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RESEARCH**

APPLICATION NUMBER:

205266Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	July 21, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 205266
Applicant Name	Novartis Pharmaceuticals Corp.
Date of Submission	September 26, 2014
PDUFA Goal Date	September 26, 2015
Proprietary Name / Established (USAN) Name	ODOMZO/ sonidegib
Dosage Forms / Strength	capsules for oral administration/ 200-mg
Proposed Indication(s)	for the treatment of patients with locally advanced basal cell carcinoma (BCC) not amenable to curative surgery or radiation therapy (b) (4)
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Health Project Manager Review	Anuja Patel
Medical Officer Review	Denise Casey
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Alexander Putman
Quality Review	William M. Adams
Quality Microbiology Review	Stephen E. Langille
Clinical Pharmacology Review	Stacy Shord
OPDP	Nicholas J. Senior
OSI	Lauren Iacono-Connors
CDTL Review	Suzanne Demko
OSE/DMEPA	Otto L. Townsend
OSE/DRISK	Amarilys Vega
Maternal Health Team Review	Carol H. Kasten
DPMH Pediatric Consult	Ethan D. Hausman
QT IRT Review	Moh Jee Ng

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 DPMH=Division of Pediatric and Maternal Health

Division Director Summary Review

1. Introduction

All review team members recommend approval for Odomzo (sonidegib) 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.

Sonidegib is an inhibitor of the Hedgehog pathway and is the second drug in this class to be considered for this indication. Sonidegib acts through inhibition of smoothed (SMO), a transmembrane protein involved in hedgehog signal transduction. The Hedgehog pathway is constitutively activated in patients with nevoid basal cell carcinoma syndrome (NBCCS), an inherited autosomal dominant disorder arising from mutations in the PTCH gene within this pathway whose major features are early development of multiple basal cell carcinomas (BCC). Activation of the Hedgehog pathway is also observed in approximately one-third of patients with sporadic BCC, through mutations in PTCH; in addition, mutations of SMO resulting in constitutive activation of Hedgehog signaling has also been described.

In support of this application, Novartis provided the efficacy results of a single trial, Study CLDE225A2201 (A2201), titled “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.” Study A2001 was a multicenter, randomized (2:1), double-blind, non-comparative, two-arm trial evaluating the efficacy and safety of sonidegib 800 mg orally, once daily, and sonidegib 200 mg orally once daily. The trial was conducted in adults with locally advanced basal cell carcinoma (laBCC) not amenable to surgical resection or radiation or those with metastatic BCC (mBCC), who had measurable disease on color photograph, MRI or CT, and who had not received a prior Hedgehog inhibitor. Patients were randomized to the 800 mg dose received four 200 mg capsules while those randomized to 200 mg received one 200 mg sonidegib capsules and three placebo capsules; randomization was stratified by disease stage (laBCC vs. mBCC), histology (aggressive vs. non-aggressive), and geographic region. The primary efficacy outcome measure was objective response rate (ORR) based on central review committee masked to investigator assessment and dose assignment. Tumor response for patients with laBCC was determined according to the Response Evaluation Criteria In Solid Tumors (RECIST), as modified by Novartis for the purpose of this study and according to RECIST version 1.1 for patients with mBCC. The key secondary endpoint was duration of response (DoR) which was also centrally reviewed.

A total of 230 patients were enrolled; 151 patients were randomized to receive sonidegib 800 mg daily and 79 were randomized to receive sonidegib 200 mg daily. Across the entire study population, the majority (84%) of those enrolled had locally advanced disease, the median age was 66 years, 63% were male, and 90% had an ECOG performance status of 0 or 1. Seven

percent (n=16) of patients carried a diagnosis of nevoid basal cell carcinoma syndrome (NBCCS). The majority of patients had prior treatment for BCC including surgery, radiation, systemic chemotherapy, and topical or photodynamic therapy. Among patients with laBCC randomized to receive ODOMZO 200 mg daily, the median age was 67 years, 58% were male, 89% were white, 67% had an ECOG performance status of 0, and three patients carried a diagnosis of NBCCS. Most (76%) had received prior therapy for treatment for BCC and approximately half of these patients (56%) had aggressive histology.

Approval was based on demonstration of independently confirmed, durable objective responses in the subgroup of patients with laBCC. The ORR was 58% (95% confidence interval: 45, 70), consisting of 3 (5%) complete responses and 35 (53%) partial responses among the 66 patients with laBCC randomized to receive sonidegib 200 mg daily. 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. In 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, the complete response rate was 20%. These findings were supported by a similar ORR observed in 128 patients with laBCC randomized to receive sonidegib 800 mg daily [ORR 44% (95% CI: 35, 52.8)]. (b) (4)

In the major efficacy study, serious and common adverse reactions and discontinuation of sonidegib for adverse reactions occurred more frequently in the 800 mg treatment arm; given the increased toxicity and similar efficacy, the recommended dose of sonidegib is 200 mg once daily, (b) (4) until disease progression or unacceptable toxicity. Adverse reactions occurring in more than 10% of patients treated in the 200 mg arm were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting and pruritus. The most frequent grade 3 and 4 laboratory abnormalities occurring in at least 5% of patients in the 200 mg arm were elevated serum creatine kinase (CK) and elevated serum lipase.

