as at least one non-nodal lesion that can be accurately measured in at least one dimension as no less than double the slice thickness or 10 mm, whichever is greater with spiral CT or MRI scan or one nodal lesion (i.e. lymph node) ≥ 15 mm in short axis with spiral CT scan or MRI scan (irrespective of slice thickness). Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions. Lesions in previously irradiated areas can only be considered measurable if they have shown clear evidence of progression since the radiotherapy, as documented in the medical records.
- WHO performance status ≤ 2
- Adequate bone marrow, liver and renal function, as specified below:
 - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/L$
 - Hemoglobin (Hgb) ≥ 9 g/dL
 - Platelets $\geq 100 \times 10^9/L$
 - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN)
 - AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present
 - Serum creatine phosphokinase (CK) < 1.5 x ULN
 - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 ml/min
- Written informed consent prior to screening

Exclusion Criteria

- Major surgery within four weeks of initiation of study medication.
- Concurrent uncontrolled medical conditions that may interfere with participation in the study or affect the interpretation of the study data.
- Unable to take oral drugs or with lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes

- Previous treatment with systemic sonidegib or with other Hh pathway inhibitors
- Patients who have neuromuscular disorders or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least two weeks prior to starting study treatment (patients who require a statin may take pravastatin).
- Patients who will begin a new strenuous exercise regimen after initiation of study treatment.
- Participation in an experimental drug study within 4 weeks of initiating study treatment.
- Receiving other anti-neoplastic therapy concurrently or within 4 weeks of starting study treatment. All toxicity from prior therapy must be ≤ Grade 1 prior to initiation of study treatment.
- Receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting study treatment. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to study treatment.
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using two forms of highly effective contraception throughout the study and for 6 months after the last treatment
- Unwilling or unable to comply with the protocol

Study Treatment

Dose Selection

Enrolled patients were randomized 2:1 to receive sonidegib at an 800 mg or a 200 mg once-daily continuous dosing schedule in a double-blind fashion. The two doses were chosen based on preclinical and clinical data suggesting that doses of sonidegib ≥ 200 mg/day provide systemic exposures associated with anti-tumor activity in the preclinical rat medulloblastoma model, as well as evidence of preliminary anti-tumor activity in patients with recurrent medulloblastoma and advanced BCC treated in the dose-finding Study X2101. The maximum tolerated dose determined from Study X2101 was 800 mg daily. The Sponsor hypothesized that sonidegib would have a dose-response effect based on pharmacodynamics data from Study X2101; therefore, the protocol included an unbalanced randomization procedure (2:1) to allow more patients to be treated at the higher dose level. The continuous daily dosing schedule was chosen because twice daily dosing, though permitting higher exposure, was also associated with increased dose-limiting toxicity (i.e. serum CK elevation) in Study X2101.

Drug Administration

Patients were instructed to take sonidegib at approximately the same time each day, and to swallow capsules whole. Sonidegib was to be taken two hours after a light breakfast, and then food intake was to be avoided for one hour following sonidegib administration. Patients were instructed to avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during

the entire study. Patients were not re-dosed for vomiting. Patients were instructed to take sonidegib within 6 hours of a missed dose and to omit that day's dose if more than six hours had passed from the skipped dose.

Treatment Duration

Patients continued on study treatment until disease progression (confirmed by central review), discontinuation due to intolerable toxicity, withdrawal of consent, death, at the discretion of the investigator.

Dose Modifications

A maximum of two dose reductions were permitted for patients randomized to the 800 mg arm (dose level -1 was 400 mg daily; dose level -2 was 200 mg daily). Patients randomized to the 200 mg dose were reduced to placebo for any dose reduction and discontinued if they required more than one dose reduction. Dose reductions were managed via an interactive response technology (IRT) system utilized during the study to ensure that blinding was maintained. For any patient who required dose interruption or delay for toxicity, if the same toxicity returned after resumption of sonidegib, the patient was required to resume sonidegib at the next lower dose level. Patients who required a dose interruption of greater than 21 days were discontinued from study treatment. Patients who discontinued study treatment due to an adverse event were followed until resolution or stabilization of the event. Table 4 describes the dose management guidelines used in Study A2201 for specific treatment-related toxicities.

Table 4: Recommended dose modifications for treatment-related toxicities

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm ³)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm ³)	Maintain dose level
Grade 3 or 4 (ANC < 1000 - 500/mm ³ or < 500/mm ³)	Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN - 75,000/mm ³)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm ³)	Maintain dose level
Grade 3 or 4 (PLT < 50,000 - 25,000/mm ³ or < 25,000/mm ³)	Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
Febrile Neutropenia	
Febrile neutropenia (ANC < 1.0 x 10 ⁹ /L, fever ≥ 38.5°C)	Omit dose until resolved, then decrease dose by 1 step
Muscle Toxicity	
Elevated creatine phosphokinase (CK)	
Asymptomatic (no new-onset muscle pain/spasm or worsening of pre-existing muscle pain/spasm) CTCAE grade 1 or 2 CK elevation	<ul style="list-style-type: none"> • For CTCAE grade 1 CK elevation, continue treatment on same dose and continue monitoring as per schedule of assessments • For sites in France: For treatment-emergent CTCAE grade 1 CK elevation, continue treatment on same dose. CK should be measured weekly until CK returns to normal for baseline value. • For CTCAE grade 2 CK elevation, collect blood sample for PK and consider performing a muscle biopsy; continue on same dose level of LDE225. CK should be measured weekly until resolution to ≤ grade 1.
Symptomatic (new-onset or worsening of pre-existing muscle pain/spasm) with CTCAE grade 1 or 2 CK elevation	<ul style="list-style-type: none"> • For CTCAE grade 1 CK with muscle pain/spasm ≥ CTCAE grade 1, continue treatment at same dose and measure CK weekly until CK returns to normal or baseline value or muscle pain/spasm resolves • For CTCAE grade 2 CK with muscle pain/spasm ≥ CTCAE grade 1, collect blood sample for PK and continue treatment at same dose level of LDE225. CK should be measured weekly until CK is ≤ CTCAE grade 1
CTCAE grade 3 or 4 CK elevation (with or without muscle pain/spasm)	<ul style="list-style-type: none"> • Omit LDE225 dose, collect sample for PK, check blood myoglobin and monitor renal function. Measure CK weekly until resolution to grade ≤ 1 • Consider performing electromyography, MRI scan of symptomatic muscle group(s) and muscle biopsy • If renal function is not impaired and resolution to ≤ CTCAE grade 1 occurs within 21 days, consider resuming treatment at a reduced dose; CK should be measured weekly for 2 months after re-administration of LDE225 • Patients who experience renal impairment (serum creatinine > 2x ULN) should be permanently discontinued from the study
Muscle pain/spasm (new onset or worsening of pre-existing muscle pain/spasm)	<ul style="list-style-type: none"> • For CTCAE grade 1 muscle pain/spasm, continue treatment on the same dose and planned assessments • For CTCAE ≥ grade 2 muscle pain/spasm, measure CK weekly until muscle pain resolves to ≤ grade 1. If CK is elevated, follow guidance for CK elevation as described above. Continue treatment with LDE225 • For new-onset CTCAE grade 3 muscle pain/spasm, interrupt LDE225. Collect blood sample for PK and CK measurement at the time of dose interruption. Provide symptomatic treatment. Measure CK weekly until the muscle pain/spasm resolves to ≤ grade 1 and resume therapy at a reduced dose. Measure CK weekly for 2 months after re-administration.

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Renal	
Serum creatinine	
Grade 1 Serum creatinine >ULN <1.5 x ULN	Maintain dose level
Grade 2 Serum creatinine 1.5-3 x ULN	Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease dose by 1 step (consider checking serum CK, if not already done)
Grade 3 Serum creatinine > 3.0 - 6.0 x ULN	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step
Grade 4 Serum creatinine > 6.0 x ULN	Omit dose and discontinue patient from study
Hepatic	
Bilirubin	
Grade 1 Total bilirubin >ULN <1.5 x ULN	Maintain dose level
Grade 2 Total bilirubin 1.5-3 x ULN	Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease by 1 step
Grade 3 Total bilirubin > 3.0 - 10.0 x ULN	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step
Grade 4 Total bilirubin > 10.0 x ULN	Omit dose and discontinue patient from study
AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level
Grade 2 (> 3.0- 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline then: <ul style="list-style-type: none"> If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease dose by 1 step
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 1 step
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Omit dose and permanently discontinue from study.
Cardiac	
Cardiac - prolonged QTc interval ≥ grade 3 (QTcF > 500 msec or >60 ms change from baseline on at least 2 separate ECGs) taken within 1 hour	First Occurrence: <ul style="list-style-type: none"> Omit dose Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. Perform a repeat ECG within one hour of the first QTcF of > 500 ms If QTcF remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTcF returns to < 480 ms. Once QTcF prolongation has resolved, study treatment may be restarted at a reduced dose level Second Occurrence: <ul style="list-style-type: none"> discontinue patient from further study treatment

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose and discontinue patient from study
Grade 4	Omit dose and discontinue patient from study
Other adverse events**	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to \leq grade 1, then decrease dose by 1 step
Grade 4	Omit dose and discontinue patient from study
All dose modifications should be based on the worst preceding toxicity.	
If the dose-limiting toxicity recurs in a patient following 2 dose reductions, then further therapy with LDE225 will not be continued. Patients assigned to 200 mg will be discontinued from further study treatment if they require a second dose reduction.	
If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose because of an LDE225-related toxicity, then the patient must be discontinued from the study (see Section 6.1.4.1.1).	
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03).	
** If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose level is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis.	

Source: Study LDE225A2201 clinical protocol, version 6

Concomitant Therapy

Medications for the treatment of cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as pain medications were allowed. Growth factors and blood transfusions were permitted in the setting of dose-limiting cytopenias. Additional concurrent anticancer treatments, including surgery and radiation were not permitted. The following medications were prohibited:

- Strong CYP3A inhibitors and inducers
- CYP2B6 and CYP2C9 substrates
- Warfarin and Coumadin derivatives
- Drugs that may increase risk of rhabdomyolysis when used concomitantly with sonidegib
 - Azoles antifungals: Itraconazole, ketoconazole, fluconazole, voriconazole
 - Macrolides: azithromycin, clarithromycin, erythromycin, telitromycin
 - Fibrates: gemfibrozil
 - 3-hydroxy-3 methyl-glutaryl (HMG) Coa reductase inhibitors: Atovastatin, Fluvastatin, Fluvastatin XL, Lovastatin, Pravastatin, Rosuvastatin- and Simvastatin (For patients that absolutely required stain treatment for hyperlipidemia, only pravastatin was permitted with frequent CK monitoring)
 - Antiretrovirals: Indonavir and ritonavir
- Others: phenobarbital, barbiturates, phenytoin and isoniazid

Efficacy Assessments

Response evaluations took place at Week 5, 9, 17, and then once every 8 weeks during the first year and once every twelve weeks thereafter. The complete schedule of efficacy assessments is shown in Table 47.

Tumor assessment for patients with mBCC

Objective response was assessed using RECIST 1.1 for patients with mBCC. Depending on the location of the tumor, imaging methods for mBCC included regular CT or MRI scans, and the same imaging method was to be used throughout the study for each patient. Color photography for skin lesions was also performed for patients with mBCC.

Tumor assessment for patients with laBCC

A protocol-specific modified RECIST (mRECIST) was used for assessing response in patients with laBCC. The mRECIST criteria were based on evaluation of multiple modalities including localized MRI scans, digital color photography and histopathology from tumor biopsy specimens, to derive a composite endpoint of “composite overall response”.

Measurements on MRI scans were made according to RECIST 1.1 guidelines. An imaging CRO was designated for the study to provide central confirmation that MRI was appropriate for the evaluation of tumors in individual patients with laBCC. Per protocol, the baseline localized/soft tissue MRI scans were sent to the imaging CRO for central review. If the imaging CRO recommended that localized/soft tissue MRI was appropriate for tumor response evaluation, the site performed MRIs at the time of each tumor response assessment in addition to color photography (if applicable) throughout the study. If the imaging CRO determined that MRI was not appropriate for evaluation of tumor response for an individual patient, only color photographs were required to be obtained at all subsequent time points on the tumor assessment schedule.

Color photography was acquired using a digital camera and included a ruler such that the size of the lesion could be determined from the photograph. Multiple views of each target lesion were taken at each scheduled assessment including a close-up view with lesion contouring (annotated photography) to include both palpable and visible components. Photography was measured according to an adapted World Health Organization (WHO) response criteria which incorporates the bi-dimensional measurements of the longest diameter and the longest in-plane perpendicular diameter for each lesion.

The histopathology evaluation was performed on punch tumor biopsies taken at baseline, week 9, week 17, at disease progression, and at end of treatment from patients with accessible laBCC. Additional biopsies were performed to confirm complete response. The protocol included detailed guidelines on the number of specimens to collect depending on the size of the lesion. All biopsies were centrally reviewed.

The composite overall response at each post-baseline assessment was determined by an Independent Review Committee (IRC) comprised of two independent oncologists and one

independent radiologist. The IRC served to integrate the results of the centrally reviewed MRI scans, photography and histopathology to determine a composite overall response. According to the mRECIST guidelines in the protocol, when overall lesion response assessments for all modalities (MRI and photography and tumor biopsy), are available, the methodologies will be prioritized when considering evidence of treatment effect, in the following order: histopathology, clinical photographs, and MRI scans. Table 5 is a summary of the composite response assessment used in patients with IaBCC.

Table 5: Composite Overall Response Assessment per mRECIST in patients with IaBCC

Composite overall response	MRI	Clinical photography	Histopathology
CR	CR	CR, PR(s/f), SD(s/f), or NA ^a	Negative
CR	NA ^b	CR, PR(s/f), or SD(s/f)	Negative
PR	PR	CR, PR(s/f), or SD(s/f)	Negative
PR	SD	CR, PR(s/f), or SD(s/f)	Negative
PR	CR	CR, PR(s/f), NA ^a	Positive or unknown
PR	CR	PR	Any
PR	PR	CR, PR(s/f)	Positive or unknown
PR	PR	PR, NA ^a	Any
PR	SD	CR, PR(s/f)	Positive or unknown
PR	SD	PR	Any
PR	NA ^b	CR, PR(s/f)	Positive or unknown
PR	NA ^b	PR	Any
SD	CR	SD	Any
SD	CR	SD(s/f)	Positive or unknown
SD	PR	SD	Any
SD	PR	SD(s/f)	Positive or unknown
SD	SD	SD, NA ^a	Any
SD	SD	SD(s/f)	Positive or unknown
SD	NA ^b	SD	Any
SD	NA ^b	SD(s/f)	Positive or unknown
Unknown	Any (except PD)	Unknown ^c	Any
Unknown	Unknown ^d	Any (except PD)	Any
PD	PD	Any	Any
PD	Any	PD	Any

CR = complete response; NA = not available; PD = disease progression; PR = partial response; SD = disease stabilization; s/f = scar/fibrosis only

^a Disease unevaluable by photography at baseline; also includes scenarios where photographic data are unavailable

^b Disease unevaluable by MRI scan at baseline; also includes scenarios where MRI data are unavailable

^c As a result of missing assessment or other reasons post-baseline while disease is evaluable by photography at baseline

^d As a result of missing assessment or other reasons post-baseline while MRI scan at baseline was available.

Source: LDE225A2201 CSR

Safety Assessments

Toxicity was assessed using the NCI CTCAE version 4.03. Patients were screened for adverse events (AE) at each clinic visit. An AE was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occurred after patient's signed informed consent had been obtained. Abnormal laboratory values or test results were considered AEs if they caused clinical signs or symptoms, were considered clinically significant, required therapy, or required interruption or dose adjustment in study medication. A serious AE (SAE) was defined as an AE that is fatal or life-threatening, results in persistent or significant disability, constitutes a congenital anomaly, requires inpatient hospitalization or prolongs an existing hospitalization, or is considered medically significant because it requires medical or surgical intervention to prevent an undesirable outcome. All SAEs, regardless of suspected causality, were required to be reported to Novartis within 24 hours of the investigator learning of its occurrence. Adverse events of special interest during the study included muscle-related events, nausea and/or vomiting, diarrhea, fatigue, dysgeusia, alopecia, decreased appetite and weight loss. All AEs were to be recorded and described in the CRF. All scheduled safety and laboratory assessments are summarized in Tables 47 and 48 in Section 9.5 of the review.

Statistical Methods

Randomization was stratified by disease stage, histology and geographic region. The primary analysis of study data was conducted when all patients had been treated for 24 weeks or discontinued treatment. The treatment assignments remained blinded from the time of randomization until the primary analysis.

The primary endpoint was centrally reviewed ORR according to mRECIST for patients with laBCC and according to RECIST 1.1 for patients with mBCC. The secondary endpoints included centrally confirmed DOR and the rate of CR, TTR, PFS, OS, investigator determined response and safety. The following populations were defined for the primary analysis:

- Full analysis set (FAS): the intent to treat (ITT) population; all patients randomized to receive sonidegib
- Primary efficacy analysis set (pEAS): the subset of the FAS including patients with laBCC eligible for tumor assessment according to mRECIST guidelines

Patients with laBCC were included in the pEAS if they met one of the following criteria:

- Patients were assessed by both MRI and annotated photograph at baseline.
- Patients were assessed by MRI and non-annotated photograph at baseline, and had documentations of the absence of palpable sub-dermal components outside the margins of the photographed lesion(s).
- Patients were assessed by photograph only at baseline and MRI scan was not done due to an appropriate and documented clinical reason (e.g. disease is not measurable or MRI is contraindicated).
- Patients were assessed by MRI only at baseline and photographs were not done due to an appropriate, documented clinical reason (e.g. lesion is in a difficult anatomical location such as auditory canal).

Per protocol, the primary and key secondary efficacy endpoints were based on the pEAS. FDA recommended that the primary and key secondary analyses be performed in the FAS, which represented the intent-to-treat population, and the Applicant agreed to additionally conduct the analyses in the FAS.

Safety analyses were performed on all patients who received at least one dose of sonidegib and had at least one post-baseline assessment. Safety evaluation was performed based on the dose of sonidegib (800 mg or 200 mg) that a patient received. Adverse events that were unrelated to treatment and occurred more than 30 days after the administration of the last dose of treatment were not reported or analyzed.

One prespecified interim analysis (IA) of safety and efficacy data was planned for when the first 48 patients randomized had completed 16 weeks of treatment or discontinued treatment. The efficacy analysis was based on the FAS, and the safety analysis was based on the safety population. A data monitoring committee (DMC) reviewed interim results.

Sample size calculation and hypothesis

The study design allowed accrual of approximately 210 patients in order to obtain 150 patients in the pEAS if both treatment arms were continued beyond the planned interim analysis. This sample size allowed for a type 1 error rate of 0.003 for 800 mg arm and 0.024 for the 200 mg arm if the true ORR on the respective arms was 20% or less. The analytic plan in the protocol states that when the 800 mg arm is terminated and the 200 mg continues to enroll 100 patients in the pEAS, the type I error rate is 0.005 if the true ORR for 200 mg arm is 20% or less.

Treatment with sonidegib was considered to be of clinical benefit if the observed ORR by central review on any treatment arm at the end of the study was 30% or higher. There were no planned statistical analyses comparing the two treatment arms, and the difference in ORR between the two treatment arms was to be summarized. DOR and rate of complete response were to be summarized with inclusion of the 95% confidence intervals (CIs) for each treatment group. The Kaplan-Meier method was used to estimate PFS and OS. The median PFS and OS times (if estimable) including 95% confidence intervals were to be summarized for each treatment arm.

Missing data/censoring

Patients with a best overall response of 'Unknown' were treated as non-responders in estimating the ORR in the primary analysis. PFS for patients who were progression-free or lost-to-follow-up at the end of the study were right-censored at their last radiologic tumor assessment date. OS time for patients who are alive at the end of the study or are lost to follow-up were right-censored at the date of last contact.

Major protocol amendments

Study A2201 was modified several times. Table 6 summarizes the key changes to the protocol with each amendment.

Table 6: Summary of Study A2201 protocol amendments

Amendment no. (date) / no. of patients recruited	Summary of amendment	Rationale and justification
Amendment 1 (19-Apr-2011) 0 patients	Wording on contraceptive precautions updated	To ensure compliance with the UK Guideline of Prevention of Pregnancies in Participants in Clinical Trials
Amendment 2 (17-Nov-2011) 26 patients	Inclusion criteria modified to clarify eligible patient population Central histopathological analysis implemented	Reasons for ineligibility for local therapies or curative surgery to be collected Initiated for confirmation of diagnosis and eligibility (NB: as a result, a majority of laBCC patients enrolled prior to this ineligible for analysis of ORR per mRECIST)
	Sample size increased from 80 to 100 in 800-mg arm and from 40 to 50 in the 200-mg arm	To collect additional safety and efficacy data
	Criteria for assessing ORR amended from RECIST 1.1 to mRECIST for patients with laBCC	Tumor response assessment in patients with laBCC when associated with ulceration, cysts, and scarring/fibrosis are not adequately covered by RECIST 1.1
	Implementation of central reading for determination of primary endpoint	To obtain more robust conclusions
Amendment 3 (23-Nov-2011) 29 patients	Patients experiencing asymptomatic treatment-emergent grade 1 CK elevation to undergo weekly monitoring until resolution	To satisfy local regulatory requirements in France
Amendment 4 (28-Jun-2012) 150 patients	Introduction of primary efficacy analysis set (pEAS)	mRECIST implemented in Amendment 2; consequently, a majority of patients with laBCC enrolled prior to this may not have been eligible for analysis of ORR per mRECIST. The pEAS defined a subset of the full analysis set (FAS) and excluded laBCC patients who were not eligible for tumor assessment per mRECIST.
	Sample size further expanded to approximately 210 patients	To ensure a sufficient number of patients in the pEAS (i.e. 50 patients on 200 mg and 100 patients on 800 mg)
Amendment 5 (03-Jun-2013) 230 patients	Statistical analysis for secondary endpoints updated	Allowed ORR according to RECIST 1.1 to be derived for central review data by MRI and photography independently without lesion matching between MRI/photograph and lesions
Amendment 6 (14-Nov-2013) 230 patients	Institution of Independent Review Committee to integrate MRI, photography, and histology data to assess composite overall response	To provide clarification on how the 3 methods of assessment per mRECIST (MRI, color photography, and histology) were to be integrated to determine the composite overall response for patients with laBCC (see Table 9-4)

Source: Table 9-3, CLDE225A2201 CSR

6 Review of Efficacy

Efficacy Summary

The results of a single, international, multi-center, randomized, blinded trial of two doses of sonidegib in 230 patients with either mBCC (n=36) or locally advanced BCC (n=194) support this application. Patients in Study A2201 were randomized 2:1 to receive sonidegib 800 mg (n=151) or 200 mg (n=79) daily. The minority of patients had mBCC in both treatment arms [13 patients (16%) in the 200 mg group; 23 patients (15%) in the 800 mg group]. Patients with mBCC were required to have measurable disease according to RECIST 1.1. Patients with laBCC were required to have disease not amenable to curative surgery or radiation therapy. Reasons for ineligibility for local therapies were collected and are summarized in Table 8. Patients were excluded if they had prior exposure to Hh inhibitors.

Patients were stratified by disease stage (laBCC versus mBCC), disease pathology (aggressive versus non-aggressive histology) and geographic region (North America versus Europe versus Australia). Patients received 200 mg or 800 mg sonidegib daily on a continuous basis until disease progression or unacceptable toxicity. Disease assessments occurred at Weeks 5, 9, 17, and then once every 8 weeks during the first year and once every twelve weeks thereafter.

The primary efficacy endpoint was centrally reviewed objective response rate (ORR) according to RECIST in patients with mBCC and according to a protocol-specific modified RECIST (mRECIST) for patients with laBCC. The mRECIST assessment involved a composite response based on integration of MRI, photographic and histopathologic criteria in patients with laBCC. All radiology, photography and pathology were centrally reviewed, and an independent review committee (IRC), consisting of two dermato-oncologists and one radiologist, was employed to determine the best overall response in each patient. See Section 5.3 for details on Study A2201 response assessments. Key secondary endpoints were centrally reviewed duration of response (DOR), complete response rate (CRR), progression free survival (PFS) and overall survival (OS).

The Applicant analyzed the primary and key secondary efficacy endpoints based on the primary efficacy analysis set (pEAS) which included the subset of patients with disease that could be measured using mRECIST; however, FDA considered the full analysis set (FAS), or the intent-to-treat population, to be the more appropriate efficacy population. The Applicant agreed to analyze key efficacy outcomes based on the FAS in addition to the pEAS and that these results would support the marketing application and be reflected in the product label. FDA efficacy analyses are based on the FAS unless otherwise specified.

The Applicant submitted efficacy data for the primary analysis (data cut-off June 28, 2013, six month analysis) which were the basis for the analyses presented in the CSR for Study A2201. Efficacy data from longer follow-up of patients (data cutoff December 31, 2013; 12 month analysis) were also submitted with the NDA, and analyses of these data were included as an

addendum to the SCE. FDA agreed to review both the primary and updated efficacy data and that the label would reflect the results from the 12 month analyses.

The 200 mg and 800 mg treatment arms for patients with laBCC both met the prespecified primary endpoint of response rate > 30% with the lower bound of the 95% CI exceeding 20%.

(b) (4)
The following key efficacy results are derived from FDA analyses based on the FAS in the 12 month analysis and confirm the results presented by the Applicant:

- The ORR in patients with laBCC treated in the 200 mg arm was 58% (95% CI: 44.8, 69.7), and the ORR in patients with laBCC treated in the 800 mg arm was 44% (95% CI: 35, 52.8).
- (b) (4)
- The median DOR was non-estimable (NE) for patients with laBCC in the 200 mg arm and 15.7 months (95% CI: NE) for patients with laBCC in the 800 mg arm. (b) (4)
- The median PFS for patients with laBCC was 22.1 months (95% CI: NE) in the 200 mg arm and 21.5 months (95% CI: NE) in the 800 mg arm. (b) (4)

Study A2201 did not demonstrate an exposure-response relationship for the primary efficacy endpoint (b) (4). The response rate for patients with laBCC was lower in the 800 mg arm (44%) compared to the 200 mg arm (58%). Furthermore, the safety results discussed in Section 7 of the review demonstrate that the 200 mg dose is more tolerable than the 800 mg dose; therefore, the Applicant appropriately selected the 200 mg daily dose as the recommended dose.

In summary, ORR of sufficient magnitude and durability is considered an acceptable measure of tumor shrinkage and clinical benefit to patients with advanced BCC. The efficacy data from Study A2201 demonstrate that patients with laBCC experienced durable and clinically meaningful response rates. These data support the approval of sonidegib at the proposed 200 mg daily dose in patients with laBCC not amenable to local therapies. (b) (4)

6.1 Indication

The proposed indication for this application is: Sonidegib is for the treatment of patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy (b) (4).

The recommended dose of sonidegib is 200 mg orally daily.

6.1.1 Methods

The efficacy review is based on the results from Study A2201 which evaluated two doses of sonidegib in patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC). Efficacy data from the primary six month analysis (data cut-off June 28, 2013) and from the twelve month analysis (data cut-off December 31, 2013) of Study A2201 were reviewed. Analyses of the primary and key secondary endpoints were performed on the data from both timepoints.

6.1.2 Demographics

Fifty-eight centers in twelve countries enrolled patients in Study A2201. The first patient enrolled on July 20, 2011 and the last patient enrolled on January 10, 2013. A total of 269 patients were screened, and 230 were randomized 2:1 to receive sonidegib 800 mg or 200 mg daily. One patient randomized to the 800 mg arm discontinued the study prior to initiating treatment.

Reasons for screen failures were reported for 30 patients. These included: absence of a confirmed diagnosis of laBCC or mBCC or measurable disease according to protocol criteria (n=11), inadequate organ function according to protocol criteria (n=8), presence of an uncontrolled medical condition that would interfere with participation in the study (n=3), non-agreement to use of a condom during the study and for six months after the last dose of sonidegib in sexually active males (n=2), receiving medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have a narrow therapeutic index, and that cannot be discontinued before starting sonidegib (n=2), World Health Organization (WHO) performance score status less than or equal to 2 (n=2), prior hedgehog inhibitor treatment (n=1), and inability to tolerate oral administration of sonidegib or lack of integrity of the gastrointestinal tract that would lead to potential malabsorption (n=1). One patient had both an uncontrolled medical condition and inadequate organ function.

Table 7 summarizes the demographic characteristics and baseline performance scores for patients in Study A2201. In general, demographics and performance scores were balanced between the two treatment arms. The majority of patients were from Europe (56%), followed by North America (39%) and Australia (5%). Median age at randomization was 67 years old in the 200 mg arm and 65 years old in the 800 mg arm; 28% of patients in the entire study were over the age of 75 years. The majority of patients in both arms (87% in the 200 mg group and 92% in the 800 mg group) had ECOG scores of 0 or 1. The majority of patients were White and male, consistent with the epidemiology of BCC. There were 86 females enrolled; sixty-nine (80%) were post-menopausal and seventeen (20%) were of child-bearing age. Eleven patients (13%) were considered fertile while six patients of child-bearing age were sterile at study entry.

Table 7: Demographics

	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All Patients N=230 n (%)
Age (25-92)			
Median Age	67	65	66
Mean Age	66	64	64
Age \geq 65	47 (60)	78 (52)	125 (54)
Age \geq 75	25 (32)	38 (25)	64 (28)
Gender			
Male	48 (61)	96 (64)	144 (63)
Female	31 (39)	55 (36)	86 (37)
Race			
White	71 (90)	145 (96)	216 (94)
Black or African	0	1 (1)	1 (<1)
Other	8 (10)	5 (3)	13 (6)
Region			
Europe	45 (57)	83 (55)	128 (56)
North America	29 (37)	61 (40)	90 (39)
Australia	5 (6)	7 (5)	12 (5)
ECOG Performance Status Score			
0	50 (63)	95 (63)	145 (63)
1	19 (24)	44 (29)	63 (27)
2	8 (10)	10 (7)	18 (8)
Unknown	2 (3)	0 (1)	4 (2)

Source: ADSL.xpt, primary analysis

Disease characteristics

All patients had an investigator-confirmed diagnosis of laBCC or mBCC at baseline. Sixteen patients (7%) had a diagnosis of nevoid BCC syndrome (i.e., Gorlin Syndrome), and one of the sixteen had mBCC. FDA requested that the Applicant provide documentation of the reasons why patients with laBCC were considered not amenable to local therapies (i.e, surgery or radiation). The most common reasons for enrollment in Study A2201 included: tumor location not amenable to surgery or radiation, risk for disfigurement, and multiple recurrences after prior local therapies. Table 8 summarizes the reasons that were collected at the time of patient enrollment for 229 patients with either laBCC or mBCC.

