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APPLICATION NUMBER:

205266Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 12, 2015
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
NDA #	205266
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	September 26, 2014
PDUFA Goal Date/Internal Goal Date	September 26, 2015/July 26, 2015
Proprietary Name / Established (USAN) names	Odomzo [®] /sonidegib
Dosage forms / Strength	Capsules/ 200mg
Proposed Indication(s)	Adults with locally advanced (b) (4) carcinoma not amenable to curative surgery or radiation therapy
Recommended:	Approval

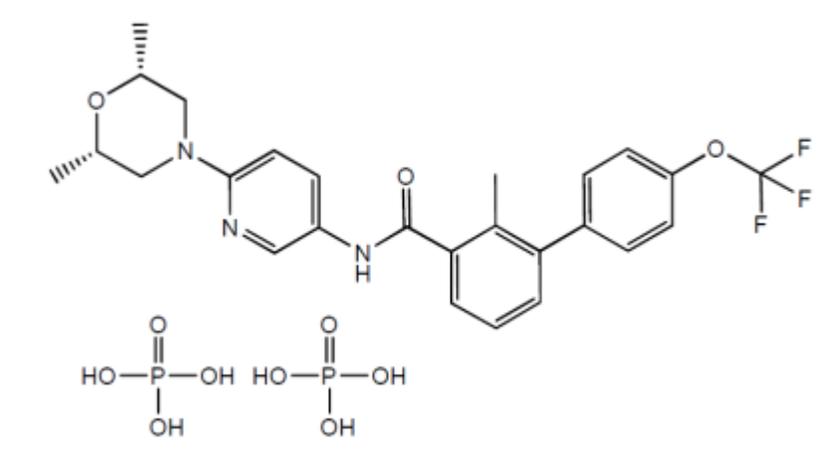
NDA 205266 Cross Discipline Team Leader Review

❖ Introduction

The information below was derived from the Clinical Review of Denise Casey, M.D.

On September 26, 2014, Novartis Pharmaceuticals Corporation (Novartis) submitted a New Drug Application (NDA) 205266 for Odomzo[®] (sonidegib) in accordance with section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50. The indication being sought is “for the treatment of patients with locally advanced basal cell carcinoma (BCC) not amenable to curative surgery or radiation therapy (b) (4)”. Priority review was requested, but not granted because, although sonidegib is a new molecular entity (NME), it is not the first drug in the class, not the first to be approved for the treatment of this patient population, nor does it represent an advantage over current FDA-approved therapy for this disease.

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 is a 200 mg hard capsule formulation. The structural formula of sonidegib follows (copied from the application):



Key regulatory activities prior to submission of the NDA are copied from the Clinical Review of Dr. Denise Casey and listed here:

- 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.
- 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.
- 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.
- 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.
- June 12, 2013: Novartis submitted a fifth amendment of Protocol CLDE225A2201. This amendment allowed for ORR, determined according to RECIST 1.1, to be derived for central review data by MRI and photography independently, without lesion matching between MRI and photographic central assessments.
- 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.
- April 15, 2014: Pre-NDA meeting held
- June 18, 2014: Pre-NDA CMC meeting held.

- 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 at the 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 would include 78 week updated data (data (data cut-off July 11, 2014).

The results from one clinical trial were submitted in support of this application. The trial, LDE225A2201 (2201) was entitled, “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;” and it was a multi-center, randomized, double-blind trial conducted in patients with laBCC or mBCC. Patients were randomized 2:1 to receive sonidegib at either 800 mg or 200 mg once daily on a continuous dosing schedule. Patients were stratified by stage of disease (locally advanced or metastatic), histology (aggressive or non-aggressive), and geographic region (Australia, Europe, and North America). The protocol design required 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 efficacy outcome of the trial was centrally reviewed overall response rate (ORR), defined as the proportion of patients with confirmed best overall response according to modified RECIST (mRECIST) for patients with laBCC and RECIST 1.1 for patients with mBCC. The modified RECIST criteria were reviewed and agreed to by FDA. Centrally reviewed duration of response (DOR), was a key secondary endpoint. Efficacy assessments were conducted at weeks 5, 9, and 17, and then once every eight weeks during the first year of treatment and once every twelve weeks thereafter.