The most serious risks of sonidegib are rhabdomyolysis and embryofetal toxicity. Across 571 patients receiving sonidegib at total daily doses ranging from 100 mg to 3000 mg, the incidence of rhabdomyolysis (defined as serum CK increase of more than ten times the baseline value with a concurrent 1.5 fold increase in serum creatinine above baseline) was 0.2%, occurring in one patient who received sonidegib 800 mg daily. In the 79 patients who received sonidegib 200 mg daily in the major efficacy study, the incidence of musculoskeletal toxicity was 68%, 29% of patients experienced musculoskeletal adverse reactions requiring medical intervention (narcotic administration, intravenous hydration, and hospitalization each required for 3% of patients), and 6% required treatment discontinuation for musculoskeletal adverse reactions.

Reproductive toxicology studies in rabbits demonstrated that sonidegib exposure during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity.

Specific issues considered during this review were [REDACTED] (b) (4)

2. Background

Indicated Population and Available Therapy

Basal cell carcinoma (BCC) is a cancer arising from the basal layer of epidermis and, together with squamous cell cancer of the skin, is commonly described as non-melanoma skin cancer. The incidence of non-melanoma skin cancers is not certain since there is no cancer registry that collects data on BCC or squamous cell carcinomas, but general estimates place the incidence at more than 2 million new cases in the United States annually. Most BCC are managed by surgical resection, which is sufficient to remove the lesion entirely in approximately 95% of cases, however this varies with the size and location of the lesion. For those with incompletely resected lesions (positive surgical margins), treatment options include watchful waiting or immediate re-excision or post-excision radiation therapy; local recurrence is estimated to occur in 30-50% of patients with incomplete resection with a peak time to local recurrence of 2 years although late recurrences (between 5 and 10 years after initial resection) are reported. Based on a large, prospective case series, watchful waiting is more likely to lead to greater surgical morbidity than early intervention.¹ Topical therapies for localized BCC include topical 5-fluorouracil and topical imiquod in carefully selected patients with low risk BCC, and photodynamic therapy. The incidence of locally advanced BCC, which are not amenable to radiation (prior radiotherapy or NBCSS) or surgical excision is more difficult to estimate, but based on the ability to completely resect disease in approximately 95% of lesions, would be expected to be 5% of fewer patients with BCC. Less than 1% of patients with BCC develop metastatic disease; where the prognosis was poor (estimated median survival of 10 months)², however, more recent data based on a single center review of cases identified between 1997 and 2011 indicate survival rates may be longer, with a median survival of 3.7 years.³

Vismodegib received FDA approval [REDACTED] (b) (4).
The approval of vismodegib was based on demonstration of clinically important tumor

¹ Recurrent basal cell carcinoma after incomplete resection. Robinson JK, Fisher SG. Arch Dermatol. 2000;136(11):1318.

² Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. Wyszong A, Aasi SZ, Tang JY; JAMA Dermatol. 2013 May;149(5):615-6.

³ Markedly improved overall survival in 10 consecutive patients with metastatic basal cell carcinoma. Danial C, Lingala B, Balise R, Oro AE, Reddy S, Colevas A, Chang AL. Br J Dermatol. 2013 Sep;169(3):673-6.

shrinkage as evidenced by durable overall response rates (ORR) in patients with locally advanced (ORR 43%, median duration 7.6 months) or metastatic (ORR 30%, median duration of response 7.6 months) BCC. While all responses were partial responses in patients with metastatic BCC, there were 13 (20.6%) patients with complete responses and 14 (22.2%) patients with partial responses among those with locally advanced BCC.

Pre-submission Regulatory History

November 17, 2008: IND 102961 for sonidegib submitted; the IND was allowed to proceed December 18, 2008.

June 9, 2011: End of Phase 1 meeting to discuss the acceptability of a single, clinical trial (Study A2201) evaluating the safety and efficacy two doses of sonidegib (200 mg or 800 mg daily) in a multi-center, randomized (2:1), double-blind, study to be conducted in 120 patients with mBCC or laBCC, could support submission of an NDA. FDA expressed concerns regarding the limited data supporting the doses chosen for further study, that eligibility criteria are specific to ensure enrollment of a homogeneous and well-defined population of patients with laBCC, that the histopathological diagnosis be centrally reviewed and confirmed, and that the primary endpoint of ORR be independently verified. FDA agreed that the primary endpoint of ORR was acceptable provided that the responses are of clinically meaningful magnitude and duration and the safety profile was acceptable. FDA recommended the first secondary endpoint for hierarchical testing be duration of response.

December 22, 2011: FDA issued an advice letter with recommendations for further revision of the proposed modifications to RECIST for assessment of objective tumor response in patients with laBCC.

July 8, 2013: FDA issued written responses in lieu of a Type C meeting request. With regard to Study A2201, FDA recommended that the primary analysis of objective response rate be performed in the intent to treat population defined as all randomized patients who received study treatment. FDA also raised the possibility that no dose-response would be identified. In addition, FDA provided preliminary advice on the data to be provided in a future NDA with regard to clinical pharmacology studies and assessment of effects on QT.