Table 8: Reasons for enrollment for patients with laBCC

Reason for Enrollment	Patients N=229 n (%)
Surgery or radiation therapy inappropriate due to location and area of lesion	77 (34)
Complete surgical resection without severe disfigurement not feasible or surgery contraindicated	69 (30)
Multiple tumor recurrence (≥ 2) after prior surgery or radiation therapy	62 (27)
Metastatic disease, basalioma metastasis, or multiple BCC	5 (2)
Radiation therapy contraindicated due to pre-existing condition	5 (2)
Patient refused surgery or radiation or requested clinical trial enrollment	5 (2)
Gorlin syndrome	4 (2)
Sarcomatoid BCC	1 (<1)
Recommendation by a multidisciplinary team	1 (<1)

Source: ZC.xpt, CRFs

Table 9 summarizes the disease characteristics of patients enrolled in Study A2201. The proportion of patients with mBCC in each treatment group was similar (16% of the 200 mg arm and 15% of the 800 mg arm). Approximately 60% of patients in both treatment arms had at least two BCC lesions, and about 50% of patients had both target and nontarget lesions at enrollment. The predominant pathologies were infiltrative and nodular BCC. The measurable baseline disease, defined as the sum of the longest diameters per RECIST, was similar between treatment arms and between patients with laBCC and mBCC.

Table 9: Disease characteristics

Disease Characteristics	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All Patients N=230 n (%)
Number of Target Lesions			
0	0	1	1
1	30 (38)	57 (38)	87 (38)
≥ 2 lesions	49 (62)	93 (62)	142 (62)
BCC Histology			
Infiltrative	31 (39)	57 (38)	88 (38)
Nodular	28 (35)	41 (27)	69 (30)
Superficial	10 (13)	24 (16)	34 (15)
Sclerosing	6 (8)	8 (5)	14 (6)

(morpheaform)			
Basosquamous (metatypic or keratonizing)	2 (3)	7 (5)	9 (4)
Multifocal	1 (1)	4 (3)	5 (2)
Micronodular	0	3 (2)	3 (1)
Clear cell	0	1 (1)	1 (<1)
Other	1 (1)	6 (4)	7 (3)
Measurable Disease at Baseline (mm)*			
laBCC, median (range)	48 (11-281)	48 (10-415)	48 (10-415)
mBCC, median (range)	38 (15-121)	53 (16-158)	49 (15-158)

Source: ADSL.xpt, ADZC.xpt, Table 11.5 and 14.1-3.2.1, Study A2201 CSR

* Measurable disease is per central review of digital photography for laBCC and MRI or CT for mBCC.

Prior treatments for BCC

Table 10 summarizes the prior therapy patients in Study A2201 received for BCC. Patients with laBCC and mBCC are separated in each arm because of the expected differences in treatment algorithms for laBCC versus mBCC. The two treatment arms were balanced with regard to prior treatments; however, as expected, more patients with mBCC received prior systemic chemotherapy (28% as compared to 2% of patients with laBCC) and prior radiation (19% as compared to 8% of patients with laBCC).

Table 10: Prior therapy indicated for BCC by disease stage and treatment arm

Prior Antineoplastic Treatments	LaBCC		mBCC	
	Sonidegib 200 mg N=66 n (%)	Sonidegib 800 mg N=128 n (%)	Sonidegib 200 mg N=13 n (%)	Sonidegib 800 mg N=23 n (%)
Surgery*	49 (74)	104 (81)	11 (85)	23 (100)
Radiotherapy	5 (8)	10 (8)	3 (23)	4 (17)
Systemic chemotherapy	0	3 (5)	3 (23)	7 (30)
Topical or phototherapy	12 (18)	17 (13)	1 (8)	0

Source: ADSL.xpt, ADZB.xpt, ADZP.xpt, ADZT.xpt, CRFs

*Surgeries included resections and prior biopsies in the database.

Reviewer: The results in Table 10 differ from the CSR because upon review of the prior therapy datasets and the CRFs, the reviewer noted that some patients received prior systemic chemotherapy drugs such as combination carboplatin and paclitaxel. Although these drugs

were considered to not have been administered for BCC based on the CRFs, the patients' medical histories did not list prior cancers or other conditions that would warrant chemotherapy administration. FDA requested that the Applicant review specific cases with this discrepancy. The Applicant provided an analysis that demonstrated that a total of 13 patients (6%) enrolled in Study A2201 most likely received prior systemic chemotherapy for BCC. The small increase in patients receiving prior chemotherapy for BCC does not substantially change the overall study population or the risk:benefit profile of sonidegib.

6.1.3 Subject Disposition

A total of 230 patients were enrolled in Study A2201 and included in the FAS (intent-to-treat population); 79 patients were randomized to receive sonidegib 200 mg daily, and 151 patients were randomized to receive sonidegib 800 mg daily. One patient in the 800 mg arm discontinued prior to initiating treatment. As of the June 28, 2013 data cut-off, 85 patients remained on study, and 144 patients had discontinued study treatment [40 (51%) in the 200 mg arm and 104 (69%) in the 800 mg arm]. The most frequently reported reasons for treatment discontinuation were development of adverse events (AEs), patient decision, progressive disease, and physician decision. The most common reason for discontinuation in the 200 mg group was disease progression while the majority of patients in the 800 mg group discontinued due to adverse events. Patient and physician decisions to discontinue sonidegib were also more frequent in the 800 mg group. Table 11 summarizes the disposition of patients in Study A2201 at the time of the primary analysis.

Table 11: Patient disposition, primary analysis

Patient Disposition	Sonidegib 200 mg (N=79) n (%)	Sonidegib 800 mg (N=151)* n (%)	Total (N=230) n (%)
Treatment ongoing	39 (50)	46 (31)	85 (37)
Treatment discontinued	40 (51)	104 (70)	144 (63)
Reasons for Discontinuation			
Adverse Events	16 (20)	48 (32)	64 (28)
Progressive Disease	15 (19)	6 (4)	21 (9)
Withdrawal by subject*	5 (6)	28 (19) *	33 (14)
Physician Decision	3 (4)	10 (7)	13 (6)
Lost to follow-up	1 (1)	4 (3)	5 (2)
Death	0	4 (3)	4 (2)
Noncompliance	0	3 (2)	3 (1)
Protocol Violation	0	1 (1)	1 (<1)

Follow-up after discontinuation			
Post-treatment follow-up	11 (14)	30 (20)	41 (18)
Survival follow-up	16 (20)	27 (18)	43 (19)

Source:ADSL.xpt, 6 month analysis, CRFs

*Some patients coded as 'withdrawal by subject' most likely discontinued sonidegib due to AEs (see Section 6.1.3). The discrepancy in this coding does not change the overall safety profile of the drug.

Reviewer: Comments were provided by the investigator for 12 patients in the 800 mg group who discontinued treatment for the reason of "withdrawal by subject" (i.e, patient decision). In at least three of the cases, the investigator's comments suggest that the patient's decision was based on an AE. The reasons reported were "anxiety over prior CK level", "unacceptable weight loss", and "patient felt his QOL negatively impacted by AE". The noted discrepancy in this coding does not substantially change the overall safety evaluation of sonidegib.

At the time of the twelve month analysis, 50 patients remained on study treatment, 21 (27%) in the 200 mg group and 29 (19%) in the 800 mg group. The proportion of patients discontinuing for adverse events was again higher in the 800 mg group (34%) as compared to the 200 mg group (25%).

Reviewer: The higher proportion of discontinuations for adverse events in the 800 mg arm in both analyses and the ability of more patients in the 200 mg arm to continue treatment until disease progression support the selection of the 200 mg daily dose for the indication.

Protocol Violations

The CSR for Study A2201 describes five major protocol deviations that led to patients being excluded from the pEAS. These included two patients starting sonidegib more than fourteen days after randomization, and three patients not meeting key eligibility criteria (absence of target and nontarget lesions, measurable disease < 10 mm, and randomization prior to histological confirmation of BCC diagnosis).

Reviewer: These five violations do not substantially impact the integrity of the study or the reliability of the study results for conducting the safety and efficacy reviews.

The reviewer additionally performed an analysis of the ADDV.xpt dataset and reviewed the line listings of all protocol violations that occurred during Study A2201 in the FAS population in the primary analysis. Table 12 summarizes this analysis. A total of 969 protocol deviation events occurred in 201 patients (87%) enrolled in the study.

Table 12: Protocol violations, primary analysis

Violation Category	Events	Patients	Reviewer Notes
Key procedures not performed	817	188	There were 42 serum CK levels not performed, 56 missing ECG assessments, 33 events of no photo or MRI evaluation within the specified time window per protocol. Some tumor biopsies were performed outside the permitted time window for tumor evaluation. Other events included missing biomarker levels, PK levels, survival information, and urinalysis assessments.
Selection Criteria Not met	79	48	There were 31 coded as 'inclusion criteria was not met' with no further details. Other violations included: no ECG done (1), baseline elevated CK (1), and no confirmation of diagnosis prior to randomization (1). Multiple patients had prolonged screening periods or delays in starting drug, randomization prior to return of central lab results, or received concomitant statin drug for brief periods without observed toxicity.
GCP-Related Deviation	55	37	GCP violations included missing informed consent forms after each amendment, erroneous pill counts or dispense amounts, and delays in safety reporting.
Treatment Deviation	9	9	Two patients had grade 3 serum CK elevation with no dose interruption; other violations involved delays in starting drug or administration of two doses in one day.
Prohibited Concomitant Therapy	9	8	Five patients had a surgical resection of a lesion during the study: nontarget lesion (1), medically indicated (1), and no further details reported (3). Two patients received concomitant coumadin, one patient received one dose of losartan, and one patient received concomitant simvastatin for 5 days.

Source: ADDV.xpt dataset, primary analysis; CRFs, Table 14.1-1.8 from Study A2201 CSR
GCP: Good clinical practice

FDA requested further information from the Applicant regarding the large number of protocol violations that occurred in Study A2201.

- FDA asked the Applicant to categorize the violations as major and minor. The Applicant stated that there were six major violations including those that led to the five patients being

excluded from the pEAS (described in the CSR and above) and one additional violation involving lack of ECOG performance status screening at baseline in one patient.

- FDA requested details regarding the protocol deviations that involved surgical resections and for commentary on whether the resection had an impact on the measurement of response or duration of response in individual patients. The Applicant stated that there were eight events in seven patients in which a surgical resection was considered a deviation because it was performed prior to the end of therapy visit and did not prompt prior censoring according to the protocol. The Applicant provided a summary table listing these patients and commentary regarding the deviation and the impact on response.

Reviewer: These cases were reviewed. In one case, the deviation was re-categorized as not meeting criteria for a deviation, and in all other cases, the reviewer agrees with the Applicant's rationale for why each event did not impact response results for that patient.

- FDA additionally asked the Applicant to clarify whether any of the deviations involving a missed or delayed MRI, tumor biopsy or photography session during the study had an impact on the objective response and duration of response data.
 - The Applicant informed FDA that for any MRI or photographic assessment that was not performed within four weeks of the scheduled date, the response result was categorized as 'unknown' using RECIST or mRECIST. For biopsy specimens that were not performed, the result 'unknown' was treated as a positive biopsy according to mRECIST and would therefore downgrade an assessment from an mRECIST composite overall response CR to a PR. The Applicant also informed FDA that in the 12 month analysis of best overall response, there were twelve patients with IaBCC and no patients with mBCC who had responses of 'unknown' after their baseline assessment and that all best overall responses that are 'unknown' were treated as nonresponders when calculating the ORR.
 - With regard to duration of response, the Applicant clarified that events occurring after two or more missing assessments were censored at the last adequate tumor assessment prior to the event. Since no patients in the 12 month analysis had events censored due to this reason, the Applicant's sensitivity analysis, in which an event occurring after two or more missing assessments is considered as a PD at the time of the next scheduled assessment following the last adequate tumor assessment, was identical to the main analysis.
 - With regard to delayed assessments, there was no action taken if an MRI or photography was delayed unless it was more than four weeks from the scheduled date. Similarly, the histology assessments were required to take place within a window of 3 days prior to the scheduled assessment to 28 days post the scheduled assessment date. Further delays would result in the result being categorized as 'unknown' and therefore similar to if the biopsy was not performed at all.

Reviewer: Although there was a large number of protocol violations that occurred during Study A2201, the majority were minor and involved missed laboratory evaluations which did not impact the efficacy review. Additionally, the Applicant's clarifications and analyses of how delayed or missing tumor assessments were handled adequately demonstrate that these violations should not have a substantial impact on the efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

Efficacy analyses of the primary endpoint were performed by Dr. Huanyu Chen, the FDA statistical reviewer for the application.

The primary efficacy endpoint for Study A2201 was ORR, defined as the proportion of patients with a centrally reviewed and confirmed best overall response of complete response (CR) or partial response (PR). Confirmation was obtained by repeated assessments at least four weeks apart. The protocol prespecified an ORR of $\geq 30\%$ with the lower bound of the 95% CI exceeding 20% in either treatment arm as criteria to establish the efficacy of sonidegib in patients with laBCC and mBCC.

Objective response in patients with mBCC was assessed according to RECIST 1.1. Objective response in patients with laBCC was assessed according to the protocol-specified mRECIST which was based on an integrated composite response derived from centrally reviewed MRIs, photography and biopsy results. The IRC was established with the sixth protocol amendment and functioned to integrate the radiographic, photographic and histologic results in order to determine the composite overall response for each patient. See Section 5.3 and Table 5 for details on the response assessment per mRECIST in patients with laBCC.

Two efficacy populations were defined in the Study A2201 protocol. All randomized patients were included in the FAS (N=230), and a subset of these patients who were eligible for response assessment using mRECIST (i.e. patients had adequate baseline MRI or annotated photography or both) formed the pEAS (N=171). The pEAS was introduced in the fourth protocol amendment because the finalized mRECIST guidelines for laBCC were not implemented until the second protocol amendment. The majority of patients with laBCC enrolled prior to the second amendment were not evaluable for response according to mRECIST due to lack of one or more required baseline disease assessments. These patients were included in the FAS but excluded from the pEAS.

The ORR primary endpoint, according to the protocol, was based on the pEAS, and ORR based on the FAS was considered supportive. FDA considered the FAS to be the more appropriate population for key efficacy analyses. The Applicant performed the primary and key secondary efficacy analyses based on the FAS in addition to the pEAS and was in agreement with FDA that the efficacy results reported in the product label would be those based on the FAS.

The Applicant submitted efficacy data from the primary analysis (data cut-off June 28, 2013) and from the updated 12 month analysis (data cut-off December 31, 2013) in support of the application. Both analyses were reviewed, and FDA agreed that it would be appropriate to include the 12 month results in the product label as these reflect response and duration of response data corresponding to an additional 6 months of follow-up.

The ORRs for both treatment arms exceeded 30% and the lower bounds of the 95% CIs exceeded 20% in the primary and 12 month analyses when patients with laBCC and mBCC were not analyzed separately. In the primary analysis, centrally reviewed ORRs in the FAS were 42% (95% CI: 30.8, 53.4) for the 200 mg group and 33% (95% CI: (25.1, 40.5) for the 800 mg group. In the 12 month analysis of the laBCC (b) (4)

Sonidegib efficacy was evaluated separately in patients with laBCC and those with mBCC as these subtypes of BCC, though having the same molecular pathogenesis, are essentially different diseases in terms of clinical presentation, management principles and overall prognoses. In patients with laBCC (N=194), the ORRs were 47% (95% CI: 34.6, 59.7) for patients treated in the 200 mg arm (N=66) and 35% (95% CI: 26.9, 44.1) for patients treated in the 800 mg arm (N=128) in the primary six month analysis. In the 12 month updated analysis, ORRs in patients with laBCC were 58% (95% CI: 41, 72.3) for the 200 mg group and 44% (95% CI: 35, 52.8) for the 800 mg group.

The subset of patients with mBCC enrolled in Study A2201 was small (N=36), consistent with the rarity of this disease. (b) (4)

Table 13 summarizes the ORRs and the proportion of complete and partial responders by treatment arm and disease stage from the primary and 12 month analyses.

Table 13: Objective response rate (ORR) per central review based on FAS

	LaBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
Primary Analysis, data cut-off June 28, 2013		
ORR n (%)	31 (47)	45 (35)
95% CI (%)	(34.6, 59.7)	(26.9, 44.1)
CR (%)	2 (3)	0
PR (%)	29 (44)	45 (35)
SD (%)	29 (44)	55 (43)
PD	1 (2)	0
Unknown	5 (8)	28 (22)
12 Month Analysis, data cut-off December 31, 2013		
ORR n (%)	38 (58)	56 (44)
95% CI (%)	(44.8, 69.7)	(35.0, 52.8)
CR (%)	3 (5)	2 (2)
PR (%)	35 (53)	54 (42)
SD (%)	22 (33)	48 (38)
PD (%)	1 (2)	1 (1)
Unknown	5 (8)	23 (18)

Source: Table created from analysis performed by Dr. Huanyu Chen, statistical reviewer
FAS: Full analysis set, ORR: objective response rate, CI: confidence interval, CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease

Reviewer: In the primary and 12 month analyses, ORR results in patients with laBCC assigned to both treatment arms met the predefined criteria for point estimates to meet or exceed 30%. The lower bounds of the associated 95% CIs exceeded 20%, the pre-specified threshold for clinical relevance according to the Study A2201 protocol.

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(b) (4)

(b) (4)

Additionally, during the review, FDA sought outside expertise via separate consultations with two Special Government Employees (SGEs) with expertise in the clinical management of patients with advanced BCC. In addition to general questions regarding the risk:benefit profile of sonidegib in patients with BCC, the SGEs were specifically asked for an opinion on

(b) (4)

See Section 9.4.

ORR based on the pEAS

FDA considered the ORR analysis based on the pEAS to be supportive. The ORRs for both treatment arms exceeded 30% and the lower bounds of the 95% CIs exceeded 20% in the primary and 12 month analyses based on the pEAS. Centrally reviewed ORRs in patients with laBCC were 43% (95% CI: 27.7, 59) in the 200 mg group and 38% (95% CI: 27.8, 48.3) in the 800 mg group. In the 12 month analysis, ORRs in patients with laBCC were 57% (95% CI: 41, 72.3) in the 200 mg group and 46% (95% CI: 35.8, 56.9) in the 800 mg group.

(b) (4)

Evaluation of medical photography supporting ORR

Centrally reviewed serial digital photography was a key assessment used in deriving the composite overall response according to mRECIST for patients with laBCC enrolled in Study A2201. The Applicant submitted the photography from patients who experienced an objective response during Study A2201 to the NDA.

The reviewer evaluated the photographic images for 36 responding patients with laBCC in the 200 mg treatment arm for tumor shrinkage from baseline in the context of each patient's IRC-determined best overall response (BOR), investigator-determined BOR, time to response (TTR), and duration of response (DOR). Response results from patients in the 800 mg group are not included in this analysis as the 200 mg daily dose is the intended dose for the indication. Table 15 summarizes this analysis. Three patients who obtained a complete response are highlighted.

Table 15: Time to response and DOR in all responders in the 200 mg arm, 12 month analysis

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
1504005	Right ear	CR	CR	113	461	C	Agree with IRC assessment of response. Lesion disappeared in the photographs by evaluation 3, and the skin remained clear at the last assessment prior to censoring.
1197009 ^b	Right ear	CR	UNK	111	302	C	Photography not performed at baseline. IRC based assessment on MRI and histology while investigator based assessment on MRI, histology and photography; therefore, investigator-assessed response was categorized as "UNK" per the criteria guidelines.
1193002	Forehead and cheek	CR	CR	118	309	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage was observed at both sites. The latest assessment prior to censoring revealed continued photographic response. Patient censored due to starting a new anticancer drug.
1150004	Left thigh, back	PR	PR	121	565	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage was observed. The latest assessment prior to censoring revealed continued photographic response.
1150007	Right ear	PR	PR	121	162	PD	Agree with IRC assessment of response at evaluation 3 and later assessment of PD. Skin surface appeared different in photographs from evaluation 5 but showed clearer evidence of progression at evaluation 6

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							(just prior to discontinuation). Response maintained for more than 5 months prior to progression.
1197013	Right upper lip, oral cavity	PR	PR	120	170	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage was observed. The latest assessment prior to censoring revealed continued photographic response.
1230001 ^a	Left anterior leg	PR	PR	231	151	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed by evaluation 4. The last assessment prior to censoring showed superficial changes to the lesion but no increase in actual linear measurement. Patient was censored due to starting a new cancer treatment.
1232004	Right scalp	PR	PR	64	133	PD	Agree with IRC assessment of response and later assessment of PD. Photographic evidence of response at evaluation 1, but evaluation 3 showed evidence of skin changes consistent with disease. Response maintained for approximately 4 months prior to progression.
1270001 ^a	Right orbit and periorbital skin	PR	PR	172	331	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at evaluation 2; first response documented at evaluation 4. The latest assessment prior to censoring revealed continued photographic response.
1312001	Left ear	PR	PR	222	88	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. Latest assessment prior to censoring revealed continued photographic response.
1393002	Right eyelid	PR	SD	175	171	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							continued photographic response. Discordance between IRC and investigator because there were evaluations of 'unknown' per the investigator after PR was determined. Biopsies were negative in at least two evaluations.
1397002	Oral cavity	PR	PR	57	362	PD	Agree with IRC assessment of response and later assessment of PD. Photographic evidence of response at evaluation 2. Response maintained for almost one year prior to progression. Lesion was still improved from baseline at the time of disease progression.
1503005 ^a	Right cheek, nose and forehead	PR	PR	118	112	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response.
1503006 ^a	Right scalp, 2 lesions	PR	PR	57	113	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response.
1503013	Left forehead	PR	SD	114	245	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response. Discordance between IRC and investigator, but details not provided. Biopsy was negative at evaluation 2.
1513013	Right leg	PR	PR	29	306	PD	Agree with IRC assessment of response. Lesion showed dramatic improvement but did not completely disappear. The last photograph showed that the annotated lesion was larger in diameter. Response was maintained for approximately 9 months.
1515001 ^a	Left scalp	PR	SD	128	57	C	Agree with IRC assessment of response. Lesion classification and response assessment differed between

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							IRC and investigator. IRC did not consider the lesion to be a target lesion by MRI. In cases where MRI is unavailable and lesions have response by photographic assessment but are still positive by biopsy, the patient can still be classified as PR according to mRECIST. This patient had impressive photographic tumor shrinkage. Censored because adequate assessment was no longer available.
1515005 ^a	Left nasal bridge	PR	CR	16	160	C	Lesion completely disappeared on photographic assessment; however, this patient did not have annotated photography at baseline or evaluation 1. Biopsy was negative at evaluations 2 and 4 when investigator assessed CR. Unclear why IRC considered patient to have a PR. Response ongoing at time of censoring.
1522001	Scalp and nose	PR	PR	120	225	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at two scalp lesions and one nasal lesion. Latest assessment prior to censoring revealed continued photographic response.
1531003	7 lesions evaluated: back (2), breast (2) shoulder (3)	PR	PR	226	113	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at all sites. Smaller breast and back lesions had obvious shrinkage earlier than larger lesions on shoulders. Latest assessment prior to censoring revealed continued photographic response.
1534004 ^a	Scalp and neck	PR	PR	113	540	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at both sites. Scalp appeared to respond quickly. Latest assessment prior to censoring revealed continued photographic response.
1601004	Nose	PR	PR	284	312	C	Agree with IRC assessment of

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							response. Large, deep, disfiguring cavitory lesion extending from nose into upper lips. Photographic evidence of tumor shrinkage over time. Skin along edges appeared fibrotic at recent assessments. Latest assessment prior to censoring revealed continued photographic response
1101001 ^a	Left cheek	PR	PR	168	169	PD	Agree with IRC assessment of response and disease progression. Photographic evidence of tumor shrinkage observed. Latest assessment showed new lesion developing at same site. Response maintained for over 5 months.
1102002	Multiple back lesions	PR	PR	283	139	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response. Some lesions appear to have completely disappeared from the reviewer's assessment of the photographs.
1151007	Right forehead	PR	PR	281	225	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response.
1151009	Ankle	PR	PR	169	225	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued photographic response. Lesion appeared almost completely disappeared in two most recent assessments.
1151011	Pelvis, lower abdomen and back	PR	PR	169	169	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage at all sites observed. The latest assessment prior to censoring revealed continued

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							photographic response. Back lesions appeared almost completely disappeared in last assessment.
1196001 ^a	Legs and abdomen	PR	PR	169	63	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage at all sites observed. The latest assessment prior to censoring revealed continued photographic response.
1197002 ^a	Abdomen and back	PR	PR	208	59	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at both sites. The latest assessment prior to censoring revealed continued photographic response.
1230004 ^a	Shoulder, back and breast	PR	SD	170	336	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage at all sites observed. The latest assessment prior to censoring revealed continued photographic response. Censored for withdrawing consent.
1237003	Right ear and breast	PR	CR	57	526	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed at both sites. The latest assessment prior to censoring revealed continued photographic response.
1350003 ^a	9 lesions: chin, nose, forehead, extremities, back	PR	PR	57	533	C	Reviewer evaluated serial photography of the chin and forehead lesions only. Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed and latest assessment prior to censoring revealed continued photographic response. Chin and forehead lesions appeared to be completely fibrotic tissue in the most recent assessments.
1513011 ^a	Back, neck	PR	PR	115	306	C	Four large disfiguring lesions at baseline. Tumor shrinkage evident at evaluation 1 at all sites. Agree with IRC assessment of response. Last

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							assessment prior to censoring demonstrated continued response and what appeared to be complete fibrosis of the neck lesion.
1522002	Right scalp	PR	PR	176	113	C	Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed what appeared to be mostly scar tissue.
1524002	Cheek, nose, forehead, neck	PR	PR	121	84	C	Disfiguring lesions on cheek and nose and smaller lesions on forehead and neck. Serial photography reviewed for cheek and nose. Agree with IRC assessment of response. Photographic evidence of tumor shrinkage observed. The latest assessment prior to censoring revealed continued response.
1529001	Bilateral lower legs	PR	PR	225	256	PD	Two lesions evaluated. One lesion exhibited more rapid tumor shrinkage but both showed evidence of response by Evaluation 5 (approximately 7 months after treatment initiation). Disease progression was evident at the lesion which was slower to respond prior to discontinuation, but response was maintained for over 8 months.
1601006	Nose	PR	PR	63	214	PD	Disfiguring lesion on the nose. Obvious tumor shrinkage and response by evaluation 2. Agree with IRC assessment of response and later disease progression. Response was maintained for over 7 months and lesion at time of progression was still much improved from a cosmetic perspective relative to baseline.
1194002 ^b	Inner canthus	PR	PR	57	366	C	Photographic assessment not feasible and not included in response assessment because primary lesion was in the inner canthus.
1102001 ^{bc}	Lung metastases	PR	SD	56	450	C	IRC and investigator both selected two baseline target lesions in the lower lobes of the lungs. Response

Patient ID	Target Lesion(s)	BOR (IRC)	BOR (INV)	TTR (days)	DOR (days)	Event	Reviewer Notes
							assessment was based on serial CT scans. IRC evaluated disease as PR from evaluation 2 through 9 at which point the patient was censored with 'ongoing response' per IRC. Investigator evaluated disease as stable at all timepoints after baseline imaging.

Source: Serial photographic images submitted as part of the Study A2201 CSR; Listings 14.2-2.1 and 14.2-3.1, SCE addendum Appendix 1

BOR: Best overall response; C: censored; CR: complete response; DOR: duration of response; INV: investigator-assessed; IRC: Independent review committee; PR: partial response; PD: progressive disease; SD: stable disease; TTR: time to response

a. Patient excluded from the pEAS but included in the FAS

b. Three patients with an objective response in the 200 mg group did not have digital photography as a modality included in their overall response assessment.

c. This patient is the one patient with mBCC with an objective response in the 200 mg arm.

Reviewer: The following general conclusions were drawn after the evaluation of serial digital photography of target lesions in patients in the 200 mg arm who experienced an objective response during Study A2201:

- *Tumor shrinkage from baseline was usually evident within the first two evaluations, and the criteria for objective response were met later.*
- *In at least 6 patients, an objective response occurred more than 6 months following treatment initiation.*
- *Large, protrusive, nodular lesions appeared to have more dramatic responses while smaller lesions had less detectable changes over the same time interval.*
- *Nine facial lesions (orbital, ear, cheek, nose, oral cavity) were considered by the reviewer to be disfiguring and showed obvious evidence of photographic improvement that was maintained at the time of disease progression in those who discontinued treatment for PD.*
- *The discordance rate between IRC and investigators in response assessment was acknowledged. In most cases of response assessment disagreements across both arms in Study A2201, objective responses were more often detected by the investigator when the IRC assessed the patient as having stable disease. The Applicant conducted a sensitivity analysis of ORR using investigator-determined response (see next section). The reviewer does not believe that the discordance rate impacts the evaluation of sonidegib's overall efficacy profile in patients with laBCC or mBCC.*

ORR sensitivity analyses

A comparative analysis of ORR concordance between central review and investigator assessment was conducted for the primary and 12 month analyses. The concordance rates

were similar in the two analyses. In the 12 month analysis, the concordance rates between the central review and investigator assessment of ORR for patients in the 200 mg group was 64% for those with laBCC and 54% for patients with mBCC. In the 800 mg group, the concordance rates were 51% and 65% for patients with laBCC and mBCC, respectively.