The primary analysis was planned and conducted when all patients had been treated for 24 weeks or had 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.

The issues with this application that will be discussed further in this review are:

- (b) (4)
?
- Are the product label and other proposed pharmacovigilance measures sufficient to inform prescribers and patients of the risk of muscle related toxicities, which were at times severe; and are these findings a class effect that should lead to Hh class labeling?
- Are the toxicities related to fetal development a class related phenomenon and should they lead to class labeling, are they described sufficiently in the product label, and are other pharmacovigilance measures sufficient to inform prescribers and patients of these risks?

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

❖ Background

The information below was derived from the Clinical Review of Denise Casey, M.D.

Basal cell carcinoma (BCC) is one of the most common non-melanoma skin cancers (NMSC) accounting for 80% of the cases of these types of cancers. An estimated 2.2 million cases of NMSC are diagnosed annually in the United States (US), but incidence rates are inexact because there is no requirement to report these types of cancers and no registry collects this data. Approximately 13 million white non-Hispanic individuals living in the United States in 2007 may have had a personal history of at least one NMSC, according to one published report.

Exposure to the sun, ultraviolet (UV) light, ionizing radiation, and certain chemicals (e.g. arsenic) are known risk factors for BCC, as are having light-colored skin, older age, male gender, previous skin cancer, long-term or severe skin inflammation or injury, psoriasis treatment, xeroderma pigmentosum, nevoid basal cell carcinoma (Gorlin syndrome), and decreased immunity. Approximately 70% of cases of BCC occur on the face.

Patients with basal cell carcinoma usually receive local therapies with recurrence rates varying from 5% to 14% after initial resection. A small proportion of BCCs progress and are no longer responsive to available treatments. In these cases, progressive disease results in considerable morbidity from local tissue invasion and destruction causing severe disfigurement. These types of lesions include both locally advanced BCCs (laBCCs) that are inoperable and those that occur in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or very rarely, metastatic BCC (mBCC).

Metastatic BCC is extremely rare with metastatic spread most often involving regional lymph nodes (40-83%). Lung (35-53%), bone (20-28%), skin (10-17%), and liver metastases have also been described. Median survival for these patients has been reported to be 8-14 months with a 5-year survival rate of approximately 10%.

Many BCCs are treated by dermatologists using various therapeutic options including surgery (Mohs micrographic surgery, curettage and electro-desiccation, and excision with postoperative margin assessment), photodynamic therapy, imiquimod, 5-fluorouracil (5-FU) and radiotherapy. Treatment of metastatic disease has primarily been palliative since most treatment modalities at this stage of the disease are ineffective.

Vismodegib (Erivedge®), a first-in-class Hedgehog pathway inhibitor, is the only FDA-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 study 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 patients with mBCC would achieve a response rate greater than 10%. In 33 patients with metastatic basal-cell carcinoma, the independently assessed ORR was 30% (95% confidence interval [CI]:16, 48). In 63 patients with laBCC, the independently assessed ORR was 43% (95% CI: 31, 56), with complete responses observed in 13 patients (21%). The median duration of response was 7.6 months in both cohorts.

❖ CMC/Device

The summary below was derived from the Chemistry Review for this application performed by Ben Stevens and Donna Christner (Drug Substance), Office of Product Quality, Branch 2, New Drug API, and William Adams and Olen Stephens (Drug Product), Office of Product Quality, Branch 2, New Drug DP, and Robert Wittorf and Mahesh Ramanadham Office of Product Quality, Branch 2, Office of Process and Facilities.

General product quality considerations

The Chemistry Review Team recommends approval for this application and I concur with this recommendation.

Drug Substance

The chemical formula for sonidegib phosphate is:

N-{6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl] pyridin-3-yl}-2- methyl-4'-(trifluoromethoxy)-[1, 1' -biphenyl]-3-carboxamide diphosphate (C₂₆H₂₆F₃N₃O₃·2H₃O₄P, MW = 681.50).