August 8, 2013: a teleconference was held to discuss FDA's concerns with regard to amendment 5 to the protocol. During the teleconference, Novartis agreed to revise the protocol to clarify that for patients with laBCC assessed with all modalities (photo, MRI and histology) the same lesion has been evaluated, i.e. surface component (by photo and biopsy), sub-dermal component (by MRI and biopsy, where practicable) and to update the protocol appendix to capture all possible assessment scenarios for tumor response.

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 provided advice regarding proposed amendments to Study A2201 and the independent review charter for assessment of the primary efficacy endpoint. FDA stated that when lesions were present on MRI, but not visible on photographs and without tumor on biopsy, such lesions should be identified as partial responses in the primary efficacy analysis due to the potential for sampling error with punch biopsy assessments. FDA also advised that whether an observed ORR of 30% would be considered evidence of clinical benefit would depend on the precision of the estimated treatment effect (95% confidence intervals) and overall risk benefit assessment.

April 15, 2014: Interdisciplinary pre-NDA meeting held under the PDUFA V Program; final agreements reached after the pre-NDA CMC meeting.

June 18, 2014: Pre-NDA CMC meeting held.

NDA Regulatory History

September 26, 2014: NDA 205266 submitted

November 26, 2014: FDA issued a letter stated that the proposed proprietary name, Odomzo, was acceptable.

January 28, 2015 meeting of the PeRC: The PeRC stated that Novartis' requested a full waiver from the requirements of PREA be granted.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the quality reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. The microbiological quality of the drug product is controlled through use of a suitable testing protocol and the microbial limits specification for the final drug product (sonidegib capsules) was acceptable. The inspection of the drug substance manufacturing site based on the manufacturing profile and recent inspection (b) (4) that did not identify significant deficiencies. The inspection of the drug product manufacturing site was acceptable. Stability testing supports an expiry of 24 months for the blister package presentation and 18 months for the 30-count bottle presentation when stored at 25°C in the original packaging. There are no outstanding issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The NDA contained non-clinical pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (in vivo and in vitro), and reproductive toxicology studies; non-clinical studies were conducted in mice, rats, and dogs. Nonclinical pharmacology studies conducted in vitro and in vivo models demonstrated that sonidegib inhibits smoothed (SMO), a transmembrane protein within the Hedgehog signaling pathway, at concentrations achievable with the recommended dose of sonidegib. The major target organs in repeat dose chronic (13- and 26-weeks) toxicology studies in rats and dogs were the skin, bones, and gastrointestinal tract. Species-specific adverse effects of sonidegib were lymphoid tissue depletion, increased creatine phosphokinase levels, hypercholesterolemia, inflammatory changes in the prostate gland, and atrophy of the uterus and ovaries in rats, whereas hypercholesterolemia, increased creatine phosphokinase levels and decreased uterine weights were inconsistently observed in dogs. In a juvenile rat study, thinning or closure of the growth plate, decreased bone length and width, hyperostosis, missing, fractured, or atrophied teeth, atrophy of the testes, ovaries, and uterus, and partial development of the prostate gland and seminal vesicles with aspermia of the epididymis, and nerve degeneration were observed. Sonidegib administration did not demonstrate evidence of neurologic, respiratory or cardiovascular effects in combined functional observational battery (FOB) neurological and respiratory assessment in rats or a cardiovascular safety pharmacology study in dogs. Sonidegib was weakly positive for inhibition in the hERG channel assay.

Sonidegib was not mutagenic or clastogenic in standard assays; carcinogenicity studies were not required for approval in the indicated population; however, given the potential for long-term use where survival for 5 or more years is possible, carcinogenicity studies in rats and mice have been required as a post-marketing requirement to further define this potential risk.

Sonidegib demonstrated impairment of fertility in female rats but did not affect the reproductive potential of male rats. Sonidegib was a potent teratogen in dedicated rabbit embryofetal toxicity study; teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal effects were observed at maternal exposures to sonidegib below the limit of detection.

To mitigate the risks of embryofetal toxicity, information has been included in product labeling (Boxed Warning) and a Medication Guide. In addition, to further characterize these risks, a Pregnancy Pharmacovigilance Study has been required under 505(o).

5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The clinical pharmacology development program included three dose-escalation trials with pharmacokinetic assessment, an ADME study, a drug interaction trial, and a food effects study. In addition, a population PK analysis was performed which included data from 336 patients enrolled in four clinical studies.

Sonidegib is poorly absorbed; less than 10% of an oral dose was absorbed under optimal (fasting) conditions. Following the administration of a dose of sonidegib (100 mg to 3000 mg) under fasted conditions in patients with cancer, the median time-to-peak concentration (T_{max}) was 2 to 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 sonidegib and the estimated accumulation at steady-state was 19-fold.