The ORRs using investigator-assessed responses were higher than per central review. The ORRs in the FAS in the 12 month analysis were 71% in patients with laBCC (b) (4) in the 200 mg arm and 58% (b) (4) in patients with laBCC (b) (4) in the 800 mg arm.

The Applicant provided a summary analysis of all patients in the 200 mg arm comparing the response assessments made by the IRC with those of the investigators and reasons for the discrepancy. The primary reasons for discrepancies were disagreement over the response assessment and disagreement over the lesion selection. In the majority of discrepant cases, the investigator assessed a response which was not supported by the IRC. The lower concordance rate for patients with laBCC is likely due to the use of multiple measures to develop a composite endpoint. The Applicant considered the discordance rate in the mBCC group was due to the small sample size.

An additional preplanned ORR sensitivity analysis in which similar response assessment methods used in the vismodegib registration study were applied to the efficacy data in Study A2201 was conducted by the Applicant. This analysis demonstrated a higher ORR and an increase the number of patients with a CR in patients with laBCC.

6.1.5 Analysis of Secondary Endpoints(s)

Duration of response and complete response rate (CRR) were key secondary endpoints, according to the study protocol, supporting ORR in Study A2201. Other secondary efficacy endpoints included PFS, overall survival OS, time to response (TTR) and investigator-assessed response.

Duration of response (DOR)

Efficacy analyses of response duration were performed by Dr. Huanyu Chen, the statistical reviewer for the application. These confirmed the results presented by the Applicant in the CSR and the SCE.

In the primary analysis, the centrally reviewed median DOR in patients with laBCC was non-estimable for both treatment arms with 87% of responders censored in the 200 mg group and 93% of responders censored in 800 mg group. (b) (4)

In the updated 12 month analysis, the median DOR in patients with laBCC was non-estimable for the 200 mg arm with an 82% censoring rate and 15.7 months (95% CI: NE) for the 800 mg

arm with an 80% censoring rate. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]. Table 16 summarizes the
DOR results in the primary and 12 month analyses.

Table 16: Centrally reviewed duration of response based on FAS

	LaBCC		
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)	
Primary Analysis, data cut-off June 28, 2013			
ORR n (%)	31 (47)	45 (35)	
Number of Events	4	3	
No. Censored	27	42	
Median (95% CI)	NE	NE	
12 Month Analysis, data cut-off December 31, 2013			
ORR	38 (58)	56 (44)	
No. of Events	7	11	
No. of Censored	31	45	
Median (95% CI)	NE	15.7 (NE)	

Source: Table created from analysis performed by Dr. Huanyu Chen, statistical reviewer
Events are defined as disease progression or death. ORR: objective response rate, NE: non-estimable
Reviewer: *The ORR of 58% in patients with laBCC who were treated at the intended dose of 200 mg daily with evidence of durability in the 12 month updated analysis is considered by the reviewer to represent clinical benefit for patients with inoperable laBCC. Additionally, the 12 month analysis demonstrates that seven patients with stable disease converted to responders (CR=1, PR=6) with longer term exposure to sonidegib.*

Duration of response according to investigator assessment

The investigator-assessed median DOR for patients with laBCC in the 12 month analysis was 20.2 months (95% CI: NE) in the 200 mg arm with 70% censored and 19.8 months (95% CI: 15.7, 20.5) in the 800 mg arm with 77% censored. [REDACTED] (b) (4)

Reviewer: *The analysis of investigator-assessed DOR and an additional sensitivity analysis performed by the Applicant applying the vismodegib response criteria do not substantially change the DOR results in Study A2201.*

Complete response rate (CRR)

(b) (4)
The CRR for patients with laBCC was 3% [N=2 (95% CI: 0.4, 10.5)] for the 200 mg arm at the time of the primary analysis. One additional patient obtained a CR in the 12 month analysis. There were no patients in the 800 mg arm who experienced a CR. The Applicant attributed the low CRRs to stringent response criteria regarding complete histological clearance, the magnitude of the baseline lesions, and the proportion of patients with mBCC who had non-nodal, distant metastases.

Reviewer: The assessment of response using mRECIST may have contributed to the low CRR in Study A2201. Although cross-trial comparisons should be interpreted with caution, the Applicant's sensitivity analysis of response in which the vismodegib response criteria was applied to the sonidegib study results for patients with laBCC demonstrated that 15% (N=10) of patients in the 200 mg arm and 27% (N=35) of patients in the 800 mg arm would have been categorized as CR using methodology similar to that used in the vismodegib study. With regard to the magnitude of baseline lesions, it is unclear if the size of lesions in patients with laBCC is a predictor of response to sonidegib or other treatments. The reviewer agrees that CR is rarely achieved in patients with mBCC, and distant metastatic disease to the bone and lungs is challenging to manage.

Time to response (TTR), Progression free survival (PFS) and overall survival (OS)

Time to response

Centrally reviewed TTR was defined as the time from the date of randomization to the date of the first documented tumor response (CR or PR). The Applicant provided TTR results by treatment arm, and these are summarized in Table 17.

Table 17: Time to response

	LaBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
Median TTR in months (95% CI)	3.9 (3.6, 4.2)	3.7 (2.6, 3.8)

(b) (4)

Source: Study A2201 CSR, Table 14.2-3.2, results are based on primary 6 month analysis

Progression-free survival

PFS was defined as the time from the date of randomization to the date of the first documented progressive disease or death due to any cause. The date of censoring was the date of the last adequate tumor assessment before the data cut-off. The median PFS for patients with laBCC was 22.1 months (95% CI: NE) in the 200 mg arm and 21.5 months (95% CI: NE) in the 800 mg arm in the updated 12 month analysis. The censoring rate in both arms

was 83%.

(b) (4)

Table 18: Progression-free survival

	LaBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
Number of events*	11	22
Number censored	55	106
Median PFS in months (95% CI)	22.1 (NE)	21.5 (NE)

(b) (4)

Source: SCE Addendum, Table 2-29, results based on the 12 month analysis

Events are disease progression or death due to any cause.

Overall survival

Overall survival was defined as the time from the date of randomization to the date of death due to any cause or the last date that a patient was known to be alive (censored) as of the data cut-off. A total of 18 deaths had occurred at the time of the data cut-off for the 12 month analysis (7% of patients with laBCC and 25% patients with mBCC). The median OS was non-estimable in both treatment arms for patients with laBCC, with 99% of patients censored in the 200 mg arm and 94% of patients censored in the 800 mg arm.

(b) (4)

Table 19: Overall survival

	LaBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
Number of events*	1	8
Number censored	65	120
Median OS in months (95% CI)	NE	NE

(b) (4)

Source: SCE Addendum, Table 2-30, results based on 12 month analysis

*Events are deaths on study

Reviewer: The PFS and OS analyses in the review were verified by the FDA statistical reviewer and are based on the 12 month efficacy update, at which point, the median duration

of treatment was 11 months and the median duration of follow-up was 20 months. Time-to-event analyses in this two dose cohort study with no internal control are difficult to interpret and cannot provide a reliable estimate of the magnitude of TTR, PFS or OS effects of sonidegib. The reviewer considers these analyses to be exploratory or supportive in the efficacy evaluation of sonidegib.

6.1.6 Other Endpoints

Gli-1 biomarker analysis

Inhibition of Gli-1 expression in the skin was the primary biomarker of sonidegib activity evaluated in Study A2201. The Applicant performed these exploratory analyses to evaluate changes in Gli-1 expression over time, potential associations between Gli-1 expression and efficacy outcomes, and potential associations between Gli-1 expression and safety outcomes.

The Applicant evaluated change from baseline for Gli-1 expression by quantitative RT-PCR and showed that the majority of patients in both treatment arms had Gli-1 inhibition. In the 200 mg arm, median Gli-1 inhibition ranged from 82% to 93% across three assessments (week 9, 17 and end of treatment visits), and in the 800 mg group, the median inhibition was approximately 96% at each of the same three assessment times. Table 20 includes the Applicant's summary of Gli-1 inhibition in the primary analysis by assessment time and treatment arm based on the FAS.

Table 20: Gli-1 inhibition during Study A2201

Dose	Visit	n (%)	Mean	Gli-1 (% inhibition)			
				SD	Median	Min	Max
Sonidegib 200 mg (n=79)	Week 9	57 (72.2)	44.9	182.09	86.7	-1190.6	99.9
	Week 17	48 (60.8)	74.8	38.31	92.8	-72.9	99.9
	EoT	16 (20.3)	34.2	101.76	81.9	-220.4	98.9
Sonidegib 800 mg (n=151)	Week 9	64 (42.4)	-543.3	5019.43	96.1	-40070.7	99.9
	Week 17	51 (33.8)	74.8	47.26	95.6	-105.6	99.9
	EoT	21 (13.9)	59.3	84.79	96.1	-222.7	99.9

Source: Table 11-28, Study A2201 CSR
EoT: End of therapy

Reviewer: The data suggests that Gli-1 inhibition was present in the majority of tissue specimens in both treatment arms at the first post-baseline assessment. There did not appear to be a significant difference in the level of Gli-1 inhibition based on stage of disease (laBCC or mBCC) or treatment arm. By the Week 17 and end of treatment timepoints, the sample size was smaller, the average percent inhibition was lower, and the median percent inhibition remained consistent. It is difficult to draw reliable conclusions from this data. The biomarker analyses were exploratory endpoints and will not be addressed in the product label.

Patient-reported outcomes

The Applicant submitted patient-reported outcome (PRO) data from Study A2201 using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and an associated head and neck cancer specific module (QLQ-H&N35). The objective of these assessments, according to the Applicant, was to evaluate changes in disease-related symptoms, function, and health status during treatment with sonidegib. The compliance rate for completion of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires were similar in both treatment arms: 93% and 94% at baseline and 44% and 45% at Week 33. Approximately 90% of patients completed at least one post-baseline assessment for both questionnaires.

Prespecified subscale scores for the C30 included physical functioning, social functioning, pain, and fatigue; pre-specified scales from the H&N35 included trouble with social contact, head and neck pain, and weight loss. The following list summarizes the Applicant's analysis of the PRO data collected at the time of the primary analysis in Study A2201:

- In patients with laBCC treated in the 200 mg arm, at least 25% of patients experienced improvements in each of the prespecified C30 scales of physical functioning (36%), social functioning (26%), pain (31%), and fatigue (38%). More than 15% of patients in this group experienced improvements in each of the prespecified H&N35 scales of trouble with social contact (43%), head and neck pain (18%), and weight loss (16%).
- In patients with mBCC treated in the 200 mg arm, at least one third of patients experienced improvements in the prespecified C30 scales of physical functioning (69%), social functioning (39%), pain (46%), and fatigue (46%). At least 15% of patients in this group experienced improvements in trouble with social contact (31%), head and neck pain (23%), and weight loss (17%).
- In patients with laBCC treated in the 800 mg arm, at least 15% of patients experienced improvements in each of the prespecified C30 scales of physical functioning (32%), social functioning (20%), pain (33%), and fatigue (19%). At least 5% of patients in this group experienced improvements in each of the prespecified H&N35 scales of trouble with social contact (30%), head and neck pain (18%), and weight loss (7%).
- In patients with mBCC treated in the 800 mg arm, more than one third of patients experienced improvements in each of the prespecified C30 scales of physical functioning (40%), social functioning (35%), pain (55%), and fatigue (40%). At least 20% of patients in this group experienced improvements in trouble with social contact (42%), head and neck pain (20%), and weight loss (26%).
- Using the prespecified C30 scales, median time to deterioration, defined as a greater than a 10 point worsening without subsequent improvement, was non-estimable in the 200 mg arm. The median time to deterioration in each of the measures in the 800 mg group were 11.1 months for physical functioning, 11.3 months for social functioning, 5.6 months for fatigue, and non-estimable for pain.

Reviewer: In general, it appears that patients with mBCC in both arms were more likely to experience an improvement in the subscale scores for the C30 when compared to patients with laBCC; however, there were too few patients with mBCC to draw any valid conclusions.

Furthermore, the lack of internal control and amount of missing data make the PRO results difficult to interpret. The applicant appropriately did not include this data in the product label.

6.1.7 Subpopulations

Prespecified subgroup analyses for the ORR endpoint were conducted based on age, disease histology, performance status, sex, race, geographic region and use of gastric pH agents in Study A2201. Table 21 summarizes key subgroup analyses by treatment arm.

Table 21: Subgroup analyses for ORR, 12 month analysis

Demographic Subgroup	Sonidegib 200 mg N=79 ORR, %	Sonidegib 800 mg N=150 ORR, %
Age		
< 65 years old	59	44
>=65 years old	43	36
Gender		
Male	44	37
Female	58	46
Tumor histology (IaBCC)		
Aggressive	60	44
Non-aggressive	55	43
ECOG		
0	60	48
>=1	33	24

Source: Figure 2-13 and 14.2-6b, SCE Addendum

Reviewer: Due to small numbers and lack of internal control these subgroup analyses are considered exploratory. The results suggest that responses were generally comparable across subgroups within treatment arms, and when there were imbalances, there were less so between groups in the 800 mg arm which had a larger sample size. In both treatment arms, there was a greater than 20% difference in ORR for patients with an ECOG performance score of 0 compared with those with a score of 1 or greater. This imbalance may be partially due to the relatively small sample size of patients with ECOG scores greater than zero in both arms (27/79 in the 200 mg group and 54/151 in the 800 mg group). There was a greater than 10% difference in ORR for patients less than 65 years of age compared with patients 65 years or older. This may be consistent with the larger number of patients over the age of 65 requiring treatment discontinuations for adverse events. See Section 7.5.3.

Nevoid Basal Cell Carcinoma Syndrome (i.e., Gorlin syndrome)

Sixteen patients with Gorlin syndrome enrolled in Study A2201. There were no prespecified sensitivity analyses for response or safety for this group of patients according to the protocol. Acknowledging that the sample size was small and that any analyses would be exploratory, FDA requested that the Applicant provide a comparative analysis of the ORR results between patients with Gorlin syndrome and the overall study population.

Only one patient with Gorlin syndrome had mBCC, and this patient was treated in the 800 mg arm and had a centrally reviewed best overall response of stable disease. The other fifteen patients had laBCC; three were treated in the 200 mg arm with an ORR of 33% (95% CI: 0.8, 90.6), and twelve were treated in the 800 mg arm with an ORR of 58%, (95% CI: 27.7, 84.8). Table 22 was adapted from the Applicant's response to FDA submitted to the NDA on May 20, 2015.

Table 22: Centrally reviewed ORRs in Study A2201 population and subset of patients with Gorlin syndrome

	Overall population		(b) (4)	Patients with Gorlin syndrome			
	12-month analysis:			12-month analysis:			
	31-Dec-2013 data cut-off			31-Dec-2013 data cut-off			
	laBCC			laBCC		mBCC	
	Sonidegib	Sonidegib		Sonidegib	Sonidegib	Sonidegib	Sonidegib
	200 mg	800 mg		200 mg	800 mg	200 mg	800 mg
	N=66	N=128		N=3	N=12	N=0	N=1
FAS							
ORR, n (%)	38 (57.6)	56 (43.8)		1 (33.3)	7 (58.3)		0
95% CI	(44.8, 69.7)	(35.0, 52.8)		(0.8, 90.6)	(27.7, 84.8)		-
BOR, n (%)							
CR	3 (4.5)	2 (1.6)		0	0		0
PR	35 (53.0)	54 (42.2)		1 (33.3)	7 (58.3)		0
SD	22 (33.3)	48 (37.5)		2 (66.7)	3 (25.0)		1 (100)
PD	1 (1.5)	1 (0.8)		0	0		0
Unknown	5 (7.6)	23 (18.0)		0	2 (16.7)		0

Source: Table 2-2, Applicant's response to FDA Information Request, May 20, 2015

Reviewer: In this exploratory analysis, it appears that patients with Gorlin syndrome did not differ from the general BCC population enrolled in Study A2201 with regard to response to sonidegib.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study A2201 employed a two-dose cohort design in which patients were randomized to receive either 200 mg or 800 mg of sonidegib on a daily and continuous basis. The 200 mg

dose was selected because it represented the lowest dose level that demonstrated antitumor activity in Study X2101, and the 800 mg dose was the established MTD in Study X2101. Twice daily dosing schedules were associated with increased toxicity in Study X2101.

The ORR results in patients with laBCC in Study A2201 demonstrated that both the 200 mg and 800 mg daily dose were effective. No formal dose-response analysis was conducted for Study A2201; however, no exposure-response relationship was observed. There was, however, an exposure-safety relationship with an increased frequency and severity of adverse events in the 800 mg arm as compared to the 200 mg arm.

Reviewer: The Applicant's selection of the 200 mg daily dose is appropriate based on there being similar antitumor effects and a more favorable safety profile.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See section 6.1.5 for a discussion of duration of response. The CSR states that upon stopping sonidegib treatment, the natural disease course for BCC should be expected.

Reviewer: Reliable conclusions cannot be made regarding the persistence of response upon discontinuation of sonidegib due to the poorly-defined and sometimes indolent natural history of laBCC and the small sample size of patients in the 200 mg arm who discontinued sonidegib for adverse events rather than disease progression. Safety analyses performed with the objective of identifying appropriate dose-modification guidelines in the setting of musculoskeletal toxicity revealed that three of 6 patients in the 200 mg arm with an objective response who discontinued sonidegib for grade 3 or 4 muscle events experienced durable responses for between 113, 198+, and 434+ days following discontinuation.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety of sonidegib was primarily evaluated in 229 patients with laBCC and mBCC enrolled in Study A2201 who were randomized to receive sonidegib at doses of 200 mg (N=79) or 800 mg (N=150) daily. The study design called for a 2:1 allocation to the 800 mg arm based on results from the sonidegib dose-escalation study which established 800 mg daily as the MTD and demonstrated an exposure-dependent inhibition of Gli-1, the biomarker of sonidegib activity measured during the study.

The safety of sonidegib was also evaluated in a pooled population of 272 patients who received sonidegib at doses ranging from 100 to 800 mg daily in Studies A2201 and X2101.

The majority of patients in the pooled analysis were from Study A2201 (N=229), and the results from the pooled data were generally consistent with those from Study A2201. For safety concerns of special interest and concern (e.g., musculoskeletal adverse reactions, lipase elevation), supplemental analyses and datasets from a larger sonidegib safety database of 571 patients were requested of the applicant and submitted to the NDA during the review of the application.

In the primary safety analysis, the median duration of exposure in Study A2201 was 8.9 months for patients in the 200 mg arm and 6.5 months for patients in the 800 mg arm. The majority of patients had between 4 and 8 months of treatment in both arms. The shorter exposure in the 800 mg group was attributed to earlier discontinuation due to adverse events rather than disease progression.

A total of 22 patients died as of the 120 day safety update (data cut-off July 11, 2014). Eight patients died while on study. Two deaths were attributed to disease progression and six deaths were attributed by investigators to adverse events not related to sonidegib treatment. Nonfatal serious adverse events (SAEs) occurred in 14% of patients receiving sonidegib 200 mg and in 30% of patients receiving 800 mg. All SAEs occurred as single incidences in the 200 mg arm. The most common SAEs in the 800 mg arm (>2% incidence) were rhabdomyolysis, serum creatine kinase (CK) elevation and vomiting. Grade 3-4 AEs and AEs requiring dose adjustments or discontinuations were more frequent in the 800 mg group.

AEs that occurred in more than 20% of patients in either treatment arm were muscle spasms, alopecia, dysgeusia, nausea, fatigue, increased serum CK, decreased weight, and diarrhea. Additional AEs that occurred in more than 20% of patients treated in the 800 mg arm were decreased appetite and myalgia. The majority of AEs occurred more frequently and with increased severity in the 800 mg arm compared to the 200 mg arm.

Musculoskeletal toxicity was a major safety signal observed in Study A2201 and appears to be a hedgehog inhibitor drug class effect. The most commonly occurring AE in both treatment arms was muscle spasms (49% in the 200 mg arm and 67% in the 800 mg arm). Muscle spasm was also the most common AE leading to treatment discontinuation in both treatment arms. Rhabdomyolysis was the most commonly reported SAE (N=6), and was reported more frequently in the 800 mg group (N=5). The Applicant requested that an independent expert committee review all cases of rhabdomyolysis and serum CK elevation in Study A2201 and across the sonidegib development program. The 6 events of rhabdomyolysis reported in Study A2201 were not adjudicated by the committee as meeting their definition of rhabdomyolysis due to lack of evidence of concurrent renal impairment. The committee's assessments and report were submitted to the NDA. A summary of these documents and a detailed discussion of the muscle toxicity risk associated with sonidegib treatment are found in Section 7.3.5 of the review.

The safety profile of sonidegib is acceptable in patients with laBCC who are not amenable to local therapies. The reviewer agrees with the Applicant's assessment of the favorability of the 200 mg dose. Although the efficacy results were similar between treatment arms, the 200 mg dose was safer, more tolerable, and allowed patients who were deriving clinical benefit from

sonidegib to remain on study treatment longer. Although the risk for musculoskeletal adverse reactions is a safety concern, the incidences of muscle-related AEs and SAEs were less in the 200 mg group. The reviewer does not recommend a risk evaluation and mitigation strategy (REMS) be implemented for sonidegib. Recommendations for safe and effective use of sonidegib, including adequate safety monitoring for serum CK elevation and musculoskeletal adverse events, will be made in the product label.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The main safety analyses were performed on the data from Study A2201, the study supporting the proposed indication. The safety review is based on this study unless otherwise specified. The safety database from A2201 included data from 229 patients exposed to sonidegib in both treatment arms (79 patients in the 200 mg arm and 150 patients in the 800 mg arm). Most analyses performed for the safety review used the data cut-off date of June 28, 2013, which corresponds to the 6 month primary endpoint analysis for Study A2201. The sponsor also submitted an analysis of 12 month safety data (data cut-off date of December 31, 2013) as an addendum to the SCS, with corresponding datasets. Key safety analyses from the 12 month dataset were reviewed and verified.

The Applicant submitted an 18 month safety analysis with corresponding datasets (data cut-off date of July 11, 2014) as a second addendum to the SCS as part of the 120-day safety update. The Applicant's side-by-side safety data from the primary (6 month) analysis and the 12 month and 18 month updated analyses were reviewed for cumulative safety results with longer exposures to sonidegib and summarized in relevant sections of the review. Key safety analyses from the 18 month dataset were verified by the reviewer for the purpose of informing the product label. Narratives of deaths and SAEs were reviewed for events that occurred up until the final data cutoff date of July 11, 2014.

Additionally, the Applicant submitted a pooled safety analysis as part of the SCS which contained data from Study A2201 pooled with data from 43 patients treated in Study X2101 with single agent sonidegib at doses equal to or less than 800 mg daily. The pooled analysis was considered as supportive safety information. Table 23 lists the clinical studies evaluated for safety to support the application.

Table 23: Clinical studies with sonidegib included in the Summary of Clinical Safety

Study No.	Population	Sample Size	Sonidegib/ Dose Schedule	Status	Comment
Pooled studies					
Study A2201	Patients with locally advanced or metastatic BCC	230 patients randomized (229 treated)	sonidegib once daily 200 or 800 mg	Enrollment completed	Phase II registration study
Study X2101	Patients with advanced solid tumors	103 patients enrolled (43 patients treated at doses of ≤800 mg)	sonidegib once daily ^a 100, 200, 400, 800, 1000, 1500 or 3000 mg or sonidegib twice daily 250, 400 or 750 mg	Enrollment completed	Phase I dose escalation study
Supportive study^b					
Study X1101 Group 1: Japanese patients	East Asian patients with advanced solid tumors	21 Japanese patients enrolled and treated	sonidegib once daily ^a 400 and 600 mg	Ongoing	Phase I Asian study Data from Japanese patients complete and included in the submission

Source: Table 1-1, Summary of Clinical Safety

a. Only patients treated with sonidegib 800 mg daily or less are included in the pooled analyses.

b. Data from Study X1101, including only Japanese patients, was summarized in the SCS; however, these patients were intentionally not included in the pooled safety population due to potential differences in tolerability of sonidegib between Western and East Asian patient populations.

7.1.2 Categorization of Adverse Events

The Applicant coded verbatim AE terms for Study A2201 using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 for the 6 month analyses and MedDRA 17.1 for the 12 and 18 month analyses. Treatment-emergent adverse events were defined as all AEs occurring from initiation of study drug through 30 days after the last dose of sonidegib. NCI CTCAE Version 4.0 was used for toxicity grading.

The reviewer assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the A2201 6 month AE.xpt dataset. Of the 2,961 line listings in the dataset, the reviewer used matching of identical verbatim and MedDRA PTs (n=960 line listings) as well as manual evaluation of the remaining verbatim terms (n=2001 line listings). Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

Muscle-related Events

The Applicant based the definition of "muscle-related events" on the MedDRA version 16.1 Standard MedDRA Queries (SMQ) broad term for rhabdomyolysis plus the preferred term

“muscle spasms” for the primary analysis and MedDRA version 17.1 SMQ broad term for rhabdomyolysis plus the PTs “muscle spasms,” “necrotizing myositis,” and “tendon discomfort” for the 12 and 18 month data analyses. The reviewer assessed the adequacy of the Applicant’s mapping of muscle AE verbatim terms to MedDRA PTs in the primary analysis dataset. Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

The Applicant’s ADAE.xpt dataset included a subgrouping of preferred terms to capture muscle-related events. This was referred to as the myopathy/rhabdomyolysis Adverse Event of Special Interest (AESI) and included both clinical signs and symptoms and laboratory abnormalities. See Section 9.6 of this review for the listing of PTs included in this category of adverse events. The Applicant also submitted separate datasets at each data cut-off date which included grade 3 or 4 muscle-related AEs including serum CK elevation (ADMUSCK.xpt) and all events of serum CK elevation grade 2 or above (ADMUSCKB.xpt) for further evaluation of this safety signal.

The reviewer considers the Applicant’s search strategy, coding and analyses adequate for the purpose of capturing possible muscle-related adverse events and further characterizing the musculoskeletal toxicity associated with sonidegib treatment. A detailed discussion of muscle toxicity related to sonidegib treatment is found in Section 7.3.5 of the review.

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

The SCS included data from patients with BCC treated in Study A2201 pooled with data from patients with various advanced solid tumors treated in Study X2101, a first-in-human dose escalation study. The pooled analysis contains data from a total of 272 patients, including the safety population from Study A2201 (N=229) and a subset of patients from Study X2101 treated with sonidegib at doses between 100 mg and 800 mg daily (N=43).

7.2 Adequacy of Safety Assessments

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

Patients in Study A2201 received four capsules daily upon study drug initiation. Patients randomized to the 200 mg arm received one 200 mg sonidegib capsule and three matching placebo capsules, and patients randomized to the 800 mg arm received four 200 mg sonidegib capsules. Of 230 randomized patients, 229 received at least 1 dose of sonidegib. One patient who was randomized to the 800 mg arm did not go on to receive study treatment and is not included in the safety population.

At the primary analysis data cut-off date, the median duration of treatment was 8.9 months for patients in the 200 mg arm and 6.5 months for patients in the 800 mg arm. The majority of patients had between 4 and 8 months of treatment in both arms; however, a higher percentage of patients in the 200 mg group (27%) continued study treatment for more than 12 months. The shorter exposure in the 800 mg group was attributed to earlier discontinuation due to decreased tolerability rather than disease progression. Table 24 summarizes sonidegib exposure during Study A2201.

Table 24: Exposure summary, primary analysis

	Sonidegib 200 mg N=79	Sonidegib 800 mg N= 148*
Median duration of treatment in months (range)	8.9 (1.3-21.4)	6.5 (0.3-19.1)
Duration of exposure (months)		
< 1	0	7 (5%)
1 - <4	7 (8%)	38 (25%)
4 - <8	29 (37%)	50 (33%)
8 - <12	22 (28%)	27 (18%)
12 - <16	14 (18%)	13 (9%)
16 - <20	6 (8%)	15 (10%)
>= 20	1 (1%)	0
Median cumulative dose (mg)	45,200	127,000
Median dose intensity (mg/day)	194 (28 to 247)	733 (237 to 3500)**
Median relative dose intensity	97%	92%

Source: ADEX.xpt, primary analysis

* Exposure statistics are based on 148 patients in the 800 mg group because two patients had missing drug accountability data per the Applicant.

**The CSR states that this maximum dose intensity is erroneous and resulted from a discrepancy between the drug accountability and dose administration records. The reviewer does not consider this error to impact the overall safety evaluation.

The Applicant provided additional exposure data from the pooled safety population (N=272) in the SCS. The median duration of exposure was similar in the larger population: 8.4 months in patients treated with 200 mg (N=85) and 6.1 months in patients treated with 800 mg sonidegib (N=176).

The data submitted with the 120-day safety update included updated exposure information based on the data cut-off date of July 11, 2014, at which all patients had been treated with sonidegib for at least 18 months or discontinued treatment earlier. The median duration of treatment in this analysis was 11 months (range: 1.3 to 33.5) for patients in the 200 mg arm

and 6.5 months for patients in the 800 mg arm. The shorter exposure in the 800 mg group was again attributed to earlier discontinuation due to adverse events.

7.2.2 Explorations for Dose Response

The Applicant supported the dose selection for Study A2201 based on results from Study X2101. In Study X2101, doses of sonidegib between 100 mg daily and 3000 mg daily were evaluated in patients with refractory solid tumors. The 200 mg daily dose was the lowest dose at which antitumor activity was observed. There was one patient with mBCC treated with 200 mg daily who experienced a prolonged stabilization of disease and one patient with medulloblastoma who experienced a partial response. The 800 mg daily dose was determined to be the MTD.