Sonidegib phosphate can exist in two common polymorphic forms:

(b) (4)

(b) (4)

The sonidegib phosphate drug substance release specifications were deemed adequate by the CMC reviewers and included: appearance, particle size, identity, related substances, solvents, heavy metals, microbial enumeration tests, total aerobic

microbial count, total combined yeasts/molds, specified microorganisms (E. coli), and assay.

(b) (4)
Acceptance
criteria for related substances are set based on ICH Q3A with the exception of (b) (4). The proposed limits for these impurities were found to be adequate by the CMC reviewer based on consultation with their nonclinical colleagues.

The applicant proposed a retest period of (b) (4) months for the sonidegib phosphate drug substance when stored below (b) (4) °C, based on the results of 18-month long-term stability at 25 °C/60% RH and 6-month accelerated stability at 40 °C/75% RH from three primary stability batches of this drug substance, as well as additional supporting long-term and accelerated stability results using related packaging materials. No significant changes in the drug substance strength and purity were noted. A statistical analysis was provided to support extrapolation of the 18 month test results to a (b) (4) month retest. The data was found to support this retest period per ICH Q1E following CMC consultation with the statistical review team. The proposed retest period was granted by the CMC review team.

Drug Product

The commercial presentation of the product is a 200 mg strength, immediate release, pink (b) (4) opaque number 00 hard gelatin capsule marked with black (b) (4) imprint “NVR” on the cap and “SONIDEGIB 200MG” on the body. Capsules are packaged in two configurations - a 30-count HDPE bottle with 1 gram desiccant and a 30-count blister pack – which are to be stored at 25°C with excursions to 15-30°C (b) (4)

Product development addressed the need for (b) (4)

The formulation uses USP/EP grade excipients and a commercially available capsule composed of gelatin (b) (4). The acceptance specifications for ingredients were adequate and appropriately justified according to the CMC review team.

The sites for manufacture and control met cGMP requirements. The manufacturing process and process parameters were well described and appropriately justified.

The proposed specifications for release and stability were acceptable to the CMC review team. The proposed tests address appearance, identity, assay, purity, (b) (4) drug release and USP requirements. The proposed analytical methods were described in sufficient detail and appropriately validated for their intended purpose. The method for

organic impurities was deemed to have adequate sensitivity. The proposed criteria were justified by USP/EP expectations; primary and supportive batch analysis data; and stability data. Reference standards for drug substance and known organic impurities were described and well characterized.

The proposed packaging systems were appropriately qualified. Components were well described and appropriate acceptance specifications were proposed. Reference to type III DMFs are provided through letters of authorization.

Registration and supportive stability studies were appropriate to address the proposed commercial presentations, and drug substance and drug product manufacturing sites. The study data was deemed adequate to support the proposed label and the initial shelf life for each presentation.

Facilities review/inspection

Drug Substance

The drug substance manufacturing process involves (b) (4) but the CMC review revealed no complex or atypical manufacturing. The drug substance manufacturing facilities are familiar with the manufacturing and testing of the respective drug substance and intermediate unit operations at their respective facilities. (b) (4) No atypical testing is performed at any of the laboratories and all firms have an acceptable inspectional history.

The (b) (4) facility was inspected in (b) (4). A five item FDA Form 483 was provided. Although a pre-approval inspection was not performed, the firm made appropriate corrective actions to compliance observations after the (b) (4) inspection and the classification was considered VAI.

All facilities were deemed acceptable for the current NDA and recommended for approval.

Drug Product

The Pantheon, Toronto (FEI 3000264888) DP manufacturer was the only facility inspected. A standard drug manufacturing process with a (b) (4) % drug load in the immediate release capsule was observed. One unique note from the review team is that there is a (b) (4) during the DP manufacturing process. (b) (4) Discussions with the process and drug product reviewers revealed that there are no inspectional concerns, and any issue can be addressed through informational requests.

Pantheon (Toronto) was inspected during 26-30 January 2014. The inspection was classified VAI. No additional concerns were noted by the team.

❖ Nonclinical Pharmacology/Toxicology

The summary below was derived from the Nonclinical Pharmacology/Toxicology reviews of Alexander H. Putman and Whitney S. Helms, Division of Hematology Oncology Toxicology.