In clinical pharmacology studies, clinically significant food effects were observed, with a 7-4-fold increase in exposure following administration of a single dose of sonidegib 800 mg with a high-fat meal (1000 calories with 50% from fat) in healthy subjects as compared to exposure in the fasted state. The population pharmacokinetic (PK) analysis suggests that geometric mean sonidegib steady-state exposure is 34% lower in patients with patients who took an acid-reducing agent than in those who did not; a PMR has been required to further evaluate this finding; the findings may indicate the need to revise the Dosage and Administration section of product labeling. Approximately 70% and 30% of the absorbed dose was excreted in feces and urine, respectively following a single 800 mg oral dose of [¹⁴C]-labeled sonidegib in healthy men; based on the population PK analysis, no dose adjustment is recommended for patients with mild hepatic impairment or for those with mild or moderate renal impairment. However, a PMR has been required to further investigate the pharmacokinetics of sonidegib in patients with moderate hepatic impairment; the results of this trial may indicate the need to revise the Dosage and Administration section of product labeling to ensure safe dosing.

In drug interaction studies, ketoconazole increased sonidegib AUC_{0-10d} by 2.2-fold and rifampicin decreased sonidegib AUC_{0-10d} by 72% following a single 800 mg dose in healthy subjects. The clinical pharmacology review team recommended that product labeling state that concurrent administration of strong and moderate CYP3A modulators should be avoided. Alternative dose strategies were not recommended because sonidegib demonstrates non-linear PK with a long elimination half-life.

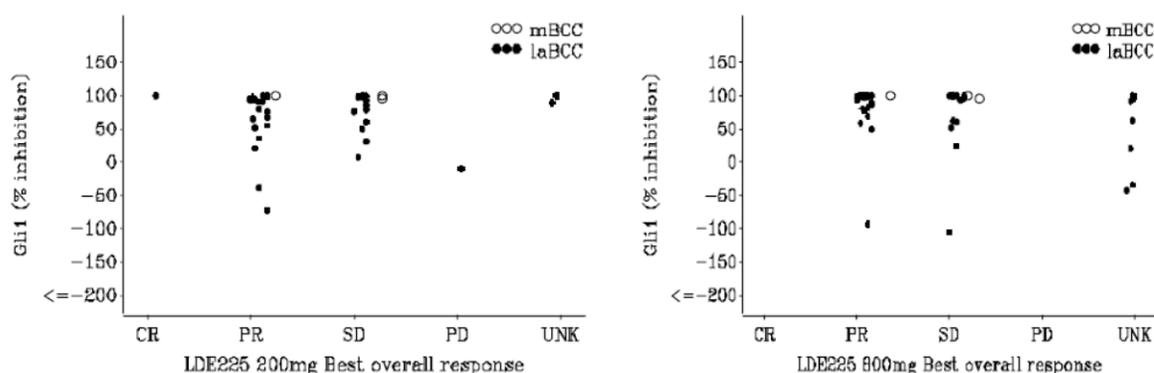
Two doses were evaluated for safety and effectiveness in the major efficacy trial. These doses were selected based primarily on the results of clinical trials demonstrating that the doses were reasonably safe and that the lowest dose demonstrating anti-tumor activity in BCC was 200 mg daily and on pharmacodynamic effects on the downstream activation of the Hedgehog pathway. Although pharmacodynamic effects of sonidegib on the Hedgehog pathway (i.e., Gli-1 expression in BCC tumor tissue and in normal skin) suggested a modest dose-response relationship in early clinical studies, in Study A2201, there was no evidence of a dose-response relationship (200 mg vs. 800 mg) for the change in Gli-1 expression in tumor at week 17. The change in Gli-1 expression in Study A2201 did not appear to correlate with achieving an objective tumor response. Data abstracted from Dr. Shord's review regarding treatment effects on Gli-1 expression are summarized below.

Percent change in baseline Gli-1 expression in tumor tissue

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

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

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



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

Based on the population PK analysis, there was no evidence of an exposure-response (E-R) relationship for efficacy. However, there was an E-R relationship for musculoskeletal toxicity with the mean probability of grade 3 or 4 creatine kinase (CK) elevation increased with higher sonidegib minimal concentrations (C_{min}).

Sonidegib can inhibit hERG channel activity at clinically relevant concentrations. Following 17 weeks of daily dosing of sonidegib 200 mg or 800 mg, no large mean change (i.e., > 20 ms) in the QTc interval were detected; however, the QT IRT reviewer noted that a “significant positive” relationship between sonidegib concentration and QTc may exist. While such risks are expected to be lower at the recommended dose of 200 mg (compared with the 800 mg tested), the QT IRT reviewer noted that a thorough QT study is feasible and should be performed. However, I concur with the recommendations of the clinical pharmacology reviewers that a single dose, thorough QT study performed in healthy volunteers would not reflect sonidegib exposure in cancer patients. Sonidegib exposure is higher in patients with cancer than in healthy subjects because exposures with daily dosing in cancer patients results in a 19-fold higher exposure in patients with cancer than in healthy individuals, due to accumulation with daily doses and 3-fold lower clearance in patients with cancer.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Two clinical sites were chosen for inspection, based on enrollment of large numbers of study subjects and the effects of efficacy results on regulatory decision-making. In addition, two Contract Research Organizations (CROs) were also inspected for their conduct of medical image analysis of MRI and CT scans as well as photograph analysis for mBCC. Based on the results of these inspections, FDA concluded that the results submitted in the NDA were reliable.