[REDACTED] (b) (4)
At the 200 mg daily dose, mean Gli-1 inhibition was 68%, and at the 800 mg daily dose mean Gli-1 inhibition was 74%. Study A2201's design included a 2:1 unbalanced allocation to the 800 mg treatment arm [REDACTED] (b) (4)

Study A2201 did not demonstrate an exposure response relationship for the primary efficacy endpoint [REDACTED] (b) (4). See Section 6.1.4. The results of Study A2201 did demonstrate an exposure-dependent relationship for safety. The safety analyses demonstrate an increase in the frequency and severity of adverse events in the 800 mg arm and a higher proportion of patients requiring discontinuation for adverse reactions.

See the FDA Clinical Pharmacology Review for detailed discussion of exposure-response analyses of serum CK elevation.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine clinical and laboratory evaluations were adequate to assess the safety of sonidegib in Study A2201. See section 5.3 and 9.5 for a description and schedule of the clinical assessments that took place during the study. Routine clinical testing and monitoring were analyzed, and the results of these analyses are described in the Lab and Safety Sections of this review (Sections 7.3 and 7.4).

7.2.5 Metabolic, Clearance, and Interaction Workup

See the FDA Clinical Pharmacology Review and section 4.4 of this review.

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

The safety profile of hedgehog inhibitors is characterized by the occurrence of frequent musculoskeletal and gastrointestinal adverse events. Vismodegib is the only approved hedgehog pathway inhibitor. It was approved in 2012 for the treatment of patients with laBCC and mBCC. Common adverse events occurring in the vismodegib registration trial included muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea [4]. These adverse events occurred with similar frequency in patients treated with sonidegib in Study A2201. The Applicant had adequate safety monitoring and reporting procedures in place to address the anticipated drug class toxicities. Study A2201 additionally included frequent serum CK monitoring based on the dose-limiting toxicity of elevated serum CK observed in Study X2101. A review of the muscle-related toxicities and other presumed drug class adverse effects is in Section 7.3.5.

In animal studies, sonidegib was embryotoxic, fetotoxic and teratogenic at maternal exposures below the recommended human dose of 200 mg daily. These toxicities were similarly observed in animal studies of vismodegib and likely represent a drug class effect on early development based on interference with the hedgehog signaling pathway. See Section 4.3 of this review for further discussion of sonidegib toxicology studies.

7.3 Major Safety Results

Based upon the primary analysis of the data, almost all patients in Study A2201 experienced adverse events (94% of patients in the 200 mg arm and 100% of patients in the 800 mg arm). Grade 3-4 adverse events and adverse events leading to dose interruption, reduction or discontinuation of sonidegib were more frequent in the 800 mg group.

Table 25: Overview of major safety results, primary analysis

	Sonidegib 200 mg N=79 (%)	Sonidegib 800 mg N= 150
Patients who experienced an AE	75 (95)	150 (100)
Patients who experienced a Gr 3-4 AE	24 (30)	84 (56)
Deaths while on study	0	4 (3)
Serious AEs	11 (14)	45 (30)
AEs leading to discontinuation	17 (22)	54 (36)
AEs requiring dose interruption/reduction	25 (32)	90 (60)

Source: ADAE.xpt, primary analysis

There were 25 additional patients who had at least one AE in which the action taken as a result of the AE was noted as “not applicable”. Line listings were reviewed, and the majority of these events occurred in patients who had other events that resulted in discontinuation or dose

adjustments. In five of the 25 patients, the AE was considered serious; however, these five patients all had a specific action taken (i.e., discontinuation, adjustment, or interruption) for other AEs that occurred during the study. The missing per event data therefore does not substantially change the overall safety results.

Section 7.5.2 of the review summarizes the longer term major safety results of Study A2201, and Table 45 compares major safety results from the primary 6, 12 and 18 month analyses.

7.3.1 Deaths

Of the 229 patients in the safety population in Study A2201, a total of 22 patients died as of the July 11, 2014, data cut-off. Eight patients died while on treatment or within 30 days of receiving the final dose of sonidegib. Of the eight on-study deaths, four deaths occurred in the primary analysis, an additional three deaths occurred in the 12 month analysis, and one additional patient died in 18 month analysis. Seven deaths occurred in patients treated in the 800 mg group, and one death occurred in a patient treated in the 200 mg group. Two deaths were attributed to disease progression.

Narratives of the six on-study deaths not attributed to progressive disease are summarized below. None were considered by investigators to be related to treatment with sonidegib. There were two events of sepsis and one respiratory arrest after a neck fracture. Three deaths were secondary to cardiac events.

Reviewer: CRFs were reviewed in addition to the narratives for the three deaths associated with cardiac events. Additionally, the Applicant had the cardiac death cases reviewed and adjudicated by a committee of independent cardiac experts. See Table 26. All of these patients had cardiac risk factors at baseline and pre-existing comorbidities that confounded the attribution analysis. Given the relative rarity of serious cardiac events across the sonidegib development program, the reviewer does not believe that the occurrence of these deaths changes the risk:benefit profile of sonidegib in patients with BCC.

Reasons provided by investigators for the fourteen deaths that occurred more than 30 days after the last dose of sonidegib were “basal cell carcinoma” (N=9), and “multi-system organ failure”, “primary brain tumor”, “age-related heart failure”, “cardiac arrest” and “natural death due to old age” for the other five patients. It does not appear that participation in Study A2201 or treatment with sonidegib contributed to the occurrence of these deaths.

Narratives of on-study deaths

Patient 1529-001: This patient was an 80 year old female with laBCC randomized to the 200 mg treatment arm. The investigator-reported cause of death was **acute respiratory distress syndrome**. On Day 99 of study treatment, she was dose-reduced (to placebo capsules) due to grade 1 lipase elevation. During the study, the patient was hospitalized multiple times for events of pneumonia, recurrent urinary tract infections, cellulitis and an upper limb fracture. On Day ^{(b) (6)}, the patient was admitted and diagnosed with acute respiratory distress syndrome, cellulitis, renal failure and septic shock. Blood cultures were positive for E coli, Pseudomonas and Streptococcus agalactia. An echocardiogram revealed endocarditis. The

patient died on Day (b) (6). The investigator did not suspect a relationship between sonidegib and the events leading up to her death.

Reviewer: The patient had been receiving placebo for over one year prior to her death which was unlikely to be related to sonidegib. She also had multiple medical problems and risk factors for developing serious infections.

Patient 1513-014: This patient was a 56 year old female with mBCC (nodal, lung and bone metastases) randomized to the 800 mg treatment arm. The investigator-reported cause of death was **sepsis**. Pertinent medical history included hepatitis C, dyspnea, hypertension and cough. On Day (b) (6) of the study, the patient developed altered mental status thought to be due to narcotic overuse. The study drug was interrupted and then permanently discontinued due to noncompliance. (b) (6) days after the last dose of sonidegib, the patient developed sepsis and pneumonia. Blood counts were not reported. Blood cultures were positive for gram positive cocci. She developed renal failure and respiratory failure and died the following day. The investigator did not suspect a relationship between sonidegib and the events leading up to her death.

Reviewer: This event was not likely related to sonidegib treatment as the patient was reportedly noncompliant with the medication and had stopped the drug (b) (6) days prior to her event. Additionally, attribution is confounded by the patient's underlying medical conditions including lung metastases.

Patient 1534-006: This patient was an 80 year old male with mBCC randomized to the 800 mg treatment arm. The primary site was the right orbit, and he had brain metastases. The investigator-reported cause of death was **respiratory arrest following a neck fracture**. Pertinent medical conditions present at study entry were presence of open wound in right ear (prior surgery and radiation to this site), hypertension, and headache. During the study, the patient had episodes of urinary tract infection, sinusitis, and deep vein thrombosis which led to temporary treatment interruptions. The last dose of study drug was administered on Day 418. The patient fell at home on Day (b) (6) and sustained two upper limb fractures and a cervical vertebral fracture. The patient was transferred to hospice and died on Day (b) (6) days after the last dose of sonidegib. The investigator did not suspect a relationship between these events and the study drug. The reviewer agrees with this assessment.

Patient 1231-009: This was an 88 year old female with laBCC randomized to the 800 mg treatment arm. The investigator-reported cause of death was **asystole**. Past medical history was significant for sepsis, staphylococcal infection, pneumonia, pulmonary embolism, cardiac failure, hypertension, hepatic steatosis and diverticulitis. The screening ECG was normal. During the study, sonidegib was temporarily interrupted multiple times for infections and because the patients was diagnosed with bladder cancer, requiring bladder resection and other procedures. The last dose of sonidegib was administered on Day 328. On Day (b) (6), the patient was hospitalized with abdominal pain thought to be secondary to "lower endothelium carcinoma" and subsequently developed a pleural effusion requiring drainage on Day (b) (6).

The patient experienced a cardiac arrest the same day and underwent cardioversion. She died the next day. The investigator assessed the development of transitional cell carcinoma as possibly related to the study drug, but did not suspect that the cardiac arrest was related to sonidegib.

Reviewer: This cardiac event and subsequent death were likely not related to sonidegib treatment. Additionally, there have been no signals across the sonidegib safety population that patients treated with sonidegib are at risk for development of secondary bladder cancer.

Patient 1270-003: This patient was an 83 year old male with laBCC randomized to the 800 mg treatment arm. The investigator-reported cause of death was **congestive heart failure**. Pertinent medical history included prior colorectal carcinoma, hyperthyroidism and hyperglycemia. ECG abnormalities present at study entry included left ventricular hypertrophy, frequent atrial premature complexes, first degree atrioventricular block, flat T-waves, and left anterior fascicular block. On Day ^{(b) (6)} of the study, sonidegib was discontinued due to congestive heart failure, and the patient died the same day. The investigator assessed the event as not related to sonidegib treatment.

Reviewer: The death was likely not related to sonidegib treatment based on the general safety profile of sonidegib and the patient's pre-existing cardiac abnormalities; however it is difficult to make a certain determination of relatedness with few details provided in the narrative and the CRF regarding the work-up performed on the day of the patient's death.

Patient 1534-001: This patient was an 80 year old male with laBCC. The investigator-reported cause of death was '**adverse event cardiac: unknown etiology**.' Pertinent medical history included abdominal aortic aneurysm, right bundle-branch block, atrial fibrillation, renal failure, chronic obstructive pulmonary disease, dyspnea and alcoholism. On Day 56 of the study, the patient was noted to be anemic. On Day ^{(b) (6)}, the patient presented with vomiting and was diagnosed with a gastrointestinal bleed and worsening anemia. The study drug was discontinued. The patients died ^{(b) (6)} days after the last dose of sonidegib was administered due to "cardiac symptoms of unknown etiology". The investigator did not assess the event as related to sonidegib treatment.

Reviewer: Given the timing of this event, the patient's underlying cardiac risk factors, and the patient's comorbid severe anemia secondary to recent gastrointestinal hemorrhage, it is unlikely that the cardiac event was related to sonidegib treatment.

Table 26 contains the reviews of the three cardiac-related deaths by an independent expert adjudication committee.

Table 26: Independent review of cardiac deaths occurring during Study A2201

Patient ID	Evaluation by Cardiac Expert Adjudication Committee
1231-009	<p>“This is an 88-year-old female who had a multitude of cardiac risk factors and cardiac disease and who had very complicated issues (mostly recurrent infections) during previous treatment. She had further issues with recurrent infections, which eventually led to a cardiac arrest and death. Although certain helpful details are not provided here, it is unlikely that the study medication was the culprit for her hospitalizations (especially as she had numerous other and similar hospitalization) prior to enrollment in the study. The complications that arose during treatment were due to non-cardiac issues (infection), which may have exacerbated underlying cardiac issues. She certainly would be predicted to have sinus tachycardia if she had an infection. The patient was noted to have "asystole/cardiac arrest", this committee does not feel a cardiac cause of death. Moreover, there is no correlation between study drug and patient death.”</p>
1270-003	<p>“This is an 83-year-old male who has a number of cardiac risk factors such as advanced age and a history of diabetes of at least 10 years with active treatment with oral medications. Therefore, the patient has at least two risk factors that may predispose to cardiac ischemic disease and heart failure. On Day ^{(b) (6)} of treatment, however, the patient was reported to have congestive cardiac failure (cardiac failure congestive; grade 4). However, this assessment appears to have been clinical assessment only with no ECG evaluation or cardiac biomarkers documentation provided. In addition, an echocardiogram (which would have indicated evidence of cardiac dysfunction) was not done. Per Investigator assessment, the patient's death was felt to be due to congestive failure. Unfortunately, once a clinical event (presumably heart failure) occurred, Investigator did not do a complete work-up. A follow-up ECG or biomarker assessment would have provided evidence for an acute cardiac event (such as acute cardiac ischemia). In addition, an echocardiogram would have assessed for cardiac dysfunction. In the absence of such diagnostic tests, it is difficult to prove cardiac involvement in this case as entire assessment was done by clinical evaluation. However, if the event was due to cardiac reasons given the temporal relationship between the start of treatment and the event a possible link between the study medication and the cardiac event cannot be completely excluded. However, it is difficult to make any definitive conclusion given the poor cardiovascular documentation of this case.”</p>

1534-001	<p>“This is an 80-year-old male who had a number of cardiac risk factors and had active cardiovascular disease. The baseline diagnosis of "aortic aneurysm and laceration" is highly concerning and it is unclear if this had been assessed/treated prior to study enrollment. The complications that arose during treatment were due to non-cardiac issues (gastrointestinal bleeding and grade 4 anemia), which may have exacerbated underlying cardiac issues. While the cause of death was graded by the Investigator to be due "to cardiac symptoms of unknown etiology (cardiac death; grade 4)", this committee does not feel a cardiac cause of death. Moreover, there is no correlation between study drug and patient death.”</p>
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Source: Summary of Clinical Safety, Addendum 2

7.3.2 Nonfatal Serious Adverse Events

Nonfatal SAEs occurred in 14% (n=11) of patients receiving sonidegib 200 mg and in 30% (n=45) of patients receiving 800 mg in the primary analysis. SAEs in the 200 mg group all occurred as single incidences. The most common SAE in the 800 mg group (N=5) was rhabdomyolysis. Rhabdomyolysis was reported as an SAE in one additional patient in the 200 mg treatment arm. Elevation of serum CK was a SAE in three patients in the 800 mg group. One of the three patients also experienced rhabdomyolysis. Two patients in the 800 mg group experienced pneumonia, and two patients experienced syncope. All other SAEs were single incidences in the 800 mg group. Table 27 summarizes all SAEs that occurred in at least one patient in Study A2201. The results of this analysis confirm those of the Applicant.

Table 27: Serious adverse events, primary analysis

Preferred term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Any SAE	11 (14)	45 (30)
Rhabdomyolysis	1 (1)	5 (3)
Blood creatine kinase increased	1 (1)	3 (2)
Pneumonia	1 (1)	2 (1)
Syncope	1 (1)	2 (1)
Angina pectoris	1 (1)	1 (1)
General physical health deterioration	1 (1)	1 (1)
Bipolar disorder	1 (1)	0
Blood creatine kinase MB increased	1 (1)	0
Bronchitis	1 (1)	0
Facial pain	1 (1)	0

Femoral neck fracture	1 (1)	0
Gastric ulcer	1 (1)	0
Lumbar vertebral fracture	1 (1)	0
Vomiting	0	4 (3)
Anemia	0	3 (2)
Nausea	0	3 (2)
Abscess limb	0	2 (1)
Decreased appetite	0	2 (1)
Dehydration	0	2 (1)
Diarrhea	0	2 (1)
Dyspnea	0	2 (1)

Source:ADAE.xpt, primary analysis

Preferred terms are presented in descending order of frequency in the 200 mg arm.

There were no new safety signals observed with longer term exposure to sonidegib, although there was a small increase in the number of SAEs that occurred in both treatment arms in the 12 and 18 month analyses. In the 18 month analysis, 18% of patients in the 200 mg group and 37% of patients in the 800 mg group had experienced at least one SAE. Table 28 is a side-by-side comparison of the incidences of SAEs at the three data cut-off dates. This table was copied from the SCS, Addendum 2, submitted to the NDA with the 120 day safety update. The reviewer has analyzed the 12 and 18 month AE datasets and has verified the results presented in this table.

Table 28: Serious adverse events: primary, 12 and 18 month analyses

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014	
	Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
Any SAE	11 (13.9)	45 (30.0)	13 (16.5)	49 (32.7)	14 (17.7)	56 (37.3)
Rhabdomyolysis	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)	1 (1.3)	5 (3.3)
Blood CK increased	1 (1.3)	3 (2.0)	1 (1.3)	4 (2.7)	1 (1.3)	5 (3.3)
Pneumonia	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	3 (2.0)
Syncope	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)
Dehydration	0	2 (1.3)	1 (1.3)	2 (1.3)	1 (1.3)	2 (1.3)
Angina pectoris	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Cellulitis	0	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
General physical health deterioration	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Sepsis	0	0	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Upper limb fracture	0	0	1 (1.3)	1 (0.7)	1 (1.3)	1 (0.7)
Urinary tract infection	0	0	1 (1.3)	1 (0.7)	1 (1.3)	2 (1.3)
Bipolar disorder	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Blood CK mb increased	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Bronchitis	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Facial pain	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Femoral neck fracture	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0

	Primary analysis: data cut-off: 28-Jun-2013		12-month analysis: data cut-off: 31-Dec-2013		18-month analysis: data cut-off: 11-Jul-2014	
	Sonidegib		Sonidegib		Sonidegib	
	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)	200 mg N=79 n (%)	800 mg N=150 n (%)
Gastric ulcer	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Lumbar vertebral fracture	1 (1.3)	0	1 (1.3)	0	1 (1.3)	0
Cerebrovascular accident	0	0	1 (1.3)	0	1 (1.3)	0
Escherichia urinary tract infection	0	0	1 (1.3)	0	1 (1.3)	0
Invasive papillary breast carcinoma	0	0	1 (1.3)	0	1 (1.3)	0
Endocarditis	0	0	0	0	1 (1.3)	0
Septic shock	0	0	0	0	1 (1.3)	0
Fall	0	0	0	0	1 (1.3)	0
Haemorrhage intracranial	0	0	0	0	1 (1.3)	0
Renal failure acute	0	1 (0.7)		1 (0.7)	1 (1.3)	1 (0.7)
Acute respiratory distress syndrome	0	0	0	0	1 (1.3)	
Hypotension	0	1 (0.7)	0	1 (0.7)	1 (1.3)	1 (0.7)
Orthostatic hypotension	0	0	0	0	1 (1.3)	0
Small intestinal obstruction	0	1 (0.7)	0	1 (0.7)	0	2 (1.3)
Basal cell carcinoma	0	0	0	1 (0.7)	0	2 (1.3)
Vomiting	0	4 (2.7)	0	4 (2.7)	0	4 (2.7)
Anaemia	0	3 (2.0)	0	3 (2.0)	0	5 (3.3)
Nausea	0	3 (2.0)	0	3 (2.0)	0	3 (2.0)
Abscess limb	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Decreased appetite	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Diarrhoea	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Dyspnoea	0	2 (1.3)	0	2 (1.3)	0	2 (1.3)
Deep vein thrombosis	0	1 (0.7)	0	2 (1.3)	0	2 (1.3)

Source: Table 2-9, SCS, Addendum 2

Narratives of nonfatal SAEs

Narratives were submitted and reviewed for all nonfatal SAEs that occurred during Study A2201 through the final data cut-off date. The most common adverse events occurring with sonidegib treatment involve muscle toxicity, and the following review groups the narratives by those that involve musculoskeletal events and those that describe non-musculoskeletal events.

Study A2201: Musculoskeletal SAEs, 200 mg treatment group

Patient 1515-004: This patient was a 64 year old male with laBCC of the neck, randomized to the 200 mg arm, who experienced the SAE **serum CK elevation**. This SAE led to discontinuation of sonidegib. Pertinent medical history for this patient included the active condition “muscular weakness”. The patient had normal serum CK and creatinine values at baseline. On day 57, the patient experienced grade 1 muscle spasms. Serum CK And creatinine were normal. On Day 85, the patient experienced grade 4 elevation of CK-MB, grade 4 elevation of serum CK (2107 U/L) and normal serum creatinine. The study medication was held and then permanently discontinued. The patient’s serum CK decreased to grade 2 seven days after the last dose of sonidegib and remained grade 2 for at least three weeks. There were no CK levels reported for an interval of approximately eight weeks, and then repeat testing revealed that the serum CK had normalized. No treatment was reported for these events. The investigator assessed the event as related to sonidegib.

Reviewer: This SAE was likely related to sonidegib treatment. It is unclear if the past medical history of “muscular weakness” may have made this patient more susceptible to muscle toxicity with sonidegib treatment.

Patient 1532-01: This patient was an 84 year old male with mBCC of the skin and lung randomized to the 200 mg arm who experienced the SAE of **rhabdomyolysis** during treatment with sonidegib. This patient had prior surgical resection of his disease and prior chemotherapy including paclitaxel and carboplatin. The patient did not have history of a muscle disorder or renal impairment at study entry. The patient’s baseline serum CK and creatinine were normal. On day (b) (6), the patient experienced grade 3 serum CK elevation, grade 3 asthenia, and rhabdomyolysis requiring hospitalization. Sonidegib was withheld during this admission. The patient was reported to have had brown urine and urinary myoglobin. The serum creatinine was normal. The patient was discharged (b) (6) days later with grade 1 serum CK elevation. On Day 344 the patient experienced grade 2 fatigue and muscular weakness. On Day 355, the study medication was restarted at a reduced dose. On Day 397, the patient was diagnosed with disease progression, and the study medication was permanently discontinued.

Reviewer: This patient was in the 200 mg treatment arm so that the dose reduction was actually to placebo capsules after the rhabdomyolysis event. The patient’s serum CK was still elevated (grade 1) (b) (6) days after the patient stopped receiving sonidegib treatment. The events of fatigue and muscular weakness were ongoing at the time of the data-cutoff. This

case was reviewed by an Independent Adjudication Committee (IAC), and the diagnosis for the SAE was adjudicated as myopathy and not rhabdomyolysis. The reviewer agrees that the patient's normal creatinine and relatively rapid decrease in serum CK within three days supports the IAC's adjudication; however, the presence of urinary myoglobin and brown urine (no additional urinalysis results reported) are concerning for a potential worsening of the patient's condition if he had not been hospitalized and treated with intravenous hydration. See section 7.3.5.

Study A2201: Musculoskeletal SAEs, 800 mg treatment group

Patient 1193-001: This patient was an 87 year old female with laBCC randomized to the 800 mg arm who experienced the SAEs of **muscle contractures and anemia** while on study. The patient's medical history was significant for prior B-cell lymphoma, hypertension and dementia. The patient was also on pravastatin for hypercholesterolemia since 1992. On Day (b) (6) of the study, the patient experienced a grade 1 confusional state, grade 1 vomiting, grade 3 anemia, grade 3 diffuse muscle contractions, and grade 2 gastrointestinal bleeding. Sonidegib was permanently discontinued. The patient was hospitalized and received intravenous hydration and blood transfusions. These events resolved two weeks following the last dose of study drug. The investigator assessed a relationship between the muscle contractures and sonidegib treatment, but did not consider the anemia and GI bleeding to be related.

Reviewer: The investigator's attribution of the events is likely correct. The narrative did not provide serum CK values at the time of the SAE. The reviewer searched the ADLB.xpt dataset of laboratory measures, and noted that this patient had four serum CK levels taken, all of which were normal. There was no documented CK level on the same day the patient presented with grade 3 muscle contractures; however, the serum CK was normal three days prior and four days after the presentation. It is uncertain if there was an elevated CK at the time of the muscle symptoms; however, multiple patients in the study experienced muscle symptoms prior to serum CK elevation, and some patients had isolated muscle symptoms with no CK elevation. Also, the patient received intravenous hydration and transfusion support during the hospitalization which may have prevented a subsequent elevation in serum CK or further muscle toxicity.

Patient 1503-009: The patient was a 52 year old female with laBCC randomized to the 800 mg arm who experienced the SAE of **rhabdomyolysis** while on study. Pertinent medical history included coronary artery disease, myocardial infarction and intermittent muscle cramps in the calves and toes for two years prior to study entry. The serum CK and creatinine were normal at study entry. On Day 18, the patient experienced grade 2 muscle spasms. No action was taken with the study medication. On Day 22, the serum CK was 2838 U/L (grade 4). On Day 23, the serum creatinine was normal, but on Day (b) (6), the serum creatinine was elevated (grade 1). Sonidegib treatment was permanently discontinued due to these events, and intravenous hydration was administered. (b) (6) days after discontinuing sonidegib, the patient had a normal serum creatinine; however, the serum CK remained elevated (5270

U/L), and the patient was hospitalized with increased myalgia requiring narcotic analgesics. The patient was diagnosed with rhabdomyolysis and cystitis by the investigator. She received intravenous antibiotics as well. The serum CK remained elevated (grade 4) during the hospitalization. The event of serum CK elevation resolved 34 days after the last dose of sonidegib. The events of muscle spasm and myalgia were ongoing at the time of the data cutoff. The investigator assessed the events of rhabdomyolysis and serum CK elevation as being related to sonidegib treatment.

Reviewer: The reviewer agrees with the investigator's attribution assessment. This case was reviewed by the IAC, and the diagnosis was adjudicated as muscle spasms and myalgia and not rhabdomyolysis. The serum creatinine was elevated, but not to 1.5 times the patient's baseline. Additionally, the committee noted that the renal impairment may have been due to the concurrent urinary tract infection. The reviewer agrees that this patient's laboratory values do not meet the definition of rhabdomyolysis provided by the IAC; however, this patient required substantial medical interventions including intravenous hydration, narcotics, hospitalization and frequent bloodwork monitoring. The rise in serum creatinine may have been due to a possible concurrent UTI; however, the patient also received intravenous hydration which could have prevented a worsening of her condition to actually meet the renal impairment parameter in the IAC's definition of rhabdomyolysis.

Patient 1509-002: This patient was a 58 year old male with laBCC randomized to the 800 mg arm who experienced the SAEs of **rhabdomyolysis, myositis and serum CK elevation**. Pertinent medical history included 'myalgia' for more than three decades prior to study entry and psoriasis. The patient had baseline normal serum CK and creatinine levels. On Day 15, the patient experienced grade 1 elevations of both serum CK and creatinine. These levels remained elevated on Day 43 (grade 1). On Day 50, the patient experienced grade 1 myalgia and muscle weakness and grade 4 serum CK elevation (2041 U/L). There was no report of interruption of sonidegib at this point; however, sonidegib was temporarily withheld starting on Day (b) (6) when the patient presented to the emergency room with persistent grade 4 CK elevation, elevated BUN, normal serum creatinine and grade 1 hematuria. The patient was treated with intravenous hydration. On Day (b) (6), the patient had an MRI scan that revealed findings consistent with myositis, and on Day (b) (6) a muscle biopsy revealed myofiber atrophy. The patient had been discharged on an unknown date after the initial presentation, but he was readmitted on Day (b) (6) due to grade 2 myalgia and grade 4 serum CK elevation (8840 U/L). The patient was diagnosed with rhabdomyolysis. He was treated with intravenous hydration in the hospital and then as an outpatient after discharge. On Day 77, the serum CK elevation was grade 3, and on Day 99, the serum CK normalized. The patient restarted sonidegib at a reduced dose upon normalization of his serum CK.

The patient experienced two recurrent episodes of serum CK elevation between Day 105 and 336, both grade 1, both times with a concurrent grade 1 elevation in serum creatinine. No action was taken with the sonidegib as of the last data cut-off. The investigator attributed the SAEs of rhabdomyolysis, serum CK elevation and myositis to the study drug.

Reviewer: The reviewer agrees with the investigator's assessment of attribution. This case was reviewed by the IAC, and the diagnosis for the event was adjudicated as myalgia, myopathy and myositis, but not rhabdomyolysis. The reviewer agrees that this patient's laboratory values do not meet the definition of rhabdomyolysis provided by the IAC; however, this patient required substantial medical interventions including intravenous hydration, at least two hospitalizations for the same SAE, a muscle biopsy and frequent bloodwork monitoring. The reviewer notes that restarting at a reduced dose in this patient did not cause further CK elevation more than grade 1 for approximately eight months; however, it is still concerning that the initial grade 4 serum CK elevation took 49 days to resolve despite the above medical interventions. It is unclear if the patient's medical history of 'myalgia' made this patient more vulnerable to the muscle toxicities associated with sonidegib treatment.

Patient 1509-003: This patient was a 38 year old female with laBCC randomized to the 800 mg arm who experienced the SAE of **rhabdomyolysis**. The patient had baseline normal serum CK and creatinine levels. On Day 34, the patient experienced grade 2 myalgia. On Day (b) (6), the myalgia worsened to grade 3, and there was a concurrent grade 3 serum CK elevation. Serum creatinine was not reported. The patient was hospitalized and diagnosed with rhabdomyolysis. Sonidegib treatment was interrupted. The patient was treated with intravenous hydration, morphine, and oxycocet. On Day (b) (6), the serum CK resolved to grade 1 and the patient was discharged. The serum CK normalized on Day 50, and sonidegib treatment resumed. The patient subsequently developed headaches, and sonidegib was permanently discontinued on Day 85. The investigator assessed a relationship between the SAEs rhabdomyolysis and serum CK elevation to sonidegib treatment, but assessed the headaches as unrelated.

Reviewer: The reviewer agrees with the investigator assessment of attribution of the muscle toxicity as related to sonidegib treatment; however, also agrees with the IAC that this case does not meet the definition of rhabdomyolysis. Other notable information about this patient is that she maintained her response for 139 days following discontinuation of sonidegib as of the last data cut-off. See Section 6.1.9 for further discussion.