The nonclinical review team recommends approval for this application. I agree with their recommendation.

Submitted with the NDA were studies of orally administered sonidegib in mice, rats, and dogs to investigate the drug's pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (in vivo and in vitro), and reproductive toxicity.

The pharmacology studies demonstrate that sonidegib is a Smoothed (Smo) antagonist. Smoothed is a transmembrane protein and an integral part of the Hedgehog (Hh) signaling pathway. Binding of Hh ligands to the Patched receptor results in release of Patched-mediated inhibition of Smo signaling and downstream nuclear translocation of the active Gli transcription factor with subsequent Gli-responsive transcriptional activation. Sonidegib inhibited Gli-dependent transcription with IC50s of between 4 and 13 nM in various *in vitro* assays. As binding of Hh ligands to Patched initiates the downstream events leading to Smo activation, the activity of sonidegib is consistent with labeling the drug as a hedgehog pathway inhibitor as its established pharmaceutical class in the opinion of the nonclinical review team.

Sprague Dawley rats and Beagle dogs were the primary models used to investigate the toxicology of sonidegib in studies of up to 26 weeks. Major target organs identified in both species included bone (growth plate closure), gastrointestinal tract, and hair follicles. Gastrointestinal toxicity and alopecia are reported clinically. In the rat the teeth were an additional major target. Findings in the teeth included atrophy of the root, malocclusion, and tooth loss. The tooth findings were associated with declining clinical condition and led to humane euthanasia of some rats at the high dose level, a dose that resulted in male exposures only slightly higher than clinical exposures at the recommended dose, in the 26-week study.

While not required to support the use of sonidegib for the current indication, the Applicant also conducted a juvenile animal study in rats. In general, findings in the juvenile animals were similar to those seen in adult rats, with the bones, teeth, gastrointestinal tract, and hair follicles being major target organs. Juvenile rats presented with delays in sexual maturation and limited signs of nerve damage compared to controls. Bone findings correlated with significant decreases in bone length and width at the end of the treatment period. These findings were enhanced at the end of an 8 week recovery period. Additionally, these findings are likely to be relevant to a pediatric patient population and the nonclinical team recommends including them in the product label.

In clinical trials, musculoskeletal toxicity was the major toxicity associated with sonidegib. The toxicity was characterized by reports of musculoskeletal pain, myalgia, and muscle spasms preceding significant increases in creatine kinase (CK). Published reports describe a role for hedgehog signaling in the proliferation and survival of satellite cells present in skeletal muscle that proliferate and differentiate in response to growth or muscle injury, and provide a plausible potential pharmacological basis for this type of toxicity. While no histopathological signs of muscle degeneration or atrophy occurred in the repeat dose toxicology studies

conducted in rats or dogs, continuous or intermittent full body tremors were observed at the highest dose level in each species as well as in the juvenile rats. In addition, transient increases of greater than 100% in creatine kinase were observed in rats. The elevations in CK along with tremors are included in the product label and are suggestive of the musculoskeletal events of muscle spasms and elevations in CK reported clinically. Sonidegib did, however, have some off target activity on the rat sodium brain channel type II which could be a factor in rat tremors at high dose levels. In addition, minimal findings of nerve degeneration occurred in juvenile rats. These observations along with sonidegib's ability to cross the blood brain barrier make a direct effect on the central nervous system another possible explanation for the tremors, although the Applicant proposes that the peripheral nerve degeneration observed in juvenile rats may be related to closures of growth plates in bones preventing nerve growth.

Sonidegib was negative in assays for genotoxicity. Carcinogenicity studies were not conducted to support the use of sonidegib in patients with locally advanced basal cell carcinoma. Since the natural history of this disease is highly variable and patients may be taking sonidegib for long periods of time, carcinogenicity studies in rats and mice were recommended by the review team as postmarketing requirements.