The trial was adequate in design to estimate the magnitude and duration of tumor shrinkage in the proposed patient population. The study design was enhanced by the inclusion of an independent review committee, masked to treatment arm and adverse reactions with the potential to unmask the dose, which verified the presence and duration of responses. It is notable that there was high concordance between the investigator and independent review assessment of response. Limitations of the trial include the relatively small sample size and failure to ensure that a sufficient number of patients with mBCC were enrolled to estimate the ORR with precision. Another limitation of the study design was the assumption regarding optimal dosing, and the study design with unbalanced allocation resulting in a smaller number of patients randomized to the treatment arm which was subsequently determined to be the optimal dose.

Trial Design – Study A2201

The trial was designed as a non-comparative, randomized (2:1), two-arm, double-blind trial with the primary analysis based on a central independent review of photographs and radiologic studies in the event of unblinding by toxicity. Randomization was stratified by disease stage (laBCC vs. mBCC), histology (aggressive vs. non-aggressive) and geographic region.

The primary objective the trial as to assess the overall response rate (ORR) in both arms, as determined by central review, according to study-specific modifications to RECIST in patients with laBCC and RECIST 1.1 in patients with mBCC. Secondary objectives included assessment of duration of response and complete response rate by central review, estimation of progression-free survival, overall survival, and time to response, and assessment of ORR, duration of response, time-to onset of response, and progression-free survival by the investigator, evaluation of safety, evaluation of effects on QT/QTc intervals (pre- and post-treatment), and further characterize the pharmacokinetics of sonidegib.

Key eligibility criteria were adults (≥ 18 years) with a histologically confirmed diagnosis of laBCC that was not amenable to radiation therapy, curative surgery, or other local therapies and measurable disease defined as at least one cutaneous lesion that could be accurately measured in at least one dimension as ≥ 10 mm with MRI scan or on color photographs, at least one non-nodal lesion that could be accurately measured in at least one dimension as no less than double the slice thickness or 10 mm, whichever was greater with spiral CT or MRI scan, one nodal lesion (i.e. lymph node) ≥ 15 mm in short axis with spiral CT scan or MRI scan (irrespective of slice thickness), or lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that could be evaluated by CT/MRI. In addition, patients were required to have adequate organ function and WHO performance status of 0-2.

Patients with neuromuscular disorders or who are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis and those who had received prior Hedgehog pathway inhibitors were ineligible. In addition, the following medications were prohibited during study treatment: strong CYP3A inhibitors and inducers, CYP2B6 and CYP2C9 substrates, and warfarin derivatives.

Tumor response assessments were performed every 4 weeks for the first 8 weeks, then every 8 weeks for the first year and every twelve weeks thereafter. 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. For patients with mBCC, the evaluation of tumor response was based on RECIST version 1.1. The response assessment criteria for laBCC are defined in detail in Dr. Casey's review.

The primary analysis was to occur after all patients received sonidegib for 24 weeks or had discontinued sonidegib. All statistical analyses were descriptive. The sample size of 140 patients in the 800 mg arm and 70 patients in the 200 mg arm were based on sufficient numbers of patients to estimate the ORR. Sonidegib would be considered to provide clinical benefit if the observed ORR by central review was $\geq 30\%$ on either arm.

Results

There were 230 patients enrolled between July 20, 2011 and January 10, 2013 at 58 study centers in 12 countries: Australia (2 centers), Belgium (2 centers), Canada (2 centers), France (5 centers), Germany (10 centers), Greece (1 center), Hungary (2 centers), Italy (1 center), Spain (3 centers), Switzerland (3 centers), United Kingdom (7 centers), and United States (21 centers). Across the study population, 36 patients (16%) had mBCC and 194 patients (94%) had laBCC. Within subgroups defined by treatment stage (laBCC or mBCC) the treatment patient characteristics were similar in the 200 mg and 800 mg arm but not similar across disease status in that patients in the mBCC subgroup, were more likely to be male, were more like to have a performance status of 2, had a greater number of prior treatments, and a greater number of sites of metastatic disease. Demographic and baseline tumor characteristics are presented in the tables below, abstracted from Dr. Chen's review.

Table 4 Baseline Demographics Characteristics (FAS)

	LaBCC		mBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)	Sonidegib 200 mg (N=13)	Sonidegib 800 mg (N=23)
Age, Mean (Range)	65 (25-92)	64 (24-93)	71 (49-86)	63 (34-88)
Age >=65, n (%)	38 (58%)	69 (54%)	9 (69%)	9 (39%)
Male, n (%)	38 (58%)	78 (61%)	10 (77%)	18 (78%)
Race White, n (%)	59 (89%)	123 (96%)	12 (92%)	22 (95%)

Table 6 Baseline Disease Characteristics and Prior Treatments (FAS)