Patient 1513-016: This patient was a 50 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAE of **elevation of serum CK, elevation of serum myoglobin and paresthesia**. The patient had baseline normal serum CK and creatinine levels. On Day 42, the patient experienced grade 3 serum CK elevation and grade 1 creatinine elevation. Sonidegib treatment was interrupted. The serum CK normalized on Day 49, and the medication was restarted at the same dose. On Day 86, the patient experienced grade 1 muscle spasms and grade 4 serum CK elevation and grade 1 creatinine elevation. Sonidegib was interrupted, and upon resolution of the serum CK to normal, sonidegib was restarted at a reduced dose. On Day (b) (6), the patient experienced a grade 4 increased serum CK (6112 U/L), and presented to the emergency room the next day with grade 2 muscle spasms, grade 4 serum CK elevation and grade 4 serum myoglobin elevation. Sonidegib was interrupted again, and the patient received intravenous hydration. The serum CK normalized on Day 114, and the study drug was restarted at a reduced dose. The patient experienced

grade 3 parasthesia and grade 2 muscle spasms which led to interruption of sonidegib for two days starting Day 156. Sonidegib was restarted at the same reduced dose. The patient experienced a fourth episode of serum CK elevation (grade 2) on Day 170, but no action was taken with regard to sonidegib treatment. The patient received the last dose of sonidegib on Day 237, but was lost to follow-up thereafter. The investigator assessed the SAEs of serum CK elevation and the repeated episodes of serum CK elevation as related to sonidegib treatment.

Reviewer: The reviewer agrees with the investigator's attribution assessment. Dose reduction in this case appeared to decrease the severity of the serum CK elevation, but there were multiple recurrences of muscle spasms and concurrent serum CK elevation after each reduction.

Patient 1524-003: This patient was a 49 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAE of **serum CK elevation**. Pertinent medical history included chronic alcohol abuse. The patient had baseline normal serum CK and creatinine levels. On Day 21, the patient experienced grade 1 serum CK elevation, but no action was taken with sonidegib treatment. On Day 43, the patient experienced grade 4 serum CK elevation (4,452 U/L) with a normal creatinine. Sonidegib treatment, according to the narrative, was permanently discontinued on Day (b) (6) when the patient experienced serum CK elevation of 10,971 U/L. The patient received intravenous hydration for the SAE. Six days following the last dose of sonidegib, the patient had a persistent and rising grade 4 serum CK (13,156 U/L) and a normal creatinine. He developed grade 3 serum AST elevation as well. The patient underwent muscle biopsy which revealed mild non-specific myopathic changes. The patient's serum CK was 1371 U/L (grade 3) thirty-four days after the last dose of sonidegib and resolved to grade 1 forty-eight days after the last dose of sonidegib. Liver function enzymes had normalized. The investigator assessed the SAE of serum CK elevation as related to sonidegib treatment.

Reviewer: The reviewer agrees with the investigator's attribution assessment. There was a prolonged time to resolution of the serum CK elevation (48 days), though the timing of drug discontinuation and medical interventions during the episode are unclear. Attribution of this patient's liver function impairment is confounded due to the patient's history of alcohol abuse although approximately 27% of all patients in Study A2201 and almost one third of patients in the 800 mg arm did experience AST elevation during treatment.

Patient 1601-002: This patient was a 71 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAEs of **serum CK elevation and rhabdomyolysis**. The patient had prior radiation therapy for BCC. Pertinent medical history included hypertension and hyperlipidemia, and the patient was treated with simvastatin for several years prior to study entry. Simvastatin was not taken beyond Day -17. The patient had baseline normal serum CK and creatinine levels. On Days 10 and 38, the patient experienced grade 2 myalgia and grade 1 muscle spasms, respectively. The patient experienced grade 4 serum CK elevation on Day 42 and rhabdomyolysis on Day 44. The serum creatinine on Day 42 was

normal. Sonidegib was interrupted on Day (b) (6) according to the narrative. The patient was hospitalized and treated with intravenous hydration, diuretics and sodium bicarbonate. The serum CK resolved to grade 1 by Day 61, and sonidegib was started at a reduced dose. The serum CK increased to grade 2 on Day 70. On Day 71, the MRI scan showed disease progression; however, the patient remained on study on Day 119. The serum CK was grade 1 on Day 111 and remained grade 1 twelve days after the final dose of sonidegib. The serum CK normalized by 54 days following the last dose of sonidegib. The investigator assessed a relationship between the SAE rhabdomyolysis and the sonidegib.

Reviewer: The muscle toxicity experienced by this patient was likely related to sonidegib treatment; however, the serum creatinine at the time of the diagnosis of rhabdomyolysis was normal; therefore, these events were adjudicated as muscle spasms and myalgia by the IAC. There was a prolonged time to resolution of this patient's serum CK to normal levels, which appears more typical at the 800 mg dose.

Patient 1601-003: This patient was an 80 year old male with laBCC randomized to the 800 mg arm who experienced the SAE of **rhabdomyolysis**. No medical history was reported. The patient had baseline normal serum CK and creatinine levels. On Day 17, the patient experienced grade 2 serum CK elevation. He developed muscle spasms and muscle pain on Day 25. Both serum CK and serum creatinine were elevated (both grade 1) at this time. There was no reported action taken with sonidegib. On Day 41, the patient experienced grade 4 serum CK elevation and grade 1 creatinine elevation, and sonidegib was interrupted on Day (b) (6). The patient was hospitalized, diagnosed with rhabdomyolysis, and received intravenous hydration and diuretics. On Day 57, the patient had a normal serum CK and a persistent grade 1 serum creatinine elevation. Sonidegib was restarted at a reduced dose. The patient developed grade 1 serum CK elevations, grade 1 creatinine elevation and grade 1 muscle spasms intermittently without a change in the sonidegib dose until at least Day 170. The patient was continuing on study at the time of the data cut-off. The investigator assessed a relationship between the event of rhabdomyolysis and sonidegib treatment.

Reviewer: The muscle toxicity experienced by this patient was likely related to sonidegib treatment; however, the serum creatinine at the time of the diagnosis of rhabdomyolysis was not 1.5 times baseline and therefore, this event did not meet the definition of rhabdomyolysis as used by the IAC. These events were adjudicated as asymptomatic serum CK elevation, muscle spasms and myalgia by the IAC. Although this patient does not meet the IAC's definition of rhabdomyolysis, he received early medical interventions including intravenous hydration and diuretics. The serum creatinine was elevated from baseline at the time of the grade 4 serum CK elevation, and the medical interventions, in addition to stopping sonidegib treatment, may have prevented worsening of the patient's renal status and an impending rhabdomyolysis.

There was one new musculoskeletal SAE reported in the 12 month safety update (patient 1195-001 described below), and no new musculoskeletal SAEs reported in the 18 month update:

Patient 1195-001: This patient was a 57 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAE of **recurrent serum CK elevation**. He had a grade 1 elevation of serum CK and a grade 1 elevation of creatinine at study entry. This patient experienced intermittent grade 1 and 2 muscle spasms and serum CK elevation during the course of the study. The maximum serum CK elevation was grade 3 on Day 281, which required a temporary interruption of sonidegib treatment. The patient restarted sonidegib at the same dose on Day 285. The patient continued to have grade 1 serum CK elevation and muscle spasms at the time of data cut-off, but was maintained on sonidegib treatment. The investigator assessed the SAE serum CK elevation to be related to sonidegib treatment.

Reviewer: Serum CK elevation was most likely related to sonidegib treatment; however, treatment interruption allowed the serum CK to return to normal relatively soon.

Study A2201: Non-musculoskeletal SAEs

The following summaries describe select non-musculoskeletal SAEs that were assessed as related to sonidegib treatment by the investigator. Most of these SAEs involved intolerable gastrointestinal toxicity at the 800 mg dose. There was one nonfatal cardiac event which the investigator considered unrelated to sonidegib treatment, and this case is also summarized (patient 1230-001).

Three events of pneumonia, one event of bronchitis and one event of acute renal failure are listed in Table 28, but are not summarized below. In these cases, the patients had clear underlying risk factors for the respective AEs prior to study entry, and the reviewer agrees with the local investigators' assessments of these SAEs as unrelated to sonidegib treatment.

Patient 1230-001: This patient was a 78 year old female with laBCC randomized to the 800 mg arm who experienced the SAE of **angina pectoris**. Pertinent medical history included prior myocardial infarction, stent placement and angioplasty, coronary artery disease and hypertension. She also had hypercholesterolemia treated with simvastatin for several years prior to study entry. She had an abnormal ECG finding (T wave inversion) on Day 1. On Day (b) (6), she presented with grade 2 coronary artery disease and angina pectoris. She was hospitalized for suspicion of myocardial infarction. Sonidegib was temporarily interrupted but restarted the next day. Sonidegib was later permanently discontinued due to patient decision. The investigator did not suspect a relationship between the angina pectoris and the study medication.

Reviewer: This SAE is unlikely to be related to sonidegib given the underlying cardiac medical history of this patient.

Patient 1150-005: This patient was a 74 year old male with laBCC randomized to the 800 mg arm, who experienced the SAEs of **hepatotoxicity and renal toxicity**. Pertinent medical history included gout, hypertension, hypercholesterolemia and prior aneurysm repair. The patient had a grade 1 elevation in serum creatinine at the time of study entry. His liver enzymes and bilirubin levels were normal. On Day 74, the patient experienced muscle spasms, grade 1 elevation in serum CK and grade 2 elevation in serum creatinine (175 umol/L). No treatment was reported for this event. On Day (b) (6), the patient experienced grade 3 dehydration, grade 3 hepatotoxicity (AST 505 U/L) and grade 3 renal toxicity (creatinine 409 umol/L). Sonidegib was permanently discontinued on Day (b) (6). The patient was treated with intravenous hydration. The patient was hospitalized again (b) (6) days after the last dose of sonidegib for renal toxicity and received intravenous hydration. He was discharged (b) (6) days later. The events were ongoing at the time of the data cut-off. The investigator attributed the events hepatotoxicity, renal toxicity and dehydration to sonidegib.

Reviewer: Sonidegib treatment likely contributed to these adverse events; however, the patient had mild renal impairment (grade 1 elevation of serum creatinine) at baseline which may have made him more susceptible to drug-related toxicities. There was no evidence of liver impairment at baseline. AST elevation occurred in 31% of patients treated in the 800 mg group, but only 5% of these patients had a grade 3 or 4 elevation. The reviewer also searched the adlb.xpt dataset for all laboratory abnormalities for this patient. Her bilirubin and alkaline phosphatase remained normal throughout the study, and the single event of elevation in liver enzymes is described in the narrative. The clinical significance of isolated and asymptomatic AST elevation is not clear.

Patient 1150-009: This patient was a 79 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAEs of **dysgeusia, dehydration, and decreased appetite**. Medical history was significant for acute renal failure, hypertension, type II diabetes mellitus, and hypercholesterolemia. The patient's body weight was 95 kg on Day 1 of the study treatment. On Day 87, the patient experienced grade 1 dysgeusia, dehydration and decreased weight (86 kg) and grade 2 decreased appetite. Sonidegib was withheld and then permanently discontinued due to the events of decreased weight, hypotension and dehydration. The patient was hospitalized (b) (6) days after the last dose of the study medication, at which time the dehydration worsened to grade 3. No treatment was reported, and the dehydration and decreased weight were ongoing at the time of the last available report. The investigator suspected a relationship between all of the events (dysgeusia, decreased appetite, weight decreased, hypotension, dehydration) and sonidegib.

Reviewer: Sonidegib likely contributed to the SAEs dysgeusia, decreased appetite and decreased weight. Both treatment arms demonstrated frequent occurrences of dysgeusia (38% in the 200 mg group, 72% in the 800 mg group), and weight loss (27% in the 200 mg group, 38% in the 800 mg group) in the primary analysis. Additionally, in patients over the age of 65 treated with sonidegib 800 mg, the incidence of decreased weight was 38% in the primary analysis and rose to 44% at the 18 month data cut-off date. See section 7.3.5 for

further discussion of the clinical impact of dysgeusia, decreased appetite and weight loss during Study A2201.

Patient 1234-005: This patient was an 85 year old female with laBCC randomized to the 800 mg treatment arm who experienced the SAEs of **diarrhea, nausea, gastritis, and vomiting**. Past medical history was significant for hypercholesterolemia, diarrhea, diabetes mellitus, renal failure, and hypertension. On Day 48, the patient experienced grade 1 nausea and grade 2 diarrhea. The patient was treated with loperamide, metoclopramide and omeprazole and coal tar. On Day 69, sonidegib was temporarily interrupted due to a grade 3 lipase elevation. Sonidegib was not restarted after this event, and the investigator reported permanent discontinuation was for diarrhea. The investigator attributed the diarrhea to study treatment, but did not attribute the patient's nausea, gastritis and vomiting to sonidegib.

Reviewer: The patient had chronic diarrhea at study entry, but given the toxicity profile of sonidegib, this patient's diarrhea was likely exacerbated with sonidegib treatment. Additionally, the patient's nausea and vomiting and the episode of lipase elevation are possibly related to sonidegib treatment given the relatively frequent incidence of these events across the study population.

Patient 1504-006: This patient was a 66 year old female with Gorlin syndrome and laBCC randomized to the 800 mg treatment arm who experienced the SAEs of **vomiting, duodenal stenosis, duodenal ulcer, and atrophic gastritis**. Past medical history was significant for arthritis, fibromyalgia, post herpetic neuralgia, chronic sinusitis, Meniere's disease, hypertension and hypercholesterolemia. The patient was taking pravastatin during the study. The baseline body weight was 68.9 kg. The patient experienced weight loss, diarrhea, nausea and vomiting during the study. On Day (b) (6), she was hospitalized for grade 3 vomiting and dehydration. Sonidegib was withheld and the permanently discontinued due to her diagnosis of duodenal ulcer and gastritis. The patient was discharged after (b) (6) days. Her body weight two weeks after her final dose of sonidegib was 49 kg. The investigator attributed the SAEs of vomiting, dehydration, duodenal stenosis, duodenal ulcer, and gastritis as related to sonidegib treatment.

Reviewer: Sonidegib likely contributed to the patient's vomiting and diarrhea and weight loss given the gastrointestinal toxicity profile of sonidegib. These events indirectly could result in the development of gastritis and duodenal ulceration.

Patient 1506-001: This patient was a 24 year old male with Gorlin syndrome and laBCC randomized to the 800 mg treatment arm who experienced the SAE of **upper gastrointestinal hemorrhage**. Past medical history was significant for medulloblastoma, prior brain tumor resection and irradiation, prior chemotherapy for medulloblastoma, hypothyroidism, hypogonadism, and dyslipidemia. On Day (b) (6), the patient presented with grade 3 upper gastrointestinal bleeding confirmed by endoscopy. The patient was treated with pantoprazole and discharged the next day. Sonidegib treatment was not interrupted or discontinued for this event. The investigator attributed the SAE as related to sonidegib treatment.

Reviewer: The CRF was reviewed to get additional information on this patient's treatment course. The patient continued on sonidegib treatment for at least another 12 months after this event and did not have a recurrence of gastrointestinal bleeding. Sonidegib treatment may have been related to the SAE given the gastrointestinal toxicity profile associated with sonidegib; however, the cause is not entirely clear, and the lack of recurrence despite drug continuation and no dose reductions suggests that sonidegib may have had less of a role in this event. The reviewer additionally analyzed the 12 month ADAE.xpt dataset and noted that there were two events of gastric ulcer occurrence and one occurrence of gastrointestinal hemorrhage on the 200 mg treatment arm. There was one occurrence of gastroenteritis not subcategorized as viral gastroenteritis. None of these gastrointestinal AEs were grade 3 or 4 in severity.

Patient 1515-003: This patient was a 55 year old male with laBCC randomized to the 800 mg treatment arm who experienced the SAEs of **nausea and vomiting**. Pertinent medical history included prior treatment with odansetron, lorazepam and prochloraperazine edisylate for nausea for four months prior to study entry. On Day ^{(b) (6)}, the patient was hospitalized for grade 3 nausea and vomiting. Sonidegib treatment was discontinued. The investigator attributed the SAEs of nausea and vomiting to sonidegib.

Reviewer: Nausea and vomiting were frequent occurrences in both treatment arms and appear to be dose-related. Almost half of all patients treated in the 800 mg group experienced nausea, and approximately 25% experienced vomiting. This patient had chronic nausea prior to study entry requiring treatment with three different medications; therefore, the patients may have been more likely to develop severe nausea and vomiting with sonidegib treatment.

Additional narratives of non-musculoskeletal SAEs were submitted as part of the twelve and eighteen month safety analyses. These were reviewed and did not reveal any new safety signals.

7.3.3 Dropouts and/or Discontinuations

Adverse events that led to discontinuation of treatment occurred in 58% (n=71) of the patients treated in Study A2201 in the primary analysis. The incidence of AEs leading to discontinuation was higher in the 800 mg group (36%) relative to the 200 mg group (22%). AEs that led to discontinuation in at least 2% of patients in the 200 mg group were muscle spasms, dysgeusia, decreased weight and nausea. AEs that led to discontinuation in at least 2% of patients in the 800 mg group were muscle spasms, dysgeusia, decreased weight, nausea, alopecia, decreased appetite, elevated serum CK, fatigue, and dehydration.

Twenty-six patients (11%) in Study A2201 experienced a grade 3 or 4 AE that led to discontinuation of sonidegib treatment. In the 200 mg treatment group, seven patients (9%) experienced grade 3 or 4 AEs that led to treatment discontinuation. Grade 3 events included muscle spasms (N=2), arthralgia (N=1), lumbar vertebral fracture (N=1), amylase and lipase

increase (N=1), and general health deterioration (N=1). The vertebral fracture and general health deterioration events were considered to be unrelated to sonidegib treatment by investigators. There was one grade 4 serum CK elevation that led to discontinuation, and this event (patient 1515-004) is described in section 7.3.2 of the review.

Nineteen patients (13%) experienced grade 3 or 4 AEs that led to discontinuation of study treatment in the 800 mg treatment group. Grade 3 events included muscle spasms (N=3), decreased appetite (N=2), muscle contractures (N=1), anemia (N=1), dehydration with hepatotoxicity (N=1), dysphagia (N=1), hypertension (N=1), decreased weight (N=1), nausea (N=1), headache (N=1), fatigue (N=1), and general health deterioration (N=1). Grade 4 AEs included serum CK elevation (N=2) and cardiac failure (N=1), anemia (N=1), and brain neoplasm (N=1). The AEs anemia, brain neoplasm and somnolence, cardiac failure and dysphagia were considered to be unrelated to sonidegib treatment by investigators. The events of grade 4 serum CK elevation (patients 1503-009 and 1524-003) are described in section 7.3.2 of the review. Table 29 summarizes the AEs that led to discontinuation of sonidegib in the primary analysis.

Table 29: Adverse events leading to discontinuation of sonidegib, primary analysis

Preferred Term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Any AE leading to discontinuation	17 (22)	54 (36)
Muscle spasms	3 (4)	13 (9)
Dysgeusia	2 (3)	7 (5)
Weight decreased	2 (3)	7 (5)
Nausea	2 (3)	6 (4)
Alopecia	1 (1)	9 (6)
Decreased appetite	1 (1)	8 (5)
Blood creatine kinase increased	1 (1)	3 (2)
Fatigue	1 (1)	3 (2)
Arthralgia	1 (1)	1 (1)
Asthenia	1 (1)	1 (1)
Dysphagia	1 (1)	1 (1)
General physical health deterioration	1 (1)	1 (1)
Abdominal pain upper	1 (1)	0
Agitation	1 (1)	0
Amylase increased	1 (1)	0

Preferred Term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Blood creatine phosphokinase MB increased	1 (1)	0
Depression	1 (1)	0
Dry mouth	1 (1)	0
Lipase increased	1 (1)	0
Lumbar vertebral fracture	1 (1)	0
Prostate cancer	1 (1)	0
Ageusia	0	3 (2)
Dehydration	0	3 (2)
Anemia	0	2 (1)
Constipation	0	2 (1)
Hypertension	0	2 (1)
Hypogeusia	0	2 (1)

Source: ADAE.xpt, primary analysis

Adverse events are presented in descending frequency in the sonidegib 200-mg column.

A patient with multiple occurrences of an AE under one treatment is counted only once.

Three patients in the 200 mg arm were “dose adjusted” by their physicians for adverse events. These patients were essentially discontinued rather than dose-reduced because patients in the 200 mg treatment group were reduced to placebo capsules per protocol. The blinded study design did not allow these investigators and patients to be aware of being reduced to placebo. Since these patients experienced AEs that prompted an action of dose reduction rather than permanent discontinuation, they are not included in this analysis or the summary table.

The safety data for the 12 and 18 month analyses were also reviewed. With longer term administration, there were more discontinuations for AEs on both treatment arms; however, there were no new safety signals. One patient experienced a grade 1 dyspnea on exertion that was considered related to sonidegib by the investigator and led to discontinuation of study treatment; however, review of the patient’s CRF showed that this patient had a medical history significant for episodes of dyspnea prior to study entry. Additionally, there were no other AEs that led to discontinuation of sonidegib within the SOC for respiratory, thoracic and mediastinal disorders in the twelve and eighteen month datasets.

7.3.4 Significant Adverse Events

Dose interruptions and reductions

AEs requiring dose interruption or reduction occurred in 50% (n=115) of patients exposed to sonidegib in both treatment arms in Study A2201 in the primary analysis. Dose adjustments

were more frequent in the 800 mg group (60%) compared to the 200 mg group (32%). The most common AEs requiring dose interruption or reduction in both arms were serum CK elevation, lipase elevation, nausea, fatigue, and diarrhea. Additional AEs requiring dose adjustments that occurred in more than 2% of patient in the 800 mg group but which were infrequent in the 200 mg group included muscle spasms, dysgeusia, vomiting, alopecia, decreased appetite, and myalgia. Table 30 summarizes the AEs necessitating dose interruption or reduction in at least one patient in either treatment arm.

Table 30: AEs requiring dose interruption or reduction, primary analysis

Preferred Term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Any AE requiring dose interruption or reduction	25 (32)	90 (60)
Blood creatine kinase increased	5 (6)	17 (11)
Lipase increased	4 (5)	6 (4)
Nausea	3 (4)	16 (11)
Fatigue	2 (3)	5 (3)
Diarrhea	2 (3)	7 (5)
Gastroenteritis viral	2 (3)	2 (1)
Hypertension	1 (1)	0
Alopecia	1 (1)	6 (4)
Decreased appetite	1 (1)	6 (4)
Rhabdomyolysis	1(1)	3 (2)
Myalgia	1 (1)	5 (3)
Alanine aminotransferase increased	1 (1)	3 (2)
Aspartate aminotransferase increased	1 (1)	3 (2)
Dizziness	1 (1)	2 (1)
Pneumonia	1 (1)	3 (2)
Muscular weakness	1 (1)	2 (1)
Vomiting	1(1)	10 (7)
Dysgeusia	1 (1)	11 (7)
Asthenia	1 (1)	1 (1)
Blood uric acid increased	1 (1)	1 (1)
General physical health deterioration	1 (1)	1 (1)

Preferred Term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Angina pectoris	1 (1)	0
Anorectal infection	1 (1)	0
Atrial fibrillation	1 (1)	0
Back pain	1 (1)	0
Bile duct stone	1 (1)	0
Blood creatinine increased	1 (1)	0
Cough	1 (1)	0
Disturbance in attention	1 (1)	0
Femoral neck fracture	1 (1)	0
Gastric ulcer	1 (1)	0
Influenza	1 (1)	0
Sleep disorder	1 (1)	0
Spinal compression fracture	1 (1)	0
Upper respiratory tract infection	1 (1)	0
Muscle spasms	0	24 (16)
Dyspnea	0	2 (1)
Myoglobin blood increased	0	3 (2)
Amylase increased	0	2 (1)
Hypogeusia	0	2 (1)
Malaise	0	2 (1)
Weight decreased	0	8 (5)

Source: ADAE.xpt, primary analysis

Adverse events are presented in descending frequency in the sonidegib 200-mg column.

A patient with multiple occurrences of an AE under is counted once per AE category.

The 12 and 18 month data analyses did not demonstrate any new safety signals. With longer term use of sonidegib, there was a small increase in the incidence of AEs requiring dose interruptions or reductions (55% and 57% in the 12 and 18 month analyses respectively). The incidence rates of AEs requiring dose adjustment by treatment group with longer term use of sonidegib were similar to the primary analysis (39% in the 200 mg group and 66% in the 800 mg group in the 18 month analysis).

Grade 3 and 4 adverse events

Grade 3 and 4 AEs occurred in 47% of patients (n=108) in Study A2201 in the primary analysis. Grade 3 and 4 AEs were more frequent for the 800 mg group (56%) compared to the

200 mg group (30%). The most common grade 3 and 4 AEs in both arms were increased serum CK, increased lipase, muscle spasms and hypertension. Grade 3 and 4 AEs that occurred in more than 2% of patients in the 800 mg group but were infrequent in the 200 mg group were decreased weight, rhabdomyolysis, increased alanine aminotransferase, increased aspartate aminotransferase, nausea, syncope and decreased appetite. Table 31 summarizes the grade 3 and 4 AEs by PT that occurred in at least 2% of patients in either treatment arm.

Table 31: Grade 3 and 4 adverse events, primary analysis

Preferred Term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Any Grade 3 or 4 AE	24 (30)	84 (56)
Blood creatine kinase increased	5 (6)	19 (13)
Lipase increased	4 (5)	8 (5)
Muscle spasms	2 (3)	8 (5)
Hypertension	2 (3)	4 (3)
Asthenia	2 (3)	0
Weight decreased	1 (1)	8 (5)
Rhabdomyolysis	1 (1)	5 (3)
Alanine aminotransferase increased	1 (1)	4 (3)
Aspartate aminotransferase increased	1 (1)	4 (3)
Nausea	1 (1)	4 (3)
Syncope	1 (1)	3 (2)
Decreased appetite	0	6 (4)
Fatigue	0	3 (2)
Myalgia	0	3 (2)
Anemia	0	3 (2)
Dehydration	0	3 (2)

Source: ADAE.xpt, primary analysis

Preferred terms are presented in descending order of frequency in the sonidegib 200 mg group.

A patient with multiple occurrences of an AE under is counted once per AE category.

The 12 and 18 month data did not reveal any new grade 3 and 4 AEs. One additional nonfatal case of pneumonia occurred in the 800 mg group so overall, grade 3 or 4 pneumonia occurred in 2% of patients (n=3) in the 800 mg group at the latest data cut-off date. The pneumonia AEs were not considered related to sonidegib treatment by investigators.

With longer term use of sonidegib, there was a small increase in the overall incidence of grade 3 and 4 AEs (52% in the 12 month and 55% in the 18 month). The incidence rates of grade 3 and 4 AEs by treatment group with longer term use of sonidegib was similar to the primary analysis (39% and 64% in the 200 mg and 800 mg groups respectively as of the 18 month data cutoff).

7.3.5 Submission Specific Primary Safety Concerns

The following groups of adverse events were flagged as Adverse Events of Special Interest (AESI) by the Applicant based on safety signals observed across the sonidegib development program.

- Muscle toxicity
- Nausea and/or vomiting
- Diarrhea
- Fatigue (asthenia)/lethargy
- Dysgeusia
- Alopecia
- Decreased appetite and/or weight loss
- Hypersensitivity
- Second primary malignancies
- Lipase and amylase elevations
- Torsades de pointes/QT prolongation
- Fractures

Hypersensitivity, second primary malignancies, lipase and amylase elevation, QT prolongation and fractures categories were not included in the primary or 12 month analyses, but were added in the 18 month analysis as AESI.

In general, the majority of AESI were grade 1 and 2 in severity, and there was an increased incidence of all AESI in the 800 mg group compared to the 200 mg group except for diarrhea and fractures which were more common in the 200 mg group. Table 32, copied from the SCS, Addendum 2, shows a side-by-side comparison of the AESI groups and the incidence rates by treatment arm at the primary, 12 month and 18 month analyses. The reviewer performed data analyses that confirm the primary and 12 month results for all AESI and analyzed the 18 month datasets to confirm the incidence and evaluate the clinical impact of muscle-related events and lipase elevations with longer term exposure to sonidegib.

Table 32: Adverse events of special interest: primary, 12 and 18 month analyses

AESI grouping	Primary analysis: data cut-off: 28-Jun-2013				12-month analysis: data cut-off: 31-Dec-2013				18-month analysis: data cut-off: 11-Jul-2014			
	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150		Sonidegib 200 mg N=79		Sonidegib 800 mg N=150		Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Muscle-related events	50 (63.3)	7 (8.9)	128 (85.3)	32 (21.3)	52 (65.8)	7 (8.9)	128 (85.3)	33 (22.0)	54 (68.4)	7 (8.9)	128 (85.3)	33 (22.0)
Alopecia	37 (46.8)	1 (1.3)	84 (56.0)	0	42 (53.2)	0	87 (58.0)	0	42 (53.2)	0	88 (58.7)	0
Nausea and/or vomiting	34 (43.0)	3 (3.8)	86 (57.3)	12 (8.0)	35 (44.3)	3 (3.8)	88 (58.7)	12 (8.0)	39 (49.4)	4 (5.1)	90 (60.0)	13 (8.7)
Dysgeusia	30 (38.0)	0	111 (74.0)	3 (2.0)	32 (40.5)	0	112 (74.7)	2 (1.3)	36 (45.6)	0	112 (74.7)	2 (1.3)
Decreased appetite and/or weight loss	30 (38.0)	1 (1.3)	78 (52.0)	13 (8.7)	32 (40.5)	2 (2.5)	84 (56.0)	14 (9.3)	33 (41.8)	3 (3.8)	85 (56.7)	14 (9.3)
Fatigue (asthenia)/lethargy	29 (36.7)	2 (2.5)	63 (42.0)	3 (2.0)	30 (38.0)	3 (3.8)	64 (42.7)	3 (2.0)	32 (40.5)	3 (3.8)	65 (43.3)	3 (2.0)
Diarrhea	19 (24.1)	0	37 (24.7)	0	25 (31.6)	1 (1.3)	39 (26.0)	0	26 (32.9)	1 (1.3)	41 (27.3)	1 (0.7)
Hypersensitivity ¹	--	--	--	--	--	--	--	--	17 (21.5)	0	35 (23.3)	2 (1.3)
Second primary malignancies ¹	--	--	--	--	--	--	--	--	10 (12.7)	2 (2.5)	23 (15.3)	8 (5.3)
Increased lipase and/or amylase ¹	--	--	--	--	--	--	--	--	6 (7.6)	5 (6.3)	13 (8.7)	8 (5.3)
Torsades de pointes/QT prolongation ¹	--	--	--	--	--	--	--	--	6 (7.6)	1 (1.3)	13 (8.7)	7 (4.7)
Fractures ¹	--	--	--	--	--	--	--	--	4 (5.1)	2 (2.5)	6 (4.0)	3 (2.0)

Source: Table 2-13, SCS Addendum 2, 18 month analysis

The review will discuss muscle-related events and lipase elevation in detail and then briefly summarize the other AESI categories.