The potential reproductive toxicity of sonidegib in dedicated fertility and embryofetal development studies in rats was investigated by the Applicant. Treatment with sonidegib resulted in a lack of fertility in female rats at doses resulting in exposures approximately 1.3 times the exposure in humans at the recommended dose of 200 mg. In the same study, increases in the number of early resorptions and decreases in the number of viable fetuses occurred at exposures as low as 0.12 times the clinical exposure. Supporting these findings, histopathological findings in female rats in the 6 month adult toxicology study included atrophy of the uterus and ovaries at twice the exposure in humans and similar findings were observed in a juvenile animal study. Based upon these observations, sonidegib could affect female fertility. Sonidegib did not appear to affect male fertility in adult animal studies, though degeneration and atrophy of the testis and delayed preputial separation were reported in a juvenile animal study.

Sonidegib is a powerful teratogen in animals. In an embryofetal development study conducted in rabbits, sonidegib administration resulted in abortion, complete resorption of fetuses, or severe malformations including vertebral, distal limb and digit, and severe craniofacial defects, at doses resulting in exposures of approximately 0.05 times the exposure in humans at the recommended dose of 200 mg. Skeletal variations were observed even when maternal exposure to sonidegib was below the limit of detection for the drug. Due to the severe findings in rabbits, an embryofetal development study in a second species was not required, consistent with the recommendations in ICH S9. Because of the severity of the findings a black box warning for embryofetal risk is included in the product label.

The half-life of ODOMZO in clinical trials was approximately 28 days. In distribution studies the drug accumulated in multiple tissues and was present at least 23 days in white fat. Because of the severe teratogenic findings and long half-life of the drug, the label includes a recommendation for females of reproductive potential to use effective contraception during and for at least 20 months following the final dose. While sonidegib is not genotoxic and had

no clear effect on adult male fertility, because of the teratogenic risk of the drug at even very low concentrations, the label includes the recommendation that males who are taking the drug and have female partners of reproductive potential use effective contraception during and for at least 8 months following the final dose of the drug. This recommendation is based on the half-life of the drug in combination with an estimated distribution in semen of approximately 10-20%.

❖ Clinical Pharmacology/Biopharmaceutics

The summary below was derived from the Clinical Pharmacology Review for this application performed by Stacy Shord and Ping Zhao, Office of Clinical Pharmacology.

The Clinical Pharmacology Review Team recommends approval for this application. I concur with this recommendation.

The study providing major support for this application was a trial in which two doses of sonidegib were administered to randomized patients, 200 mg daily or 800 mg daily. The 200 mg dose was chosen because it was the lowest dose at which anti-tumor activity was observed in the earlier dose finding trial while the 800 mg dose was chosen because it was determined to be the maximum tolerated dose (MTD) in the same trial. The dose proposed for approval, 200 mg, is supported by lack of an exposure–response (E-R) relationship observed for best overall response and the mean probability of grade 3 or 4 creatine kinase (CK) elevation that increased with higher sonidegib concentrations in the study supporting the application. No dose modifications were recommended by the clinical pharmacology team in the product label because any dose reduction for patients treated in the 200 mg arm of the trial was equivalent to patients receiving placebo. In addition, the clinical data suggest that patients experienced a durable response despite discontinuing therapy.

Sonidegib exposure increased in a less than dose proportional manner with doses up to 3000 mg in fasted conditions consistent with dose-dependent absorption (b) (4)

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

Sonidegib is metabolized by CYP3A4 to several inactive metabolites. Ketoconazole increased sonidegib AUC_{0-10d} by 2.2-fold and rifampicin decreased sonidegib AUC_{0-10d} by 72% following a single 800 mg dose in healthy subjects. Simulations suggest that moderate inhibitors given for 14 days will increase steady-state exposure of sonidegib by 1.8-fold and moderate inducers given for 14 days will decrease steady-state exposure of sonidegib by 56%. The clinical pharmacology review team recommended that patients avoid taking strong and moderate CYP3A modulators with sonidegib and this was included in the product label. Dose

interruption or an alternative sonidegib dose or schedule to provide similar sonidegib exposure to the 200 mg dose is not feasible, because sonidegib demonstrates non-linear PK with a long elimination half-life.

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

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

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

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

Baseline age had a statistically significant, but not clinically meaningful effect on sonidegib clearance in the population PK analyses. The original final model suggested gender had a statistically significant, but not clinically meaningful effect on sonidegib clearance.