	LaBCC		mBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)	Sonidegib 200 mg (N=13)	Sonidegib 800 mg (N=23)
ECOG PS 0	44 (67%)	87 (68%)	6 (46%)	8 (35%)
1	16 (24%)	33 (26%)	3 (23%)	11 (48%)
2	4 (6%)	6 (5%)	4 (31%)	4 (17%)
Missing	2 (3%)	2 (2%)	0	0
Prior Antineoplastic therapy				
Surgery	49 (74%)	104 (81%)	11 (85%)	23 (100%)
Radiotherapy	5 (8%)	10 (8%)	3 (23%)	4 (17%)
Regimens	4 (6%)	5 (4%)	0	1 (4%)
Measurable Disease, IRC	62 (94%)	122 (95%)	12 (92%)	21 (91%)
IRC Lesions # >1	33 (50%)	81 (63%)	12 (93%)	18 (78%)
IRC Lesion: Both	43 (65%)	97 (76%)	12 (92%)	21 (91%)
Target	19 (29%)	25 (20%)	0	0
Non-Target	2 (3%)	3 (2%)	1 (7%)	2 (9%)
Metastatic sites	2 (2%)	1 (1%)	13 (100%)	22 (96%)
Predominant histology/cytology (site)				
Aggressive	33 (50%)	62 (48%)	7 (54%)	14 (61%)
Non-aggressive	33 (50%)	63 (49%)	5 (38%)	5 (22%)

The following table abstracted from Dr. Chen's review displays the primary efficacy results, by disease stage and treatment arm, with 6 months follow-up on all patients and with 12 months follow-up. No formal analyses comparing results by dose were planned, however based on the exploratory analyses summarized in the table below, there is no suggestion that the 800 mg dose provides greater efficacy compared with the 200 mg dose. (b) (4)

Table 7 ORR Results (FAS)

	IaBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
12-Months Analysis		
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%)
ORR diff* . (95% CI)	-13.8 (-28.27, 1.52)	
Primary Analysis (6 months)		
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%)
ORR diff* . (95% CI)	-11.8 (-26.51, 3.10)	

(b) (4)

**the study was not designed to compare the two treatment doses*

Based on the findings of similar efficacy and less toxicity with the 200 mg dose as compared to the 800 mg daily dose, product labeling is limited to the 200 mg dose as the recommended dose. 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.

I concur with the clinical reviewers

(b) (4)

(b) (4)

8. Safety

Size of the database

The incidence of serious adverse reactions were evaluated in a pooled safety analysis of 571 patients with various cancers who received sonidegib at doses ranging from 100 mg to 3000 mg across 12 clinical studies. This database is adequate to detect serious adverse reactions occurring at an incidence of 1%.

The assessment of adverse reactions of any severity (NCI CTCAE Grades 1-5) were assessed primarily in Study A2201; in this trial, 79 patients received sonidegib 200 mg daily and 150 received sonidegib 800 mg daily. Since the incidence of many common adverse reactions (muscle spasms, alopecia, dysgeusia, fatigue, nausea, decreased weight, decreased appetite, myalgia, pain, and vomiting) were higher among patients who received sonidegib 800 mg daily as compared to those who received 200 mg daily.

Based on the findings of increased toxicity without a commensurate increase in efficacy at the 800 mg dose, the recommended dose for sonidegib is 200 mg orally, once daily.

The median duration of treatment with sonidegib 200 mg daily in Study A2201 was 11.0 months (range 1.3 to 33.5 months). Sonidegib 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 (5%), dysgeusia (5%), asthenia (4%), increased lipase (4%), nausea (4%), fatigue (3%), decreased appetite (3%), alopecia (3%), and decreased weight (3%). The most common adverse reactions occurring in $\geq 10\%$ of patients receiving sonidegib 200 mg daily were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

Major safety concerns related to labeling

The major safety concerns considered under this NDA were the risks of embryofetal toxicity and the risks of rhabdomyolysis. The risks of embryofetal can only be mitigated by effective contraceptive use as described in product labeling, which extends for a sufficient period of time given the unusually long half-life (28 days) of sonidegib.

Novartis included a subsection in Warnings with regard to musculoskeletal adverse reactions, which is considered appropriate in light of the 0.2% incidence of rhabdomyolysis in the larger safety database and the 4% incidence of serious musculoskeletal adverse reactions (i.e., those requiring hospitalization or intravenous hydration) within the 29% of patients in Study A2201 who required medical management (including narcotics/other analgesics, muscle relaxants, or magnesium supplementation). The overall incidence of musculoskeletal adverse reactions (all grades) in the 79 patients who received sonidegib 200 mg daily in Study Q2201 was 68%; the incidence of severe or life-threatening musculoskeletal adverse reactions was 9%.

Musculoskeletal adverse reactions were characterized by muscle spasms (54%), musculoskeletal pain (32%), and myalgia (19%); the incidence of creatine phosphokinase elevation was 61%, with an 8% incidence of Grade 3 or 4 CPK elevations. Based on the data from Study A2201, the incidence and severity of musculoskeletal adverse reactions was dose-related.