Muscle-related events

Musculoskeletal toxicity appears to be a drug class effect with hedgehog inhibitors. SMO inhibitors have been shown to induce muscle contraction and muscle fiber twitching in primary human muscle cells, which may be related to inducing changes in normal calcium influx.[6] This be the underlying cause of the frequent muscle spasms and other muscle symptoms experienced by patients treated with vismodegib and sonidegib.

The following methods were used to evaluate this safety signal in patients exposed to sonidegib:

- A MAED analysis of the six month safety data from Study A2201 using broad and narrow Standard MedDRA Queries (SMQs) for rhabdomyolysis was performed.
- Safety analyses using the AE.xpt, LB.xpt, MUSCK.xpt and MUSCKB.xpt primary and 12 month datasets for Study A2201 were performed.

- Narratives and CRFs for patients who experienced muscle-related SAEs were reviewed (See Section 7.3.2).
- The Applicant's analysis of muscle-related AEs in a pooled safety population from twelve clinical studies across the sonidegib development program was reviewed.
- The summary statement as well as patient narratives and the adjudication assessment forms from the "Independent Safety Review and Adjudication Committee for Muscular Events Report" were reviewed. See below for background on the formation and roles of the Independent Adjudication Committee (IAC).

Independent Safety Review and Adjudication Committee for Muscular Events

The Applicant requested that the IAC be formed to review pooled safety data of musculoskeletal AEs that occurred during eleven clinical studies in the sonidegib development program. This request was prompted after a case of rhabdomyolysis with associated renal failure was reported in a drug-drug interaction study of sonidegib (CLDE225A2112) in June, 2013. The narrative for this case is summarized here:

Patient 0006-00001: This patient was a 27 year old male with metastatic nasopharyngeal squamous cell carcinoma who received sonidegib 800 mg daily and experienced the SAEs anemia, pyrexia, nausea, vomiting, rhabdomyolysis, and renal failure during treatment with sonidegib. Prior chemotherapy for his disease included fluorouracil, cisplatin, carboplatin, paclitaxel and gemcitabine. The patient had normal serum CK and creatinine levels at study entry. On Day 22, the patient experienced grade 3 anemia, back pain and muscle cramps. Sonidegib was discontinued on Day 28 for disease progression. On Day (b) (6), he experienced muscle spasms, myalgia, weakness, renal failure with oliguria, increased serum CK (>20,500 U/L) and increased serum creatine (max value reported prior to dialysis was 6.31 mg/dL). The patient required hemodialysis. Sonidegib had been discontinued five days prior to these events. The patient elected to stop dialysis and transition to hospice (b) (6) days after the last dose of sonidegib and died (b) (6) days later.

The IAC consisted of three external experts with experience in statin-related muscle toxicity. The Applicant provided the IAC with listings, tables and narratives of reported musculoskeletal adverse events including relevant medical history, concomitant medications, and laboratory results. The pooled safety population included 505 patients exposed to sonidegib (437 patients received sonidegib monotherapy and 68 patients received sonidegib in combination with other oncology drugs) at the data cut-off date of August 15, 2013.

The Applicant requested that the IAC perform the following tasks:

- Review cases of musculoskeletal AEs, including rhabdomyolysis and serum CK elevation
- Provide a definition of rhabdomyolysis
- Adjudicate all reported cases of rhabdomyolysis
- Recommend additional measures for patient management and risk mitigation

The IAC defined rhabdomyolysis as a serum CK level greater than 10 fold above the patient's baseline level plus a 1.5 fold increase in serum creatinine from the patient's baseline level or greater than 10 times upper limit of normal (ULN) if no baseline level was reported. Myositis was defined as asymptomatic or symptomatic CK elevations greater than 10 fold above baseline level or greater than 10 times ULN if no baseline level was reported. Only patients who had a serum CK elevation 10 times ULN were adjudicated by the IAC. Fifty-three narratives were included in the IAC report. All patients in the narratives had elevation of serum CK. There were fifteen narratives of patients with investigator-assessed rhabdomyolysis events. These narratives were reviewed and summarized in Table 33. Only one event was adjudicated by the IAC as meeting the definition of rhabdomyolysis, and this case is summarized above (Patient 0006-00001).

Table 33: Investigator-reported rhabdomyolysis events in sonidegib clinical studies

Study ID	Dose (mg)	Day ^a	Max CK level	Adjudicated Diagnosis ^b	IVF	Reviewer Notes
Study CLDE225A2112						
0006-00001	800	32	171 x BL	Rhabdomyolysis	Yes	See summary of narrative above.
Study CLDE225A2201						
1532-001	200	335	23x BL	Myopathy	Yes	Patient had urinary myoglobin present and muscle symptoms. Serum Cr not reported. Drug restarted and later discontinued for progressive disease.
1503-009	800	22	103x BL	Muscle spasms, Myalgia	Yes	Serum Cr increased from BL (0.65 to 1.01). Possible concurrent UTI. Permanent discontinuation due to event.
1509-002	800	50	70x BL	Myalgia, Myopathy, Myositis	Yes	MRI showed myositis; muscle biopsy showed myofiber atrophy. Serum CK elevated > 40 days; no Cr abnormalities
1509-003	800	34	273 x BL	Myalgia	Yes	Cr was 1.44 x BL at time of event. Required IV narcotics for muscle pain. Restarted drug and later discontinued for adverse event of headache.
1601-002	800	38	78x BL	Muscle spasms, Myalgia	Yes	Serum Cr not reported. Sonidegib interrupted Day 41 and restarted Day 67. Patient had persistent grade 1 spasms when discontinued for disease progression > 80 days from event.

Study ID	Dose (mg)	Day ^a	Max CK level	Adjudicated Diagnosis ^b	IVF	Reviewer Notes
1601-003	800	25	70 x BL	Myalgia, Muscle spasms	Yes	Interrupted sonidegib Day 41. Restarted lower dose Day 61 and had subsequent muscle symptoms but no CK elevation and normal Cr.
Study CLDE225AX1101						
0101-00011	400	28	79 x BL	Myalgia, Myopathy, Asymptomatic CK Elevation	Yes	Normal serum Cr. Concurrent hepatic impairment. Permanent discontinuation due to event.
0101-00006	600	32	> 50 x ULN	Myalgia	Yes	Elevated myoglobin and BUN; normal Cr. Muscle pain required IV narcotics; patient had difficulty walking. Permanent discontinuation due to event.
Study CLDE225AX2101						
0020-00104	3000	35	341 x BL	Myalgia, Myositis, Myopathy	Yes	Normal Cr. MRI showed myositis; muscle biopsy showed necrosis. Permanent discontinuation due to event. CK normalized 37 days after last dose of sonidegib.
0020-00111	800	27	70 x BL	Myalgia, Muscle spasms	Yes	Normal Cr; additional CK values not reported. Concurrent hepatic impairment. Permanent discontinuation due to event.
0502-00117	1500	29	274 x BL	Myalgia, Muscle Spasms, Asymptomatic CK Elevation	Yes	No Cr reported. MRI showed muscle abnormalities; muscle biopsy showed neurogenic changes and cytochrome oxidase deficient fibers, but no inflammation or necrosis. CK remained elevated >46 days after last dose of sonidegib. Symptoms were ongoing at time of last report. Permanent discontinuation due to event.
Study CLDE225X2104						
0032-00200	600	25	171 x BL	Myalgia, muscle spasms	Yes	Myoglobin elevated; low Cr. No muscle symptoms reported. Event occurred 7 days after last dose of sonidegib.

Study ID	Dose (mg)	Day ^a	Max CK level	Adjudicated Diagnosis ^b	IVF	Reviewer Notes
Study CLDE225XUS02T						
XUS02 T-004	800	27	46 x BL	Myalgia	Yes	No Cr reported at time of event. Received narcotics for muscle pain. Permanent discontinuation due to event.
Study CLDE225XUS03T						
XUS03 T-0009	600	32	163 x BL	Myalgia	Yes	Patient taking simvastatin at time of event. No Cr reported. Patient admitted twice for hydration. Serum CK elevated for 25 days after last dose. Permanent discontinuation due to event..

Source: IAC Report narratives, ADLB.xpt

BL:baseline; IVF: intravenous fluids; CK: creatine kinase; Cr: creatinine; BUN: blood urea nitrogen, ULN: upper limit of normal; ¹Day of study when event began or was reported; ²Diagnosis provided by the IAC

Reviewer: Of the fifteen investigator-reported rhabdomyolysis events described in the table above, most cases were adjudicated as myalgia or myositis or muscle spasms rather than rhabdomyolysis because there was lack of evidence of renal impairment. In some cases however, renal function labs were not reported, and in all cases, patients were hospitalized and received intravenous hydration which may have prevented worsening of the patients' condition such that it would be within the parameters of the IAC's definition of rhabdomyolysis. Additionally, the range of maximum serum CK elevation during each event ranged from 23 to 341 times baseline CK values (all grade 4). The IAC acknowledged that it is possible that some patients may have developed renal failure if they were not treated with intravenous hydration and other supportive care measures. Muscle toxicity appears to be dose-dependent, and only one of the cases in Table 33 occurred at the 200 mg dose. The reviewer recommends that the product label include sufficient details regarding the musculoskeletal adverse reactions that occurred during clinical studies of sonidegib such that prescribers are adequately informed of this risk and the safety monitoring that should be in place when treating patients with sonidegib.

The IAC made the following general observations in the analysis of the pooled safety data with regard to muscle toxicity observed in sonidegib clinical studies:

- The majority of patients had symptoms, most often muscle spasms or cramps, which preceded an elevation in serum CK.
- Some patients had no symptoms preceding the elevation in serum CK, and were diagnosed with "asymptomatic myositis."

- The magnitude of serum CK elevation varied widely.
- Approximately 60 percent of the reviewed cases included patients who received supplemental hydration or were hospitalized for intravenous hydration or had documented myoglobinuria.

The Applicant requested that the IAC recommend risk mitigation strategies and dose modification guidelines to address the musculoskeletal toxicity observed with sonidegib treatment. The IAC recommended that drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins) be discontinued two weeks prior to initiating treatment with sonidegib and that patients avoid any drugs that have been associated with myopathy or rhabdomyolysis while taking sonidegib. The IAC provided the Applicant with the following table of dose modification and management guidelines for serum CK elevations in patients receiving sonidegib.

Table 34: IAC recommended dose modifications and management of CK-related toxicities

<p>Grade 1 [CK elevation >ULN - 2.5 x ULN]</p>	<ul style="list-style-type: none"> Continue treatment at the same dose and monitor CK levels weekly until resolution to baseline level and then monthly thereafter. Monitor muscle symptoms for changes until resolution to baseline. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
<p>Grade 2 [CK elevation >2.5 x ULN - 5 x ULN]</p>	<ul style="list-style-type: none"> Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume treatment at the reduced dose level and measure CK monthly thereafter. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
<p>Asymptomatic or Symptomatic CK elevation</p>	
<p>Grade 3 or 4 without renal impairment [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [Grade or 4 (CK elevation >10 x ULN)]</p>	<ul style="list-style-type: none"> Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. If renal function is not impaired (normal serum creatinine) and CK resolves to baseline level, consider resuming treatment at a reduced dose. CK levels should be measured weekly for 2 months after re-administration of sonidegib and monthly thereafter.
<p>Grade 3 or 4 with renal impairment</p>	<ul style="list-style-type: none"> Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. If renal function is impaired ($\geq 50\%$ above the baseline level), interrupt treatment. Ensure patient is adequately hydrated and evaluate other secondary causes. Continue monitoring of CK and creatinine levels weekly. If CK levels return to baseline level and creatinine levels return to baseline, consider resuming treatment at the reduced dose otherwise discontinue treatment permanently.

Source: IAC Report, Section 4, February 2014

Musculoskeletal toxicity in Study A2201

The adequacy of the Applicant's search strategy to capture musculoskeletal events experienced by patients enrolled in Study A2201 is discussed in Section 7.1.2.

Musculoskeletal adverse reactions occurred frequently in both treatment arms. The frequency of all musculoskeletal AEs was higher in the 800 mg group. Six patients experienced AEs which investigators reported as rhabdomyolysis. One of these six patients was receiving the 200 mg dose. These cases were not adjudicated as rhabdomyolysis by the IAC. See the narrative summaries in Section 7.3.2 and Table 33 for further details on these events. Table 35 summarizes the musculoskeletal AE data for Study A2201 in the 12 month analysis.

Table 35: Clinical impact of musculoskeletal adverse events, 12 month analysis

Preferred Term	Sonidegib 200 mg N= 79 n (%)	Sonidegib 800 mg N= 150 n (%)
Common muscle-related AEs (more than 2% of patients in either arm)	52 (66)	128 (85)
Muscle spasms	41 (52)	104 (69)
Blood CK increased	24 (30)	56 (37)
Myalgia	15 (19)	39 (26)
Muscular weakness	3 (4)	8 (5)
Rhabdomyolysis	1 (1)	5 (3)
Musculoskeletal pain	4 (5)	5 (3)
Blood creatinine increased	2 (3)	3 (2)
Chromaturia	2 (3)	0
Myoglobin blood increased	0	3 (2)
All Grade 3-4 AEs	7 (9)	33 (22)
Blood CK increased	5 (6)	20 (13)
Muscle spasms	2 (3)	8 (5)
Rhabdomyolysis	1 (1)	5 (3)
Myalgia	0	3 (2)
Myoglobin blood increased	0	2 (1)
Muscular weakness	0	1 (1)
Myositis	0	1 (1)
Serious adverse events	2 (3)	10 (7)
Rhabdomyolysis	1 (1)	5 (3)

Preferred Term	Sonidegib 200 mg N= 79 n (%)	Sonidegib 800 mg N= 150 n (%)
Blood CK increased	1 (1)	4 (3)
Renal failure acute	0	1 (1)
Myoglobin blood increased	0	1 (1)
Myositis	0	1 (1)
Muscular weakness	0	1 (1)
Renal impairment	0	1 (1)
AEs requiring discontinuation	5 (6)	17 (11)
Muscle spasms	4 (5)	13 (9)
Blood CPK increased	1 (1)	3 (2)
Myalgia	0	1 (1)

Source: ADAE.xpt, ADMUSCKB.xpt, 12 month analysis

Adverse events are presented in descending frequency in the sonidegib 200-mg column.

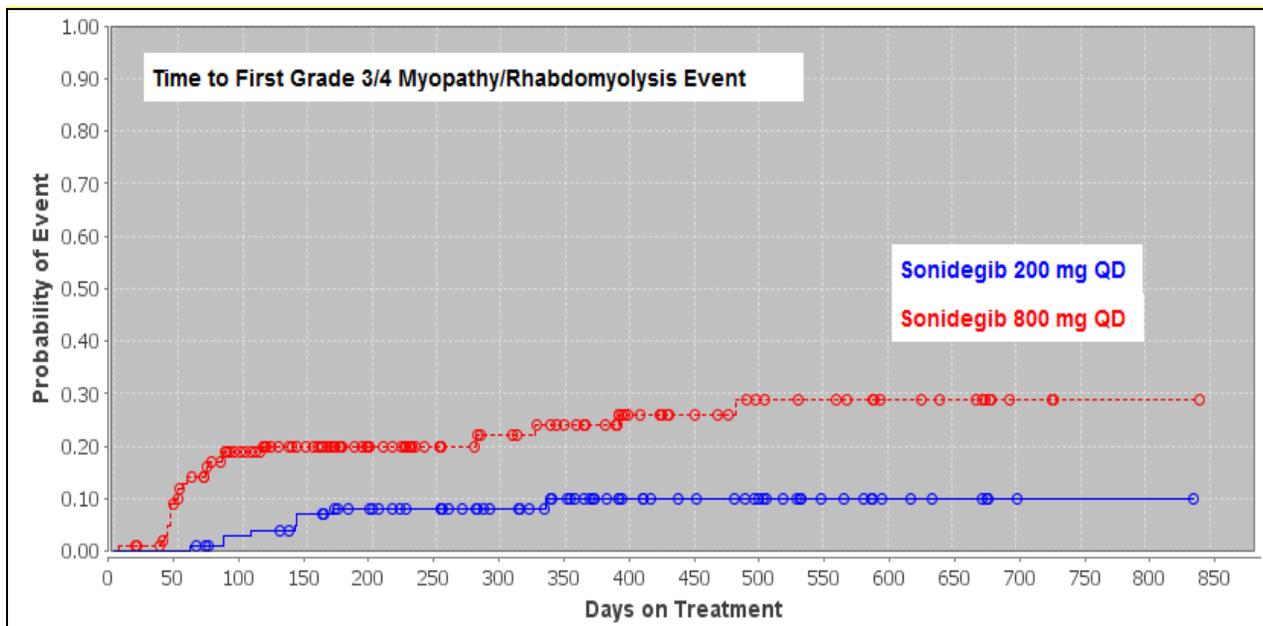
A patient with multiple occurrences of an AE under one treatment is counted only once.

Time to onset of grade 3 or 4 musculoskeletal AEs

A time to event analysis was performed using the twelve month ADAE.xpt and ADLB.xpt datasets to evaluate for trends in the occurrences of serious muscle-related AEs in patients exposed to sonidegib during Study A2201. The median time to onset of grade 3 and 4 musculoskeletal toxicity, including serum CK elevation, was not estimable because the majority of patients were censored in both treatment arms. See Figure 3.

For the seven patients (9%) in the 200 mg treatment group that experienced grade 3 or 4 muscle-related AEs, the time to initial onset of the events ranged from 1.9 to 11 months in the 200 mg group. For the 33 patients (22%) in the 800 mg treatment group that experienced grade 3 or 4 AEs, the time to first onset ranged from 0.1 month to 15.8 months.

Figure 3: Time to first onset of grade 3 or 4 musculoskeletal toxicity, 12 month analysis



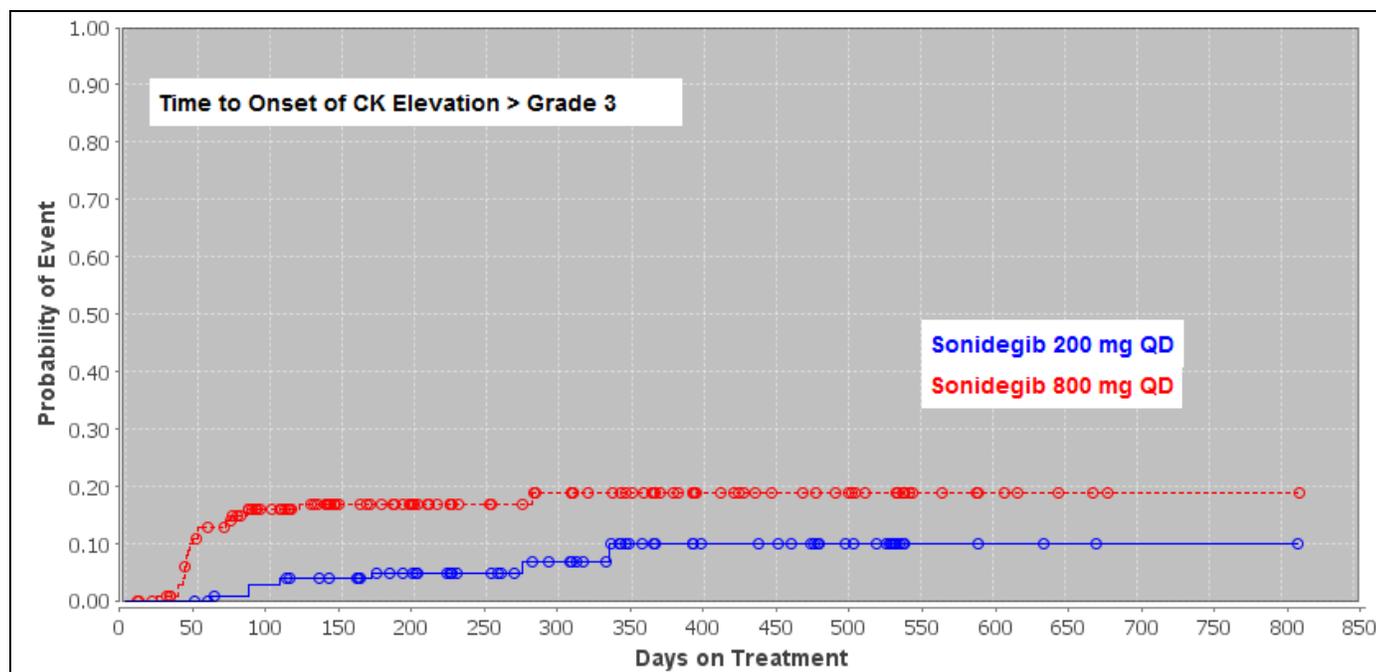
Source: JReview analysis of AE.xpt, LB.xpt from 12 month data

Observed Trends in Serum CK elevation

Elevation of serum CK occurred in 62% and 67% of patients in the 200 and 800 mg treatment groups respectively in the 12 month analysis. Grade 3 or 4 CK elevations occurred in 8% (200 mg dose) and 17% (800 mg dose) of patients. The time to onset of grade 3 or 4 serum CK elevations ranged from 8 weeks to 48 weeks in the 200 mg group and 3 weeks to 40 weeks in the 800 mg group. See Figure 4.

The median time to resolution (to \leq grade 1) of the first grade 3 or 4 CK elevation was 8 days (range of 4 to 32 days) in the sonidegib 200 mg group compared with 15 days (range of 13 to 22 days) in the 800 mg group.

Figure 4: Time to onset of grade 3 and 4 serum CK elevation , 12 month analysis



Source: JReview analysis of AE.xpt, LB.xpt from 12 month data

The magnitude of serum CK elevations varied across patients in Study A2201, and in some cases, the serum CK elevation was not accompanied by muscle symptoms. Upon FDA request, the Applicant submitted an analysis of patients in Study A2201 who experienced asymptomatic serum CK elevation. Asymptomatic serum CK elevation occurred in 12% (n=27) of patients in the study. Three patients in the 800 mg arm required dose interruption or reduction. No patient with asymptomatic CK elevation required discontinuation.

Some patients in Study A2201 experienced muscle symptoms and did not have evidence of serum CK elevation during the AE. To better understand the clinical impact of muscle toxicity not associated with concurrent serum CK elevations, FDA requested that the Applicant submit an analysis of patients who experienced musculoskeletal AEs that required dose adjustments or discontinuations in the setting of normal serum CK levels. According to the Applicant's analysis, 14% (n=31) of patients experienced a musculoskeletal AE in the setting of normal or baseline serum CK levels which led to a dose interruption, reduction, or discontinuation. Fifteen of these patients had a normal/baseline CK level at the closest time point relative to the onset of the muscle-related AE and during the AE period, and 16 patients had a normal CK level at the closest time point relative to the onset of the event with subsequent CK elevation noted during the course of the AE. The most common AE that required dose adjustment of sonidegib in this group of patients was grade 2 and 3 muscle spasms.

Reviewer: The available data suggests that serum CK elevation is dose-related, but the magnitude of CK elevations varies among patients and between treatment arms. Upon

discontinuation of sonidegib for serum CK elevation, it took longer for a patient's CK level to return to baseline at the 800 mg dose compared to the 200 mg dose. Events of asymptomatic serum CK elevation and muscle symptoms without concurrent serum CK elevation occurred and led to dose adjustments or discontinuation in some patients. The numbers of patients in these subgroups were small, and all analyses are considered exploratory.

Recurrence of musculoskeletal toxicity after dose reduction

To evaluate whether dose reduction decreases the recurrence risk for musculoskeletal AEs, safety data from the 12 month analysis were reviewed for both treatment arms. In the 200 mg group, two patients (3%) required dose reductions for AEs of muscle weakness and myalgia; however, these patients were dose reduced from 200 mg to placebo per protocol. A reduced dose or different dose schedule was not studied. In the 800 mg group, twenty patients (13%) experienced muscle AEs that required dose reduction. Ten of these patients experienced severe muscle spasms, and six patients had serum CK elevation requiring dose reduction. Twelve of eighteen patients (67%) with documented follow-up after a dose reduction experienced a recurrence of muscle symptoms or serum CK elevation at the reduced dose.

Reviewer: The IAC's dose modification guidelines (Table 34) recommend interruption of sonidegib followed by dose reduction for patients who experience \geq grade 2 serum CK elevation. Given the recurrence rate of muscle AEs after dose reduction in the 800 mg group, the lack of experience with reduced dosing in the 200 mg group, and evidence that doses of sonidegib less than 200 mg daily are not associated with reasonable antitumor activity, the reviewer does not agree with the IAC's recommendation for dose reduction. Additionally, of the six patients in the 200 mg group that required discontinuation of sonidegib for muscle-related toxicity, there were three patients with an objective response observed prior to discontinuation, and these responses were durable for at least 113 days after the final dose of sonidegib. See Section 6.1.9.

Risk factors for muscle toxicity with sonidegib treatment

Specific patient risk factors were not identified in the evaluation of muscle toxicity in patients enrolled in Study A2201. The study excluded patients with underlying muscular disorders or renal impairment. Additionally, it was recommended that patients stop taking statin drugs for at least two weeks prior to initiating sonidegib given the known risk for rhabdomyolysis with HMG-CoA reductase inhibitors. Thirty-one patients (14%) continued treatment with a statin (pravastatin was permitted) during Study A2201. The incidence of muscle symptoms and serum CK elevation was not substantially different between those who were not taking concomitant statins and those patients who were receiving pravastatin. Eight patients received a statin other than pravastatin during the study; this group was too small to draw any conclusions regarding the potential for increased muscle toxicity with statin drugs other than pravastatin. See Section 7.5.5 for further discussion of drug-drug interactions.

Medical interventions for musculoskeletal toxicity

To further evaluate the risk of muscle toxicity with sonidegib, FDA requested that the Applicant provide an analysis of musculoskeletal events that occurred across the sonidegib clinical

development program. The Applicant was specifically asked to include information describing the medical interventions that were required for treatment of musculoskeletal adverse reactions occurring during sonidegib treatment. The Applicant performed this additional safety analysis using a population of 571 patients treated in 12 clinical studies of sonidegib.

A total of 154 (27%) out of 571 patients across the sonidegib clinical development program experienced one or more muscle-related AEs requiring medical intervention. The majority of these interventions included magnesium administration or non-narcotic analgesics. Five percent of patients required narcotics, 5% required IV hydration, and 4% of patients were hospitalized for musculoskeletal AEs.

In Study A2201, The requirement for medical interventions for muscle events was slightly increased. A total of 24 patients (30%) in the 200 mg arm and 64 patients (43%) in the 800 mg group experienced muscle-related AEs requiring medical intervention. Examples included narcotic administration, IV hydration, or hospitalization. Tables 36 and 37 summarize musculoskeletal AEs requiring medical intervention during Study A2201 and in the pooled population. These tables are copied from the Applicant’s response to an FDA information request.

Table 36: Summary of clinically important medical interventions for muscle-related AEs, Study A2201

	Total no. of patients treated with sonidegib	Total no. of patients with muscle-related AE leading to medical intervention	No. of patients hospitalized due to muscle-related AE	No. of patients treated with IV hydration due to muscle-related AE	No. of patients treated with narcotics for pain due to muscle-related AE
Study A2201 Randomized dose	N	n (%) ^a	n (%) ^b	n (%) ^b	n (%) ^b
200 mg QD	79	24 (30)	2 (3)	2 (3)	2 (3)
800 mg QD	150	64 (43)	9 (6)	10 (7)	9 (6)
Total	229	88 (38)	11 (5)	12 (5)	11 (5)

Source: Response to FDA IR 23, April 7, 2015

Table 37: Summary of clinically important medical interventions for muscle-related AEs in sonidegib-treated patients across the sonidegib development program

	Total no. of patients treated with sonidegib	Total no. of patients with muscle-related AE leading to medical intervention	No. of patients hospitalized due to muscle-related AE	No. of patients treated with IV hydration due to muscle-related AE	No. of patients treated with narcotics for pain due to muscle-related AE
Study No.	N	n (%) ^a	n (%) ^b	n (%) ^b	n (%) ^b
CLDE225A2201	229	88 (38)	11 (5)	12 (5)	11 (5)
CLDE225X2101	103	26 (25)	5 (5)	7 (7)	8 (8)
CLDE225X1101	45	9 (20)	0	6 (13)	1 (2)
CLDE225X2104	76	14 (18)	3 (4)	3 (4)	5 (7)
CLDE225X2103	18	2 (11)	0	0	1 (6)
CLDE225C2301	10	1 (10)	1 (10)	1 (10)	0
CAMN107Y2101	11	5 (45)	0	0	0
CLDE225X2114	46	2 (4)	2 (4)	1 (2)	1 (2)
CLDE225A2112	10	2 (20)	1 (10)	1 (10)	2 (20)
CLDE225X2203	9	3 (33)	1 (11)	0	0
CLDE225X2116	6	1 (17)	0	0	1 (17)
CLDE225B2209	8	1 (13)	0	0	0
Total	571	154 (27)	24 (4)	31 (5)	30 (5)

Source: Response to FDA IR 23, April 7, 2015

Lipase and amylase elevation

Lipase elevation was a frequent occurrence in both treatment arms of Study A2201. At the 12 month data cut-off, 43% of patients in the 200 mg group had at least one elevated lipase level, and 13% had grade 3 or 4 lipase elevations. In the 800 mg group, 53% of patients had at least one occurrence of increased lipase and 13% experienced grade 3 or 4 lipase elevation.

Amylase elevation was less frequent, occurring in 17% and 19% of patients in the 200 and 800 mg groups respectively.

Lipase elevation was reported as an AE in 8% of the patients in both treatment arms. Grade 3 or 4 lipase elevation was reported in 6% of patients in the 200 mg arm and 5% of patients in the 800 mg group. There were no reported cases of pancreatitis. Lipase elevation required discontinuation of sonidegib treatment in one patient in each arm.

FDA requested that the Applicant conduct a review of increased lipase events across a larger pooled safety population to better evaluate the clinical implications of this safety signal. Overall, 24 of 571 patients (4%) experienced an AE of lipase increased, of which 18 (3%) were Grade 3-4 in severity. The majority lipase elevation events occurred as isolated laboratory findings.

There was one SAE of pancreatitis which occurred in Study A2201 after the 18 month analysis data cut-off date (therefore not included in the safety analyses conducted for the review). The narrative is summarized below.

Patient 1233006: This patient was a 57 year old male with laBCC enrolled in Study A2201 who was receiving sonidegib on study for more than 3 years at the time he experienced the **SAE of pancreatitis**. Pertinent medical history included cholelithiasis. All liver function tests were elevated and lipase was 34.5 ukat/l (normal: 0.222 to 1.00 ukat/l) when the patient presented with abdominal pain resulting in hospitalization. Sonidegib treatment was interrupted. The patient was discharged after (b) (6) days and then readmitted for recurrent pancreatitis (b) (6) days later. A cholecystectomy was planned for a few weeks later at the time of the most recent follow-up report. The event was considered by the investigator to be unrelated to treatment with sonidegib and secondary to cholelithiasis.

Reviewer: Although lipase elevation was common in Study A2201 and in other clinical studies of sonidegib, the clinical significance of this isolated laboratory finding is unclear. The one SAE of pancreatitis described above occurred after three years of sonidegib exposure and then recurred when the patient was off sonidegib for more than 20 days. It is unclear whether sonidegib exposure made the patient more vulnerable to developing pancreatitis in the setting of his comorbid conditions. This event does not substantially change the risk:benefit profile of sonidegib for patients with BCC.

Clinical Impact of Other AESI

- **Nausea and vomiting** were frequent AEs occurring in both treatment arms. Grade 3 or 4 nausea or vomiting occurred in 4% of patients in the 200 mg group and 8% of patients in the 800 mg group in the 12 month analysis. The same percentages of patients discontinued sonidegib for these AEs.
- **Dysgeusia** was common in both arms occurring in 41% and 60% of patients in the 200 mg and 800 mg groups respectively. Grade 3 or 4 dysgeusia was experienced by one patient in the 800 mg group and none in the 200 mg arm. Dysgeusia led to discontinuation of treatment in 4 and 8% of patients in the 200 mg and 800 mg arms respectively.
- **Decreased appetite or weight loss** were frequent AEs in both treatment arms (41% in the 200 mg group and 56% in the 800 mg group). Weight loss from baseline occurred in 30% of patients in the 200 mg group and 42% of patients in the 800 mg group. Grade 3 or

4 weight loss occurred in 3% and 6% of patients in the 200 and 800 mg arms respectively and led to treatment discontinuation in 3 and 5% of patients in these groups. Weight loss was frequently accompanied by decreased appetite and other gastrointestinal AEs in the same patient.

- **Fatigue-related events** (preferred terms: fatigue, asthenia, malaise and lethargy) were experienced by 38% of patients in the 200 mg group and 43% of patients in the 800 mg group. Grade 3 or 4 AEs occurred in 4% and 2% of the 200 mg and 800 mg groups respectively. These AEs led to treatment discontinuation in 6% of patients in the 200 mg group and 2% of patients in the 800 mg group.
- **Diarrhea-related events** were experienced by 32% of patients in the 200 mg group and 26% of patients in the 800 mg group. There was one case of grade 3 or 4 diarrhea in the 200 mg arm and none in the 800 mg arm. One patient in the study (800 mg dose) required treatment discontinuation for diarrhea.
- **Hypersensitivity** reactions occurred at a similar frequency across treatment arms. The most common events included low grade pruritus and rash. There were no grade 3 or 4 hypersensitivity reactions that were considered by investigators to be related to study drug. A total of four patients (2%) discontinued treatment for pruritus in the 18 month analysis.
- **Second primary malignancies** occurred in 28 patients (12%) in Study A2201 in the 18 month analysis; the incidence was similar across treatment arms. The most frequently reported secondary neoplasms were squamous cell carcinoma or squamous cell carcinoma of the skin (5% of patients in both treatment arms), and malignant melanoma (3% of patients treated with 200 mg and 1% of patients treated with 800 mg).

Reviewer: Squamous cell carcinoma (SCC) has been reported following treatment of BCC with vismodegib[17]. In some cases, the lesion developed at the site of the BCC, and there are other reports of patients who have developed squamous cell carcinoma of the skin at distant locations during treatment with vismodegib[18, 19]. It has been hypothesized that there can be histological transdifferentiation of BCC to SCC with hedgehog pathway interference, but the clinical significance of SCC development in patients treated with hedgehog inhibitors has not been determined.

- **Fractures** were reported in 5% of patients in the 200 mg group and 4% of patients in the 800 mg group. No fracture events were determined by the investigators to be related to treatment with sonidegib.
- **QT prolongation** is discussed in Section 7.4.4 of the review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse events: primary analysis

The primary safety database for study A2201 was analyzed at each level of the MedDRA hierarchy for common AEs. The tables in this section summarize the incidence of treatment emergent AEs. Almost all patients treated in Study A2201 had at least one AE during treatment with sonidegib at the time of the primary analysis (95% of patients treated in the 200 mg arm and 100% of patients treated in the 800 mg arm). In general, the frequency and severity of AEs were higher on the 800 mg arm relative to the 200 mg arm.

At the system organ class (SOC) level, the most frequently affected systems ($\geq 20\%$ incidence) were musculoskeletal and connective tissue disorders, skin and subcutaneous disorders, nervous system disorders, gastrointestinal disorders, investigations, general disorders/administrative site conditions, infections and infestations, respiratory, thoracic and mediastinal disorders, and metabolism and nutrition disorders. SOCs which contained at least a 10% increase in incidence of AEs in the 800 mg group as compared with the 200 mg group included: metabolism and nutrition disorders, nervous system disorders, investigations, and gastrointestinal disorders.

Table 38 summarizes all AEs by SOC in the primary analysis. These data confirm the results presented in the Clinical Study Report for Study A2201.

Table 38: AEs occurring in at least 10% of patients by system organ class, primary analysis

System Organ Class	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3-4	All grades	Grade 3-4
Musculoskeletal and connective tissue disorders	57 (72)	4 (5)	119 (79)	19 (13)
Skin and subcutaneous tissue disorders	51 (65)	1 (1)	95 (63)	0
Nervous system disorders	51 (65)	1 (1)	122 (81)	9 (6)
Gastrointestinal disorders	49 (62)	2 (3)	109 (73)	9 (6)
Investigations	43 (54)	10 (13)	102 (68)	42 (28)
General disorders and administration site conditions	38 (48)	4 (5)	77 (51)	5 (3)
Infections and infestations	38 (48)	0	64 (43)	6 (4)
Respiratory, thoracic and mediastinal disorders	21 (27)	0	43 (29)	3 (2)

System Organ Class	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3-4	All grades	Grade 3-4
Metabolism and nutrition disorders	19 (24)	0	62 (41)	12 (8)
Vascular disorders	11 (14)	3 (4)	26 (17)	6 (4)
Psychiatric disorders	10 (13)	0	26 (17)	0
Injury, poisoning and procedural complications	10 (13)	2 (3)	21 (14)	2 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (10)	0	14 (9)	5 (3)
Renal and urinary disorders	8 (10)	0	14 (9)	2 (1)
Cardiac disorders	5 (6)	1 (1)	20 (13)	4 (3)
Eye disorders	5 (6)	0	19 (13)	1 (1)
Reproductive system and breast disorders	4 (5)	1 (1)	9 (6)	0
Blood and lymphatic system disorders	3 (4)	0	15 (10)	3 (2)
Ear and labyrinth disorders	2 (3)	0	15 (10)	1 (1)
Hepatobiliary disorders	1 (1)	0	3 (2)	1 (1)
Congenital, familial and genetic disorders	1 (1)	0	1 (1)	0
Immune system disorders	0	0	3 (2)	0

Source: ADAE.xpt, primary analysis

SOCs are presented in descending order of frequency in the sonidegib 200-mg group.

A patient with multiple occurrences of an AE under one treatment is counted only once.

At the PT level, AEs that occurred in more than 20% of patients treated in both arms were muscle spasms, alopecia, dysgeusia, nausea, fatigue, increased blood CK, decreased weight, and diarrhea. Additional AEs that occurred in more than 20% of patients treated in the 800 mg arm included decreased appetite and myalgia. Adverse events that occurred more frequently in the 800 mg treatment group (with at least a 10% difference relative to the 200 mg group) included dysgeusia (+22%), vomiting (+21%), muscle spasms (+18%), alopecia (+15%), nausea (+13%), decreased appetite (+12%), and decreased weight (+11%). The only AEs that occurred more frequently in the 200 mg arm as compared with the 800 mg arm were arthralgia (13 vs 8%), and UTI (8 vs 3%).

Grade 3 and 4 AEs were infrequent in both arms. The most common grade 3 or 4 AE in both arms was serum CK elevation which occurred in 6% of patients in the 200 mg group and 13% of patients in the 800 mg group. Grade 3-4 AEs that occurred in at least 2% of patients in either treatment arm included muscle spasms, serum CK elevation, increased lipase, nausea, fatigue, decreased weight, decreased appetite, myalgia, upper abdominal pain, increased

aspartate aminotransferase, hypertension, dehydration, and anemia. Table 39 summarizes the incidence and grade of AEs that occurred in more than 5% of patients treated in Study A2201. This data confirms the results presented in the Study A2201 CSR.

Table 39: Adverse events by preferred term, primary analysis

Preferred Term	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Muscle spasms	39 (49)	2 (3)	100 (67)	8 (5)
Alopecia	34 (43)	1 (1)	83 (55)	0
Dysgeusia	30 (38)	0	89 (59)	1 (1)
Nausea	26 (33)	1 (1)	68 (45)	4 (3)
Blood creatine kinase increased	23 (29)	5 (6)	56 (37)	19 (13)
Fatigue	23 (29)	0	54 (36)	3 (2)
Weight decreased	21 (27)	1 (1)	54 (36)	8 (5)
Diarrhea	19 (24)	0	33 (22)	0
Decreased appetite	15 (19)	0	46 (31)	6 (4)
Myalgia	15 (19)	0	39 (26)	3 (2)
Headache	12 (15)	0	20 (13)	1 (1)
Arthralgia	10 (13)	1	12 (8)	1 (1)
Abdominal pain	7 (9)	0	7 (5)	0
Dizziness	7 (9)	1 (1)	14 (9)	0
Cough	7 (9)	0	11 (7)	0
Constipation	6 (8)	1 (1)	20 (13)	0
Lipase increased	6 (8)	4 (5)	12 (8)	8 (5)
Abdominal pain upper	6 (8)	0	11 (7)	0
Asthenia	6 (8)	2 (3)	8 (5)	0
Nasopharyngitis	6 (8)	0	9 (6)	0
Urinary tract infection	6 (8)	0	5 (3)	0
Back pain	5 (6)	0	15 (10)	0
Pruritus	5 (6)	0	7 (5)	0
Hypertension	5 (6)	2 (3)	11 (7)	4 (3)

Preferred Term	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Pneumonia	5 (6)	0	5 (3)	2 (1)
Upper respiratory tract infection	5 (6)	0	5 (3)	0
Vomiting	5 (6)	1 (1)	39 (26)	2 (1)
Bronchitis	4 (5)	0	5 (3)	0
Dry mouth	4 (5)	0	7 (5)	0
Dyspepsia	4 (5)	0	8 (5)	0
Influenza	4 (5)	0	7 (5)	0
Musculoskeletal pain	4 (5)	0	4 (3)	0
Pain in extremity	4 (5)	0	8 (5)	0
Muscular weakness	3 (4)	0	8 (5)	1 (1)
Paraesthesia	3 (4)	0	7 (5)	1 (1)
Anemia	2 (3)	0	10 (7)	3 (2)
Depression	2 (3)	0	8 (5)	0
Dyspnea	2 (3)	0	7 (5)	2 (1)
Aspartate aminotransferase increased	1 (1)	1 (1)	7 (5)	4 (3)
Ageusia	0	0	13 (9)	0
Vertigo	0	0	9 (6)	1 (1)
Dehydration	0	0	8 (5)	3 (2)
Hypogeusia	0	0	8 (5)	2 (1)

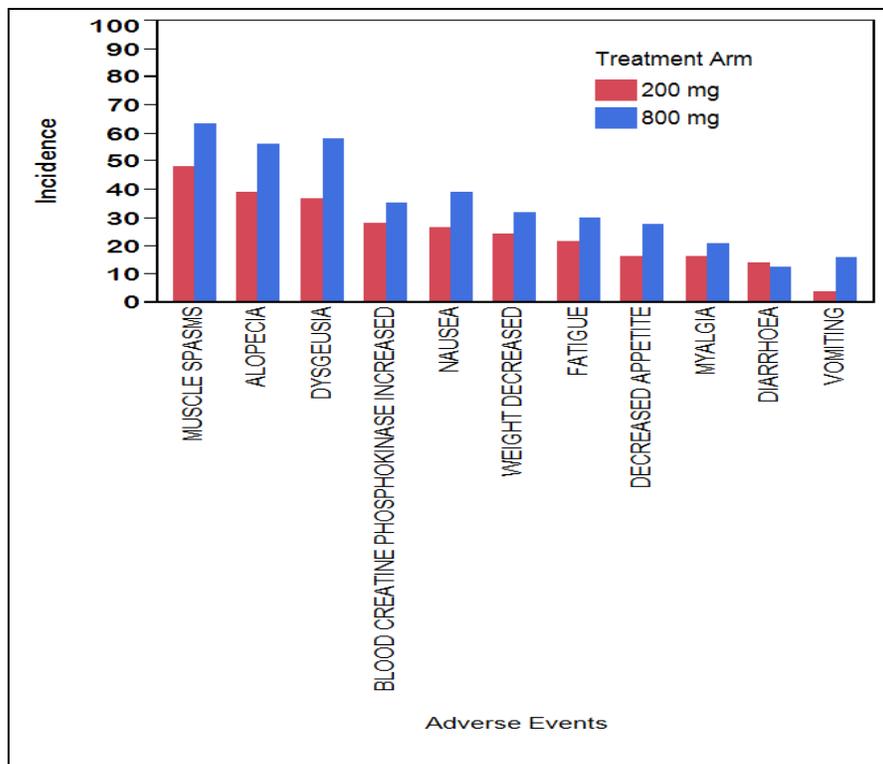
Source: ADAE.xpt, primary analysis

Preferred terms are presented in descending order of frequency in the sonidegib 200-mg group.

A patient with multiple occurrences of an AE is counted once at the event with maximum severity.

Figure 5 shows the incidence of AEs by treatment arm that occurred in more than 10% of patients in the primary analysis.

Figure 5: AE incidence by treatment arm, primary analysis



Source: ADAE.xpt, primary analysis

Common adverse events: 12 and 18 month analyses

The reviewer analyzed and verified the 12 month AE incidence data submitted with the NDA and discussed in the SCS Addendum. The Applicant's analysis of the 18 month data submitted with the 120 day safety update was also reviewed, and key analyses were performed on the 18 month data to confirm the Applicant's results. In general, there were small increases in the frequency of common AEs and no new safety signals with longer term exposure to sonidegib.

FDA agreed to the Applicant's proposal to report the safety results from the 18 month analysis in relevant sections of the product label as these data are reflective of a longer term exposure to sonidegib. It is the reviewer's opinion that given the indolent nature of BCC in some patients, and the potential for extended treatment duration, the cumulative safety profile is important information to provide for prescribers.

Tables 40 and 41 summarize the frequency and severity of common AEs in the 18 month analysis categorized by SOC and PTs. Grade 3 and 4 AEs remained infrequent. The incidence difference between the 200 mg and 800 mg treatment arms was similar to the primary analysis.

Table 40: Adverse events by system organ class, 18 month analysis

System Organ Class	Sonidegib 200 mg N=150 n (%)		Sonidegib 800 mg N=150 n (%)	
	All grades	Grade 3/4	All Grades	Grade 3/4
Musculoskeletal and Connective Tissue Disorders	59 (75)	4 (5)	119 (79)	19 (13)
Nervous System Disorders	55 (70)	3 (4)	124 (83)	10 (7)
Skin and Subcutaneous Tissue Disorders	54 (68)	0	98 (65)	0
Gastrointestinal Disorders	52 (66)	4 (5)	112 (75)	12 (8)
Investigations	47 (59)	12 (15)	106 (71)	43 (29)
General Disorders and Administration Site Conditions	42 (53)	5 (6)	81	5 (3)
Infections and Infestations	38 (48)	1 (1)	77 (54)	10 (7)
Metabolism and Nutrition Disorders	24 (30)	2 (3)	67 (45)	12 (8)
Respiratory, Thoracic and Mediastinal Disorders	22 (28)	1 (1)	47 (31)	4 (3)
Vascular Disorders	17 (22)	4 (5)	32 (21)	8 (5)
Injury, Poisoning and Procedural Complications	12 (15)	3 (4)	23 (15)	3 (2)
Psychiatric Disorders	12 (15)	1 (1)	28 (19)	1 (1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	10 (13)	2 (3)	23 (15)	8 (5)
Renal and Urinary Disorders	9 (11)	0	14 (9)	2 (1)
Cardiac Disorders	6 (8)	1 (1)	21 (14)	5 (3)
Eye Disorders	6 (8)	0	18 (12)	1 (1)
Blood and Lymphatic System Disorders	5 (6)	0	16 (11)	6 (4)
Reproductive System and Breast Disorders	4 (5)	1 (1)	9 (6)	0
Ear and Labyrinth Disorders	2 (3)	0	19 (13)	1 (1)
Congenital, Familial and Genetic Disorders	1 (1)	0	2 (1)	0
Hepatobiliary Disorders	1 (1)	0	4 (3)	1 (1)
Endocrine Disorders	0	0	2 (1)	0

System Organ Class	Sonidegib 200 mg N=150 n (%)		Sonidegib 800 mg N=150 n (%)	
	All grades	Grade 3/4	All Grades	Grade 3/4
Immune System Disorders	0	0	0	4 (3)

Source: ADAE.xpt, 18 month analysis

SOCs are presented in descending order of frequency in the sonidegib 200 mg group.

A patient with multiple occurrences of an AE under one treatment is counted once in the AE category.

Table 41: Adverse events by preferred term, 18 month analysis

Preferred Term	Sonidegib 200 mg N=150 n (%)		Sonidegib 800 mg N=150 n (%)	
	All grades	Grade 3/4	All Grades	Grade 3/4
Muscle spasms	43 (54)	2 (3)	104 (69)	8 (5)
Alopecia	39 (49)	0	87 (58)	0
Dysgeusia	35 (44)	0	90 (60)	0
Nausea	31 (39)	1 (1)	71 (47)	4 (4)
Diarrhoea	25 (32)	1 (1)	36 (24)	0
Blood creatine kinase increased	24 (30)	5 (6)	56 (37)	20 (13)
Weight decreased	24 (30)	2 (3)	64 (43)	9 (6)
Fatigue	23 (29)	0	55 (37)	3 (2)
Decreased appetite	18 (23)	1 (1)	52 (35)	6 (4)
Myalgia	15 (19)	0	42 (28)	3 (2)
Arthralgia	13 (16)	1 (1)	17 (11)	1 (1)
Headache	12 (15)	1 (1)	20 (13)	1 (1)
Asthenia	10 (13)	3 (4)	9 (6)	0
Vomiting	9 (11)	1 (1)	42 (28)	2 (1)
Abdominal pain	8 (10)	0	8 (5)	0
Abdominal pain upper	7 (9)	0	12 (8)	0
Cough	7 (9)	0	11 (7)	0
Dizziness	7 (9)	1 (1)	15 (10)	0
Dyspepsia	7 (9)	1 (1)	10 (7)	0
Hypertension	7 (9)	2 (3)	13 (9)	5 (3)

Preferred Term	Sonidegib 200 mg N=150 n (%)		Sonidegib 800 mg N=150 n (%)	
	All grades	Grade 3/4	All Grades	Grade 3/4
Nasopharyngitis	7 (9)	0	12 *)	0
Urinary tract infection	7 (9)	1 (1)	8 (5)	1 (1)
Constipation	6 (8)	1 (1)	23 (15)	0
Lipase increased	6 (8)	5 (6)	12 (8)	8 (5)
Pruritus	6 (8)	0	10 (7)	0
Back pain	5 (6)	0	15 (10)	0
Fall	5 (6)	1 (1)	4 (3)	0
Pneumonia	5 (6)	0	6 (4)	3 (2)
Upper respiratory tract infection	5 (6)	0	9 (6)	0
Anaemia	4 (5)	0	13 (9)	6 (4)
Bronchitis	4 (5)	0	6 (4)	0
Dry mouth	4 (5)	0	8 (5)	0
Hypotension	4 (5)	2 (3)	5 (3)	1 (1)
Influenza	4 (5)	0	7 (5)	0
Musculoskeletal pain	4 (5)	0	5 (3)	0
Oropharyngeal pain	4 (5)	0	6 (4)	0
Pain in extremity	4 (5)	0	8 (5)	0
Paraesthesia	4 (5)	0	7 (5)	1 (1)
Pyrexia	4 (5)	0	4 (3)	0
Depression	3 (4)	0	9 (6)	0
Muscular weakness	3 (4)	0	8 (5)	1 (1)
Dyspnea	2 (3)	0	7 (5)	2 (1)
Ageusia	1 (1)	0	14 (9)	0
Aspartate aminotransferase increased	1 (1)	1 (1)	7 (5)	4 (3)

Source: ADAE.xpt, 18 month analysis

Table includes AEs that occurred with > 5% incidence in either arm.

Preferred terms are presented in descending order of frequency in the sonidegib 200 mg group.

A patient with multiple occurrences of an AE is counted once per AE.

Adverse events in the pooled safety analysis

The pooled analysis contains data from a total of 272 patients, including the safety population from Study A2201 (N=229) and a subset of patients from Study X2101 (N=43). Patients in the pooled populations were treated with sonidegib at doses between 100 and 800 mg daily. The data indicate that most AEs increase in frequency with increasing doses of sonidegib. The results from the pooled analysis do not substantially differ from the safety results from Study A2201. Similar to Study A2201, the pooled data demonstrates that the most common AEs (occurring in more than 20% of patients treated with sonidegib 200 mg daily) included muscle spasms, alopecia, dysgeusia, nausea, fatigue, serum CK elevation, diarrhea and decreased weight and appetite.

7.4.2 Laboratory Findings

In Study A220, laboratory tests including complete blood count (CBC) with differential, and serum chemistries including electrolytes, glucose, BUN, creatinine, uric acid, total protein, albumin, liver function tests, amylase, lipase, and LDH and cholesterol were performed at baseline and every two weeks until Week 13 and then every four weeks until Week 77 and then as clinically indicated.

Given the risk for serum CK elevation and muscle toxicity with sonidegib treatment, patients were required to have baseline normal serum CK levels to enroll, and there was frequent monitoring of CK throughout the study. Serum CK levels were obtained within three days of starting sonidegib treatment, weekly for the first two months and then every four weeks thereafter while receiving sonidegib. Patients who were receiving concomitant pravastatin were required to have serum CK levels evaluated weekly for eight weeks, then every two weeks for another 8 weeks and then every four weeks thereafter while receiving sonidegib. See section 7.3.5 for discussion of serum CK elevation and musculoskeletal toxicity associated with sonidegib.

The reviewer analyzed the ADLB.xpt data from the primary and 12 month analyses. Table 42 is based on the 12 month analysis and summarizes the common laboratory abnormalities for patients in Study A2201. Hematological abnormalities that occurred in more than 20% of patients in both treatment arms included anemia and lymphopenia. Grade 3 or 4 events were uncommon. More patients had hematological abnormalities in the 800 mg group as compared with the 200 mg group.

The majority of patients experienced chemistry abnormalities during treatment with sonidegib. Abnormalities that occurred in at least 20% of patients on either treatment arm included elevations of serum creatinine, cholesterol, CK, lipase, glucose, calcium, magnesium, alanine aminotransferase, or aspartate aminotransferase or hypoglycemia. Almost all patients experienced at least a grade 1 elevation of serum creatinine. This is partly due to the CTCAE definition of grade 1 including any increase from baseline (>1 to 1.5-fold increase). For the majority of patients, grade 1 serum creatinine elevation resulted in values that were still within

normal range. There were no shifts in creatinine from grade 1 to grade 3 in the 200 mg group, and two patients (1%) had shifts to grade 3 in the 800-mg group.

The most frequently reported grade 3 or 4 chemistry abnormalities in more than 2% of patients in either treatment arm were elevations in serum CK, lipase, glucose, alanine aminotransferase, aspartate aminotransferase and amylase. See Section 7.3.5 for further discussion of the clinical relevance of serum CK and lipase elevations.

Table 42: Laboratory abnormalities occurring in greater than 10% of patients, 12 months

Preferred Term	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Chemistry				
Increased creatinine	73 (93)	0	139 (93)	2 (1)
Increased cholesterol*	56 (71)	0	107 (71)	0
Increased serum creatine kinase	49 (62)	6 (8)	100 (67)	25 (17)
Increased lipase	34 (43)	10 (13)	79 (53)	19 (13)
Hyperglycemia	38 (48)	3 (4)	86 (57)	4 (3)
Hypercalcemia	18 (23)	0	41 (27)	0
Hypomagnesimias	24 (30)	0	43 (29)	1 (1)
Hypoglycemia	17 (22)	0	34 (23)	0
Hypophosphatemia	15 (19)	0	15 (10)	0
Increased alanine aminotransferase	14 (18)	2 (3)	44 (29)	6 (4)
Increased alkaline phosphatase	14 (18)	0	21 (14)	1 (1)
Hyperkalemia	14 (18)	3 (4)	17 (11)	4 (3)
Hypocalcemia	13 (17)	0	13 (9)	0
Increased aspartate aminotransferase	14 (18)	2 (3)	46 (31)	8 (5)
Increased amylase	13 (17)	1 (1)	29 (19)	4 (3)
Increased sodium	13 (17)	0	19 (13)	1 (1)
Hematology				
Anemia	25 (32)	0	54 (36)	1 (1)
Lymphopenia	21 (27)	1 (1)	51 (34)	5 (3)

Preferred Term	Sonidegib 200 mg N=79 n (%)		Sonidegib 800 mg N=150 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Leukopenia	5 (6)	0	22 (15)	1 (1)
Thrombocytopenia	5 (6)	0	18 (12)	1 (1)

Source: ADLB.xpt, 12 month dataset; Tables 3-1 and 3-2, SCS Addendum 2

*More than 40% of patients in both arms had Grade 1 or 2 cholesterol elevation at baseline.

Reviewer: The laboratory abnormalities information in the product label is based on the results of the 18 month analysis submitted with the 120 day safety update. Key results from the 18 month analysis were verified for the purpose of product labeling. Specifically, common laboratory abnormalities that occurred in the sonidegib 200 mg treatment group are summarized in Table 43. With longer exposure to sonidegib, there were small increases in the frequency of laboratory abnormalities, but no new signals were observed.

Table 43: Common laboratory abnormalities occurring in > 10% of patients, 200 mg treatment arm, 18 month analysis

Laboratory Test	ODOMZO 200 mg (N=79)	
	All grades %	Grades 3-4%
Chemistry		
Increased serum creatinine	92	0
Increased serum creatine kinase (CK)	61	8
Hyperglycemia	51	4
Increased lipase	43	13
Hypomagnesemia	30	0
Hypercalcemia	23	0
Increased alanine aminotransferase	19	4
Increased aspartate aminotransferase	19	4
Increased alkaline phosphatase	19	0
Hematology		
Anemia	32	0
Lymphopenia	28	3

Source: ADLB.xpt, 18 month analysis; Tables 3-1 and 3-2, SCS, Addendum 2

7.4.3 Vital Signs

Vital signs (temperature, pulse and blood pressure) were collected at baseline and every four weeks during Study A2201. Overall, there were no notable differences in vital sign changes between patients treated with 200 mg and patients treated with 800 mg sonidegib.

Blood pressure

The Applicant's analysis of vital signs in the SCS reports not observing any notable change in mean blood pressure during the study in either treatment group.

The reviewer's analysis of the 12 month ADVS.xpt dataset demonstrates that there were 146 events of systolic blood pressure (SBP) readings above 150 mmHg or greater than 20 mmHg above baseline (range: 150-230 mmHg) that occurred in 58 patients (25%) enrolled in study A2201. In the 200 mg group, 24 patients (30%) experienced at least one event of SBP elevation according to those parameters. The median change from baseline was 29 mmHg in patients with elevated SBP treated in the 200 mg group.

There were 47 events of diastolic blood pressure (DBP) elevation above 90 mmHg or greater than 20 mmHg above baseline (range: 90-120 mmHg) in 24 patients (10%) enrolled in Study A2201 at the 12 month data cut-off date. In the 200 mg group, 11 patients (14%) experienced at least one event of elevated blood pressure using these parameters. The median value of elevated DBPs in the 200 mg group was 94 mmHg.

Reviewer: Although more than 10% of patients in Study A2201 experienced elevations in SBP or DBP according to the parameters set forth in the protocol, fewer patients were reported to have an AE of hypertension. At the 18 month data cut-off, 9% of patients in both treatment groups experienced hypertension, and 3% of patients in each group experienced grade 3 or 4 hypertension. Two patients (1%), both in the 800 mg group, discontinued sonidegib treatment due to hypertension. Given that 98 patients (43%) enrolled in Study A2201 had medical history significant for hypertension, the majority of which were on antihypertensive medications during the study, the reviewer does not consider the incidence of hypertension to substantially impact the risk:benefit profile of sonidegib treatment for patients with BCC.