[REDACTED] (b) (4)

as discussed in the clinical pharmacology and clinical reviews, resumption of sonidegib among patients in the 800 mg arm required multiple dose reductions upon resumption of dosing. For patients in the 200 mg arm, while resumption of dosing was better tolerated, it appeared to be unnecessary for clinical benefit (see Table below, abstracted

from Dr. Shord's review). Among three patients with objective responses who discontinued sonidegib 200 mg daily, the onset of response occurred prior to drug discontinuation and was maintained for months after sonidegib was discontinued.

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

Patient ID	Preferred term (CTC grade)	Creatine phosphokinase level (U/L) ^a	Sonidegib PK level (ng/mL) ^b	Time of onset (days)	Action taken	Time to resolution (days)	Confirmed BOR	Time to BOR (days)	DOR (days)
1536-001	Blood creatinine increased (G2)	18	522	141	Drug interrupted	8	PD	-	-

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

REMS

Novartis submitted a risk management plan (RMP) in the NDA to manage the risks of teratogenicity and musculoskeletal toxicity including rhabdomyolysis. This plan consisted of

(b) (4)

A revised RMP that
(b) (4)

was submitted on January 23, 2015.

I concur with the recommendations of the clinical review team and the DRISK consultant, who agree that a REMS is not required to ensure safe and effective use of this drug and that the risks of teratogenicity and musculoskeletal toxicity can be effectively mitigated through product labeling and, in the case of musculoskeletal toxicity, through a recommended dose of sonidegib 200 mg daily. In addition, FDA has required a post-marketing study to 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). Collection of this targeted data will inform further modifications of labeling or other actions, in the event that cases of teratogenicity are observed.

PMRs and PMCs

There are five studies which the clinical and clinical pharmacology review teams have identified as necessary to further characterize the safety or obtain information to enhance safe use of sonidegib. A more detailed description of these studies is provided in section 13 of this summary review, but briefly, these PMRs are

- To conduct and submit the results of a carcinogenicity study in mice;
- To conduct and submit the results of a carcinogenicity study in rats;
- To conduct and submit annual reports on a dedicated Pregnancy Pharmacovigilance Study that evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib;
- To conduct and submit the results of a dedicated hepatic impairment study; and
- To submit the results of an ongoing pharmacokinetic study that will further characterize effects on acid-reducing agents on the relative bioavailability of sonidegib.

9. Advisory Committee Meeting

This NDA for a new molecular entity was not referred for review to the Oncologic Drugs Advisory Committee because this drug is not the first in its class; the safety profile with regard to teratogenicity is similar to that of other drugs approved for this indication and the safety profile with regard to musculoskeletal toxicity is acceptable 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; the clinical trial design is similar to previously approved products in the class; and the application did not raise significant public health questions on the role of the drug in the treatment of this disease.

Three Special Government Employees (SGEs) were consulted by FDA on this application; two of these SGE's were subject matter experts in the treatment of BCC and one SGE was a patient advocate for those with BCC and nevoid basal-cell carcinoma syndrome (NBCCS). These SGE agreed that the risk:benefit profile was favorable and that the magnitude and duration of the objective responses observed in patients with laBCC were clinically meaningful. In addition, all three agreed that [REDACTED] (b) (4)

10. Pediatrics

Novartis submitted a request for waiver from the requirements of the Pediatric Research Equity Act (PREA) based on their statement that the necessary studies are impossible or

highly impracticable. The request for waiver from all requirements of PREA was granted by the Pediatric Review Committee (PeRC) on January 28, 2015.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The review team and DMEPA consultant agreed that the proposed proprietary name was acceptable and did not suggest promotional claims or carry risks of medication errors.
- Physician labeling
 - Boxed Warning: added information regarding duration of contraceptive use in males and females; (b) (4)
 - Indications and Usage: (b) (4) patients with laBCC (b) (4) whose disease has recurred following surgery or radiation therapy as well as for those whose disease is not amenable to surgery or radiation as those with recurrent disease after effective treatment are also at high risk for morbidity. (b) (4)
 - Dosage and Administration: Extensively edited for brevity; recommendations for (b) (4) removed as there was no clinical data to support this (not employed in clinical studies); (b) (4)
 - Dosage Forms and Strengths: Editorial revisions only.
 - Contraindications: Revised to state “None” as there are no reported cases of (b) (4) with sonidegib.
 - Warnings and Precautions: Edited title of first warning for consistency with other sections of labeling (Embryofetal Toxicity), edited for consistency with the Pregnancy and Lactation Labeling Rule content and format, and to provide recommended duration of contraceptive use based on nonclinical studies and known half-life of the drugs in humans. Combined subsection on Blood Donation under the Embryofetal Toxicity subsection to clarify the underlying risk with blood donation is inadvertent exposure for transfusions recipients who may become pregnant. Retitled the subsection (b) (4) to read “Musculoskeletal Adverse Reactions,” extensively edited to provide descriptive information on the incidence of adverse events and description of serious adverse reactions.
 - Adverse Reactions: Provided demographic and exposure information for the safety population as per FDA guidance for this section of product labeling; created a second