Body weight

Body weight was measured with vital signs every four weeks during Study A2201. More patients in the 800 mg group experienced a decrease in weight from baseline than those in the 200 mg group. In the primary analysis, weight loss was observed in 17% of patients in the 200 mg group and 31% of patients in the 800 mg group.

Weight loss was more prevalent with longer duration of sonidegib treatment and continued to be dose-related. The sponsor's 18 month safety analysis reports that among patients with duration of exposure to sonidegib of at least 12 months, a greater than 10% weight loss was observed in 27% of patients in the 200 mg group and 71% of patients in the 800 mg group.

See Section 7.3.5 for further discussion of the clinical impact of weight loss during Study A2201.

7.4.4 Electrocardiograms (ECGs)

QTc abnormalities

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.

No mean change greater than 20 ms in the QTc interval was detected at the 200 mg daily dose in Study A2201. According to the CSR, four patients (2%) in Study A2201 experienced a QTc > 480ms, and two of these patients experienced a QTc > 500 ms. Three patients were part of the 800 mg group and one patient was in the 200 mg group. The two patients with the QTc > 500 ms had baseline ECG findings of prolonged QTc intervals. No action was taken for these patients in relation to the study treatment at the time of the ECG findings. There were no cardiac AEs reported for any of these patients during the study. Additionally, no AEs with the preferred term of 'ECG QT prolonged' or 'Torsades de pointes' were reported in any patients in either treatment arm in the primary analysis.

See the FDA Clinical Pharmacology Review for additional discussion of risk for QT prolongation with sonidegib.

Other ECG abnormalities

Among 225 patients with reported ECG data in Study A2201, 47% had at least one new ECG abnormality as compared to baseline during treatment with sonidegib. Table 44 summarizes ECG abnormalities that occurred in at least 5% of patients in the primary analysis dataset. The more common abnormalities observed were premature atrial contractions, premature ventricular contractions, and first degree atrioventricular block. The clinical significance of these findings is not clear, and the incidence of severe cardiac events was low. Although there were three deaths attributed to cardiac events during the study, all of the patients had multiple cardiac risk factors at baseline and pre-existing comorbidities that confounded the attribution analysis. Additionally, an independent committee reviewed the cardiac deaths and did not determine a relationship to sonidegib treatment. See Section 7.3.1.

The Applicant reported that the safety database for Study A2201 was reviewed and that all patients with an ECG abnormality at any time on study and reported cardiac events at any time on study were evaluated to determine if there was an association between the ECG finding, a cardiac adverse event and sonidegib treatment. The Applicant reported that no apparent trends were observed in this analysis. The ADEG.xpt primary dataset and line listings of ECG findings were reviewed and are summarized in Table 44.

Table 44: ECG Abnormalities, primary analysis

ECG Finding	Sonidegib 200 mg N=79	Sonidegib 800 mg N= 150
Any new ECG change from baseline	47 (60)	59 (40)
Conduction	20 (25)	23 (16)
First degree AV block	10 (15)	11 (9)
Intraventricular conduction delay	4 (5)	5 (4)
Left anterior fascicular block	4 (6)	6 (5)
Ectopy	23 (29)	23 (16)
Premature ventricular complex	13 (17)	11 (8)
Premature atrial complex	16 (22)	13 (10)
Rhythm	13 (17)	26 (18)
Sinus bradycardia	6 (8)	14 (10)
Sinus tachycardia	4 (5)	6(4)
Other ECG abnormalities		
ST depression	6 (8)	2(1)
Flattened T wave	9 (12)	6 (4)
Inverted T wave	7 (10)	6 (4)
Biphasic T wave	6 (8)	2(1)

Source: ADEG.xpt, primary analysis, Table 14.3-4.7, Study A2201 CSR

Percentages are based on the total number of patients with both baseline and postbaseline measures therefore the denominator was not always 79 and 150 in the two treatment arms.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

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

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The frequency and severity of AEs were higher in patients treated with sonidegib 800 mg daily as compared to patients treated with sonidegib 200 mg daily. The clinical impact of AEs in

terms of SAE incidence, early treatment discontinuations, dose reductions and dose interruptions was larger in the 800 mg group. More patients in the 800 mg group discontinued treatment due to AEs while more patients in the 200 mg group discontinued treatment for disease progression. The objective response rates were similar in both treatment arms. The reviewer agrees with the Applicant's proposed dose selection of 200 mg daily for patients with laBCC.

7.5.2 Time Dependency for Adverse Events

Table 45 summarizes major AE categories that occurred in the primary, 12 and 18 month analyses. There was a small increase in the incidence of all AEs with longer term exposure to sonidegib, but the between arm differences remained similar with more AEs occurring in the 800 mg group as compared to the 200 mg group.

Table 45: Summary of adverse events with longer term sonidegib treatment

	Primary Analysis		12-Month Analysis		18-Month Analysis	
	200 mg N=79 (%)	800 mg N= 150 n (%)	200 mg N=79 n (%)	800 mg N= 150 n (%)	200 mg N=79 (%)	800 mg N= 150 n (%)
Any AE	75 (95)	150 (100)	77 (98)	150 (100)	77 (98)	150 (100)
Grade 3-4 AEs	24 (30)	84 (56%)	30 (38)	89 (59)	31 (39)	95 (63)
Deaths while on study	0	4 (3)	0	7 (5)	1 (1)	7 (5)
Serious AEs	11 (14)	45 (30)	13 (17)	49 (33)	14 (18)	56 (37)
AEs leading to discontinuation	17 (22)	54 (36)	22 (28)	56 (37)	24 (30)	59 (39)
AEs requiring dose interruption/ reduction	25 (32)	90 (60)	30 (38)	96 (64)	31 (39)	99 (66)

Source: ADAE.xpt from primary, 12 month and 18 month datasets

7.5.3 Drug-Demographic Interactions

Subgroup analyses were performed to evaluate the impact of race, gender and age on the safety profile of sonidegib in patients treated in Study A2201.

Race: No conclusions can be drawn with regard to the effect of race as there were a limited number of non-White patients (N=14) in the study.

Gender: Females comprised 38% of the Study A2201 population. Females in both treatment arms experienced more frequent common AEs including dysgeusia, alopecia, nausea, diarrhea, headache, arthralgia, myalgia, constipation, vomiting, urinary tract infections, back

pain and lipase elevation. The incidences of muscle spasms and serum CK elevation were higher in males in the 200 mg group; however, at the 800 mg dose, the incidence of these events was similar between males and females. Other common AEs occurred more frequently in females in one arm but more frequently in males in the other arm, suggesting no significant patterns with regard to the sonidegib safety profile and gender.

Age: Patients 65 years and older comprised 54% of the Study A2201 population, and 28% were 75 years and older. There was a higher incidence of serious adverse events, Grades 3 and 4 adverse events, and adverse events requiring discontinuation or dose interruption in patients \geq 65 years compared with younger patients; however, this was not attributable to an increase in any specific adverse event.

Reviewer: Age and gender comparisons should be considered exploratory and limited by the small number of patients.

7.5.4 Drug-Disease Interactions

None.

7.5.5 Drug-Drug Interactions

Sonidegib is primarily metabolized by CYP3A4 and co-administration of drugs which inhibit CYP3A4 may have the potential to inhibit metabolism or increase exposure to sonidegib. Refer to clinical pharmacology review for a detailed discussion of healthy volunteer and in vitro sonidegib drug interaction studies.

Concomitant HMG-CoA reductase inhibitors

Patients enrolled in Study A2201 were prohibited from using HMG-CoA reductase inhibitors (statins) that could not be stopped two weeks prior to initiation sonidegib. This was due to the risk for potential overlapping musculoskeletal toxicities including rhabdomyolysis. If patients needed to remain on statin therapy to treat hyperlipidemia, pravastatin was permitted because it has the lowest potential to cause rhabdomyolysis compared with other statins and the lowest risk for drug-drug interactions with sonidegib, as it is primarily transformed in the liver by sulfonation and not by CYP2C9 or CYP3A4.

A total of 31 patients (14%) of the safety population in Study A2201 were receiving concomitant statin treatment; 23 were taking pravastatin and 8 patients were taking other statins. There does not appear to be differences in the incidence of muscle-related symptoms or serum CK elevation in patients taking statins concomitant with sonidegib compared to those not taking statins; however, this subgroup is too small to make any definitive conclusions regarding the risk for musculoskeletal toxicity with concomitant statin and sonidegib administration.

7.6 Additional Safety Evaluations

Safety findings in patients with nevoid BCC syndrome (i.e., Gorlin syndrome)

Sixteen patients with Gorlin syndrome enrolled in Study A2201, three in the 200 mg arm and thirteen in the 800 mg arm. One patient in the 800 mg group had mBCC, and the other fifteen patients had laBCC. Understanding the limitations of performing comparative analyses on a small sample of patients, FDA requested that the Applicant summarize the major safety findings for this group of patients as compared to the general safety population enrolled in Study A2201.

This analysis was requested to evaluate any additional safety signals or increased risk that might characterize this group of patients with underlying mutations in the *PTCH1* gene. Table 46 was adapted from the Applicant's response to the FDA Information Request and provides an overview of major safety events in the Gorlin syndrome population.

Table 46: Summary of adverse events for the Study A2201 population and for patients with Gorlin syndrome

	Overall population 18-month analysis: 11-Jul-2014 data cut-off			Patients with Gorlin syndrome 18-month analysis: 11-Jul-2014 data cut-off		
	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150	All patients N=229	Sonidegib 200 mg N=3	Sonidegib 800 mg N=13	All patients N=16
	Adverse events (AEs)	77 (97.5)	150 (100.0)	227 (99.1)	3 (100.0)	13 (100.0)
Grade 3-4 AEs	31 (39.2)	95 (63.3)	126 (55.0)	2 (66.7)	7 (53.8)	9 (56.3)
AEs with suspected causality	70 (88.6)	143 (95.3)	213 (93.0)	3 (100.0)	13 (100.0)	16 (100.0)
Grade 3-4 AEs with suspected causality	23 (29.1)	65 (43.3)	88 (38.4)	2 (66.7)	5 (38.5)	7 (43.8)
Deaths on treatment	1 (1.3)	7 (4.7)	8 (3.5)	0	0	0
Serious AEs (SAEs)	14 (17.7)	56 (37.3)	70 (30.6)	1 (33.3)	3 (23.1)	4 (25.0)
SAEs with suspected causality	2 (2.5)	23 (15.3)	25 (10.9)	0	2 (15.4)	2 (12.5)
AEs leading to discontinuation	24 (30.4)	59 (39.3)	83 (36.2)	0	2 (15.4)	2 (12.5)
AEs requiring dose interruption and/or dose reduction	31 (39.2)	99 (66.0)	130 (56.8)	2 (66.7)	8 (61.5)	10 (62.5)
AEs requiring additional therapy	67 (84.8)	131 (87.3)	198 (86.5)	2 (66.7)	13 (100.0)	15 (93.8)

Source: Table 2-4, Applicant Response to FDA Information Request, May 20, 2015

The median duration of exposure to sonidegib was 12.9 months. The common AEs experienced by patients with Gorlin syndrome treated in Study A2201 were similar to the general safety population. Common AEs occurring in more than 20% of patients with Gorlin

syndrome included nausea, dysgeusia, muscle spasms, myalgia, fatigue, vomiting, decreased weight, decreased appetite, serum CK elevation and extremity pain. There were few grade 3 or 4 AEs.

Reviewer: Although there were very few patients with Gorlin syndrome within the larger safety population to make an accurate comparison, this analysis revealed no new safety signals. Patients were able to tolerate sonidegib similar to the general safety population and the safety profile did not appear to be different from the non-Gorlin syndrome patients in the study. One concern with regard to the use of sonidegib in the Gorlin syndrome population relates to the risk for fetal harm and teratogenic effects. This risk may be of greater relevance in patients with Gorlin syndrome who are generally younger than the general BCC population and more likely to require treatment during the childbearing years. The risk for fetal harm and teratogenic effects is discussed in Section 4.3 of the review.

7.6.1 Human Carcinogenicity

Carcinogenicity studies of sonidegib have not been performed. There will be a PMR to conduct a carcinogenicity study. See FDA Nonclinical review for details.

7.6.2 Human Reproduction and Pregnancy Data

The applicant did not submit studies of sonidegib in pregnant or breast feeding women. Pregnant females were excluded from clinical studies of sonidegib due to the embryofetal toxicities and teratogenic effects observed in animals in preclinical studies. See Section 4.3 for further discussion of animal studies. Female patients of child-bearing potential enrolled in Study A2201 were required to use two forms of contraception during treatment and for six months after the last dose of sonidegib.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant requested a waiver of pediatric studies for the BCC indication based on the condition being essentially limited to the adult population. (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In dose-escalation studies in humans, sonidegib was administered at single doses up to 3000 mg (N=10). The dose-limiting toxicity at this dose was serum CK elevation. There are no known antidotes for sonidegib overdose. No studies have been conducted to evaluate the abuse potential with sonidegib. No studies have been conducted with sonidegib to assess withdrawal or rebound effects of sonidegib.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Not applicable. Sonidegib is a new molecular entity with no prior approval history.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling negotiations were ongoing at the time of completing this review. A discussion of labeling recommendations will be provided as an addendum to the clinical review at a later date.

9.3 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this application as the safety profile is acceptable based on the indicated population; the primary efficacy outcome measures are acceptable and similar to those used for previously approved products for patients with laBCC and mBCC; the application did not raise significant public health questions on the role of sonidegib in patients with advanced BCC who are not amenable to local therapies. There were no controversial issues that would benefit from advisory committee discussion.

9.4 Special Government Employee (SGE) Consultation

Outside expertise was sought via consultation with two SGEs with expertise in the clinical management of patients with BCC. A briefing document summarizing the key efficacy and safety data was provided to the SGEs for evaluation, and separate teleconferences were held to obtain their feedback. The following list includes key points made by SGEs pertaining to the characteristics of advanced BCC, the risk:benefit profile of sonidegib in this population and the proposed product label:

- It is challenging to assess response in patients with laBCC due to the heterogenous presentation of the tumor including different locations, histologic subtypes, and occasional nerve involvement. The Study A2201 response criteria

were considered acceptable if palpable portions of the tumor were included in the annotated photography, biopsies were performed correctly and central reviewers had expertise in the clinical and histological presentations of BCC.

-  (b) (4)
-  (b) (4)
- The overall risk:benefit profile of sonidegib at the 200 mg dose is favorable for the treatment of patients with laBCC given the morbidity of the disease and lack of treatment alternatives when surgical resection is not feasible. Both SGEs expressed concern regarding the longterm toxicity profile of sonidegib and inquired whether further studies would be conducted to determine an optimal treatment duration for patients who are expected to have a long lifespan.
- The product label provides sufficient details regarding the risk of teratogenicity.
- The product label clearly describes the safety profile but could be more informative to providers if there was a description of the impact certain adverse events had on patient's daily living and the reversibility of specific AEs upon discontinuation.

Please refer to the FDA teleconference meeting minutes for further details of the discussions with SGEs.

9.5 Schedules of Clinical and Laboratory Assessments, Study A2201

Table 47: Schedule of clinical assessments, Study A2201

Week (W) no.	Category D: Database S: Source	Section reference	Screening	Treatment											
				1	2	3	4	5	6	7	8	9	11	13	
Visit name			Screening	W1	W2	W3	W4	W5	W6	W7	W8	W9	W11	W13	
Assessment window			-21 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Informed consent	D	10.3.	X												
Demography	D	6.1.2.3.	X												
Inclusion/ exclusion criteria	D	4.1, 4.2.	X												
Eligibility checklist	S	6.1.2.1.	X												
IRT registration/ treatment discontinuation	S	6.1.2, 6.1.2.1, 6.1.4.	X												
Patient Diary	S	5.1.2.		X	X	X	X	X	X	X	X	X	X	X	
Screening Phase Disposition	D	6.1.2.2.	X												
Relevant medical history	D	6.1.2.3.	X												
Prior anti-neoplastic therapy	D	6.1.2.3.	X												
Diagnosis and extent of cancer	D	6.1.2.3.	X												
Height	D	6.2.3.3.	X												
Weight	D	6.2.3.3.	X	X				X				X		X	
Vital signs: sitting pulse, sitting blood pressure	D	6.2.3.2.	X	X				X				X		X	
Temperature	S	6.2.3.2.	X	X				X				X		X	
Full physical examination	S	6.2.3.1.	X												

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Week (W) no.	Category D: Database S: Source	Section reference	Screening	Treatment											
				-2	1	2	3	4	5	6	7	8	9	11	13
Visit name			Screening	W1	W2	W3	W4	W5	W6	W7	W8	W9	W11	W13	
Assessment window			-21 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
WHO performance status	D	6.2.3.4.	X												
ECG	D	6.2.3.7.1.	X	X				X				X		X	
ECG (for approximately 60 patients (identified sequentially at enrollment))	D	6.2.3.7.1.	X (12-lead triplicate ECG)												
Chest X-ray	D	6.1.2.	X												
Bone Scan	D	6.1.2.	As clinically indicated					As clinically indicated				As clinically indicated			
Tumor response evaluation	D	6.2.1.	X					X (+/- 3 days) (PR and CR must be confirmed by repeat assessments performed no less than 4 weeks)				X (+/- 3 days) (PR and CR must be confirmed by repeat assessments performed no less than 4 weeks)			
Patient Reported Outcomes	D	6.2.5.1, 6.2.5.2.		X EORTC + SF36								X EORTC			
Collection of archival paraffin block/slides (only for patients who do not have accessible lesions)	D	3.	X												
Fresh tumor biopsy (See Tumor biopsy Section)	D	3.	X									X			

Week (W) no.	Category D: Database S: Source	Section reference	Screening	Treatment											
				-2	1	2	3	4	5	6	7	8	9	11	13
Visit name			Screening	W1	W2	W3	W4	W5	W6	W7	W8	W9	W11	W13	
Assessment window			-21 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Anti-neoplastic therapies since discontinuation of study treatment	D	6.1.6.													
Survival follow-up (e.g., phone call contact)	D	6.1.7.													
LDE225 dosing	D	5.1.1.		Daily dosing											
Concomitant medications	D	6.1.2.3, 5.1.7.		Continuous monitoring											
Adverse events	D	7.1.		Continuous Monitoring (up to 30 days post study discontinuation)											

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Odomzo® (sonidegib)

	Subsequent treatment (every 4 weeks)	Subsequent treatment (every 4 weeks)	Subsequent treatments (every 4 weeks)	End of Treatment	End of Post Treatment Follow-Up	Survival (every 12 weeks)
Week (W) no.	17-77	81-157	169+			
Visit name	W17-77	W81-157	W169+	EOT	End of Post Treatment Follow-up	Survival
Assessment window	±3	±3	±3	Within 21 days after last dose		
Informed consent						
Demography						
Inclusion/ exclusion criteria						
Eligibility checklist						
IRT registration/ treatment discontinuation				X		
Patient Diary	X	X	X	X		
Screening Phase Disposition						
Relevant medical history						
Prior anti-neoplastic therapy						
Diagnosis and extent of cancer						
Height						
Weight	X			X		
Vital signs: sitting pulse, sitting blood pressure	X	X Every 12 weeks (± 3 days)		X		
Temperature	X	X Every 12 weeks (± 3 days)		X		
Full physical examination				X		

	Subsequent treatment (every 4 weeks)	Subsequent treatment (every 4 weeks)	Subsequent treatments (every 4 weeks)	End of Treatment	End of Post Treatment Follow-Up	Survival (every 12 weeks)
Week (W) no.	17-77	81-157	169+			
Visit name	W17-77	W81-157	W169+	EOT	End of Post Treatment Follow-up	Survival
Assessment window	±3	±3	±3	Within 21 days after last dose		
WHO performance status				X		
ECG	X			X		
ECG (for approximately 60 patients (identified sequentially at enrollment))	X (W17 only, 12-lead triplicate ECG at pre-dose, 1, 2, 4, and 6 hours post- dose)					
Chest X-ray						
Bone Scan	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated		
Tumor response evaluation	X Every 8 weeks (± 3 days) during the first year and every 12 weeks (± 3 days) after the first year (PR and CR must be confirmed by repeat assessments performed no less than 4 weeks	X Every 12 weeks (± 3 days) (PR and CR must be confirmed by repeat assessments performed no less than 4 weeks	X Every 12 weeks (± 3 days) (PR and CR must be confirmed by repeat assessments performed no less than 4 weeks	X	X Every 8 weeks (± 3 days) during the first year and every 12 weeks (± 3 days) after the first year	
Patient Reported Outcomes	X EORTC every 8 weeks during the first year and every 12 weeks thereafter SF36 every 16 weeks first year and every 24 weeks thereafter			X EORTC + SF36		

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NDA 205266
Odomzo® (sonidegib)

	Subsequent treatment (every 4 weeks)	Subsequent treatment (every 4 weeks)	Subsequent treatments (every 4 weeks)	End of Treatment	End of Post Treatment Follow-Up	Survival (every 12 weeks)
Week (W) no.	17-77	81-157	169+			
Visit name	W17-77	W81-157	W169+	EOT	End of Post Treatment Follow-up	Survival
Assessment window	±3	±3	±3	Within 21 days after last dose		
collection of archival paraffin block/slides (only for patients who do not have accessible lesions)						
Fresh tumor biopsy	X W17 only			X	X	
Anti-neoplastic therapies since discontinuation of study treatment					X	X
Survival follow-up (e.g., phone call contact)						X
LDE225 dosing	Daily dosing					
Concomitant medications	Continuous monitoring					
Adverse events	Continuous Monitoring (up to 30 days post study discontinuation)					

Source: Study LDE225A2201 clinical protocol, version 6

Table 48: Laboratory assessment schedule, Study A2201

Week (W) no.	Category D: Database S: Source	Section reference	Screening	Treatment													Subsequent treatments (every 4 weeks)	Subsequent treatments (every 4 weeks)	Subsequent treatments (every 4 weeks)	End of Treatment
				1	2	3	4	5	6	7	8	9	11	13						
Week (W) no.			-2	1	2	3	4	5	6	7	8	9	11	13	17-77	81-157	169+			
Visit name			Screening	W1	W2	W3	W4	W5	W6	W7	W8	W9	W11	W13	W17-77	W81-157	W169+	EOT		
Assessment window			-21 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	Within 21 days after last dose		
Pregnancy Test	D	6.2.3.5.4.	X	X			X					X		X	X	X	X	X		
Hematology	D	6.2.3.5.1.	X			X	X		X			X	X	X	X	As clinically indicated	As clinically indicated	X		
Biochemistry	D	6.2.3.5.2.	X			X	X		X			X	X	X	X	As clinically indicated	As clinically indicated	X		
PK blood sampling trough (pre-dose)	D	6.2.4.		X		X	X					X		X	Every 4 weeks up to 21 weeks and every 12 weeks thereafter					
PK blood samples (for approximately 60 patients (identified sequentially at enrollment))	D	6.2.4.													W17 only (pre-dose, 1 hour, 2 hours, 4 hours, 6 hours post study drug administration)					
Blood for mutational analysis	D	6.2.6.1.3.	X																	
Blood for pharmacogenetic analysis	D	6.2.6.2.	X																	
Urinalysis	D	6.2.3.5.3.	X	As clinically indicated																
Cardiac Enzymes	D	6.2.3.7.3.	X	As clinically indicated																
CK	D	6.2.3.7.3.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	As clinically indicated	As clinically indicated	X (1 week after last dose)

Source: Study LDE225A2201 clinical protocol, version 6

9.6 Preferred terms for AESI of myopathy/rhabdomyolysis, Study A2201

Preferred term code	MedDRA preferred term	SYMPTOM
10048602	Achilles tendon discomfort	clinical sign/symptom
10002847	Anuria	clinical sign/symptom
10004803	Biopsy muscle abnormal	lab abnormality
10005395	Blood calcium decreased	lab abnormality
10005477	Blood creatine phosphokinase MM increased	lab abnormality
10005468	Blood creatine phosphokinase abnormal	lab abnormality
10005470	Blood creatine phosphokinase increased	lab abnormality
10005481	Blood creatinine abnormal	lab abnormality
10005483	Blood creatinine increased	lab abnormality
10008796	Chromaturia	clinical sign/symptom
10010121	Compartment syndrome	clinical sign/symptom
10068447	Creatinine renal clearance abnormal	lab abnormality
10011372	Creatinine renal clearance decreased	lab abnormality
10012708	Diaphragm muscle weakness	clinical sign/symptom
10014431	Electromyogram abnormal	lab abnormality
10018356	Glomerular filtration rate abnormal	lab abnormality
10018358	Glomerular filtration rate decreased	lab abnormality
10062747	Hypercreatininaemia	lab abnormality
10020947	Hypocalcaemia	lab abnormality
10028300	Muscle disorder	clinical sign/symptom
10057945	Muscle enzyme increased	lab abnormality
10049565	Muscle fatigue	clinical sign/symptom
10028309	Muscle haemorrhage	clinical sign/symptom
10028320	Muscle necrosis	clinical sign/symptom
10028331	Muscle rupture	clinical sign/symptom
10028334	Muscle spasms	clinical sign/symptom
10028372	Muscular weakness	clinical sign/symptom
10053156	Musculoskeletal discomfort	clinical sign/symptom
10048592	Musculoskeletal disorder	clinical sign/symptom
10028391	Musculoskeletal pain	clinical sign/symptom
10028411	Myalgia	clinical sign/symptom
10028413	Myalgia intercostal	clinical sign/symptom
10028625	Myoglobin blood increased	lab abnormality
10059888	Myoglobin blood present	lab abnormality
10028631	Myoglobin urine present	lab abnormality
10058735	Myoglobinaemia	lab abnormality
10028629	Myoglobinuria	lab abnormality
10028641	Myopathy	clinical sign/symptom
10028648	Myopathy toxic	clinical sign/symptom
10028653	Myositis	clinical sign/symptom

Preferred term code	MedDRA preferred term	SYMPTOM
10030302	Oliguria	clinical sign/symptom
10038435	Renal failure	lab abnormality
10038436	Renal failure acute	lab abnormality
10038444	Renal failure chronic	lab abnormality
10062237	Renal impairment	lab abnormality
10038540	Renal tubular necrosis	lab abnormality
10039020	Rhabdomyolysis	clinical sign/symptom

Source: Table 3.6 from "ADaM Study Data Reviewer's Guide"

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/s/

DENISE A CASEY
05/29/2015

SUZANNE G DEMKO
06/01/2015

I agree with the content and conclusions of this review.

Medical Officer Review of Sponsor Submission

NDA: 205266

SDN: 4 and 5

Drug: Sonidegib

Sponsor: Novartis

Date Received: 11/14/14 and 11/17/14

SDNs 4 and 5 include Novartis' preliminary and formal responses to a clinical/statistical information request (IR) sent on November 12, 2014. The IR pertained to the data structure of the sonidegib NDA submitted on September 26, 2014. FDA requested that Novartis provide the executive programs and case report form source data used to generate the analysis sets, the executive SAS programs with adequate documentation to reproduce study tables, figures, and the safety analysis, a revised define.pdf document with adequate hyperlinks and comments, and a copy of the data monitoring committee (DMC) meeting minutes.

SDN 4 is the preliminary responses provided prior to a teleconference between Novartis and FDA on November 13, 2014. SDN 5 is the formal submission of the responses in addition to the requested analyses, documents and the DMC minutes. Novartis also states that the requested datasets and programs can now be found in Module 5.3.5.1. The data monitoring committee minutes are compiled within the Summary of Clinical Efficacy Addendum Appendix 3 found in Module 2.7.3.

Reviewer: The sponsor's responses are adequate. The NDA has been deemed fileable.

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/s/

DENISE A CASEY
12/03/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205266

Applicant: Novartis

Stamp Date: September 26, 2014

Drug Name: Sonidegib (LDE225) NDA/BLA Type: NDA

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			(eCTD)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The draft label appears to be in acceptable PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		Agreement made on July 8, 2013, FDA written responses to sponsor; the narrative portions of ISE and ISS are located in Module 2 in SCE (2.7.3) and SCS (2.7.4).
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		See comment in number 9.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Located in the Clinical Overview, Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: CLDE225A2201				Two doses were studied in the pivotal Study A2201 (200mg and 800 mg) based on

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Study Title: 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</p> <p>Sample Size: 230</p> <p>Arms: randomized to 200 mg vs 800 mg</p> <p>Location in submission: CSR</p>				X2101 results. 79 patients received the 200 mg dose which was more tolerable and had a similar response rate.
EFFICACY					
17.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: Study A2201 Title: 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 Sample size: 230 Indication: (b) (4) laBCC that is recurrent and not amenable to surgery or radiation.</p> <p>Pivotal Study #2 NA</p>	X			FDA agreed that a single trial could support a marketing application.
18.	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</p>	X			(b) (4)
19.	<p>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</p>	X			
20.	<p>Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</p>	X			Largest fraction of patients were screened in U.S. centers (n=96)
SAFETY					
21.	<p>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</p>	X			
22.	<p>Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?</p>	X			QT analysis report submitted. It includes a pooled analysis of four studies in patients with solid tumors and in healthy volunteers.
23.	<p>Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?</p>	X			

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	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			354 patients from three clinical studies are included in the safety database.
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Elevated CK and rhabdomyolysis-an expert committee reviewed all cases and made recommendations on the dose modification algorithm.
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		DSMB meeting minutes need to be requested.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver submitted-located in Module 1.9.1.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Largest fraction of patients on Study A2201 were screened in U.S. centers (n=96)
DATASETS					
34.	Has the applicant submitted datasets in a format to allow	X			

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

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

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			On initial review.
37.	Are all datasets to support the critical safety analyses available and complete?	X			On initial review.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			On initial review.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Statement is located on page 2 of the CSR for Study A2201.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

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

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

Denise A. Casey -A Digitally signed by Denise A. Casey A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People
0923421920030010011=2001106760, cn=Denise A. Casey A
Date: 2014.11.19 08:30:13 -0500

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

DENISE A CASEY
11/19/2014

SUZANNE G DEMKO
11/19/2014