- tabular listing to separate clinical adverse reactions from laboratory abnormalities and limited the table of laboratory abnormalities to those with clinical significance (i.e., those which occurred in Grade 3-4 severity in some patients). (b) (4)
- (b) (4) revised text section on amenorrhea to provide additional information on duration and population at risk (2 of 14 premenopausal women).
- Drug Interactions: Edited for essential information; removed (b) (4); moved (b) (4) to Section 12 of product labeling.
 - Use in Specific Populations: Edited section 8.1-8.3 for consistency with the Pregnancy and Lactation Labeling Rule (PLLR) content and format; included results of juvenile rat study under Pediatric Use subsection; revised Geriatric Use subsection to include required information based on the entire study population of (b) (4) patients in Study A2201; modified sections on renal and hepatic impairment to include (b) (4).
 - Overdosage: Modified this section to denote that there are no specific and data-driven recommendations for management of overdose.
 - Description: Edited for brevity and accuracy.
 - Clinical Pharmacology: Subsection on Mechanism of Action edited to remove (b) (4) and to remove (b) (4). Subsection on (b) (4) deleted (b) (4); edited information on effects on cardiac electrophysiology for brevity and essential information. Subsection on Clinical Pharmacology edited for conformance with applicable FDA guidance on this section of product labeling, for brevity, and to include data supporting recommendations in Section 2, 7, and 8 of product labeling.
 - Nonclinical Pharmacology/Toxicology: Moved information on reproductive toxicology studies from Subsection 13.2 to 13.1; added nonclinical data in Subsection 13.2 regarding musculoskeletal toxicity in animals which may further inform prescribers regarding this adverse drug reaction.
 - Clinical Experience: Added details regarding the trial design and endpoint definitions, given that the modifications to RECIST were unique to this trial; added additional information regarding the study population with emphasis on those laBCC randomized to the sonidegib 200 mg arm. (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4) the range for durations of response was provided. Provide descriptive information on ORR in patients with laBCC randomized to the sonidegib 800 mg arm.
 - How Supplied/Storage: Removed information on (b) (4).
 - Patient Counseling: Edited for conformance with FDA guidance on this section of product labeling and for active voice.

- Carton and immediate container labels: Novartis incorporated changes requested by FDA regarding storage of the carton and containers and changes to the proposed colors describing product strength. Final carton/immediate container labeling are acceptable.
- Patient labeling/Medication guide: Novartis submitted a Medication Guide, which is appropriate in light of the serious risks of embryofetal toxicity and musculoskeletal toxicity. All FDA requested edits for conformance with applicable guidances were incorporated. Edited for consistency with final physician package insert.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that the application be approved, pending agreement on product labeling.
- Risk Benefit Assessment:

All review team members and consultants recommended approval of this application. I concur with that recommendation based on evidence of durable objective tumor responses observed in patients with recurrent locally advanced basal cell cancer (BCC) and those with locally advanced BCC whose tumors are not amenable to treatment with surgery or radiotherapy. These patients have a serious disease with significant morbidity and disfigurement. Although there is one drug (vismodegib) that is currently approved for this population, additional drugs are needed to avoid vulnerability in the drug supply. In this population, the observed response rate of 58% (95% confidence intervals: 44.8%, 69.7%) where approximately half of the responses are durable for at least 6 months, represents clinical benefit. The risks of sonidegib in this population are qualitatively similar to that observed with vismodegib, can be mitigated through dose modification and use of effective contraception, and have been deemed acceptable to the medical and patient community as confirmed by advice provided by Special Government Employees consulted during review of this NDA. ^(b)₍₄₎


- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
I concur with the recommendations with the clinical review team that Risk Evaluation and Mitigation Strategies (REMS) are not required to ensure safe and effective use of sonidegib for the proposed indication.

- Recommendation for other Postmarketing Requirements and Commitments
 - To conduct a 6-month rodent carcinogenicity study in the transgenic mouse.
 - To conduct a long-term rodent carcinogenicity study in the rat.

The two post-marketing studies above have been required under the provisions of 505(o) to evaluate the tumorigenic potential of sonidegib in mice and in rats in order to assess the relevant risk to humans, given the life expectancy of the intended patient population (≥ 5 years after first exposure to sonidegib). In general, carcinogenicity studies are not required for drugs intended to treat metastatic and unresectable cancer due to the short life-expectancy of such patients and the long latency period for development of secondary cancers.

- 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 (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these 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.

- Conduct an hepatic impairment pharmacokinetic trial

This post-marketing study was required under the provisions of 505(o) because the mass balance study suggests that hepatic elimination is the major route of elimination. Patients with hepatic impairment may have higher sonidegib exposures than patients with normal hepatic function, which may lead to more treatment limiting severe musculoskeletal toxicity.

- Submit the final study report for the completed pharmacokinetic trial to determine how to dose sonidegib in patients taking an acid-reducing agent.

This post-marketing study was required under the provisions of 505(o) based on the results of a population PK analysis that suggests that acid-reducing agents reduce mean sonidegib steady-state exposure by 34%. Patients who take acid-reducing agents may receive be effectively underdosed for anti-tumor activity but still at risk for the adverse reactions of sonidegib.

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/s/

PATRICIA KEEGAN
07/22/2015