The exposure observed in Japanese subjects at a dose of 200 mg is not likely to exceed the exposure observed at a dose of 800 mg in the registration trial and therefore, the clinical pharmacology review team concluded that a 200 mg dose in Japanese subjects should not lead to an increase in toxicity.

The clinical pharmacology review team concluded that it is unlikely that renal impairment will have a clinically meaningful effect on sonidegib exposure, since less than 1% of the absorbed radiolabeled dose was eliminated in urine as unchanged sonidegib and the population PK model suggests mild or moderate renal impairment is unlikely to influence sonidegib exposure.

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

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

❖ Clinical Microbiology

The following was excerpted from the microbiology review of Stephen E. Langille, Ph.D. DMA Branch 3, NDMS, OPS, CDER.

The microbial limits specification for sonidegib capsules were deemed acceptable by the microbiology reviewer who recommended that the application be approved from the standpoint of product quality microbiology. I agree with this recommendation.

Dr. Langille stated as follows:

“Sonidegib is a capsule for oral administration. The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The microbial limits acceptance criteria are consistent with USP Chapter <111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).”

❖ Clinical/Statistical- Efficacy

The following summary was derived from the Statistical Review of Huanyu (Jade) Chen, Division of Biometrics V, and the Clinical Review of Denise Casey, DOP2, OHOP

The following summarizes the key statistically-related regulatory history for study A2201:

- September 27, 2011: Applicant submitted modified RECIST (mRECIST) guidelines for review.
- November 17, 2011: Protocol Amendment 2 submitted:
 - ❖ Implemented mRECIST criteria for laBCC patients because those lesions associated with ulceration, cysts, and scarring/fibrosis were not adequately covered by RECIST 1.1.
 - ❖ Sample size increased to 100 in 800mg and to 50 in the 200mg arm.
 - ❖ Implemented central reading for determination of primary endpoint
- June 28, 2012: Protocol Amendment 4 submitted:
 - ❖ Defined the primary efficacy analysis set (pEAS), a subset of treated population.
 - ❖ Sample size expanded to approximately 210 patients to ensure sufficient patients in the pEAS (50 on 200mg and 100 on 800 mg).
- April 3, 2013: Applicant submitted request for advice on the planned analyses in preparation for NDA submission. FDA recommended that the primary analysis of objective response rate (ORR) be performed in the intent to treat population (same as full analysis set).
- June 12, 2013: Protocol Amendment 5 submitted
 - ❖ Updated statistical analysis for secondary endpoints allowing centrally reviewed ORR assessment according to RECIST 1.1 to be derived data by MRI and photography independently without lesion matching between MRI/photograph and lesions
 - ❖ FDA advised [REDACTED] (b) (4) [REDACTED] 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 overall response assessment for each target lesion should incorporate photographic, MRI and histological evaluation as described in Appendix 2 of the protocol.
- November 7, 2013: FDA issued comments to draft protocol amendment 6 and IRC charter submitted on October 1, 2013:
 - ❖ 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
 - ❖ Whether the observed ORR of 30% can be considered an adequate measure of effectiveness will be based on the overall risk benefit assessment and the lower bound of the 95% confidence interval of the observed ORR.
- November 14, 2013: Revised Protocol Amendment 6 submitted:
 - ❖ 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 via the Independent Review Committee (IRC)
- April 15, 2014: Pre-NDA meeting held.
 - ❖ Updated efficacy data for ORR and duration of response in addition to the updated safety data would be included in the 120-day safety update.

- ❖ Agreement reached on the proposal for submission of electronic datasets and the proposed contents for the NDA.
- September 26, 2014: NDA 205266 submitted.

The single study submitted to support this application was Study CLDE225A2201(A2001), a multicenter, randomized, double blinded, non-comparative, parallel trial evaluating the efficacy and safety of two dose levels of sonidegib (200 mg QD vs. 800 mg QD on a continuous schedule). The primary efficacy outcome measure was objective response rate (ORR) based on central review using modified RECIST (mRECIST) 1.1 to determine outcomes in patients with laBCC and RECIST 1.1 for patients with mBCC patients. The key secondary endpoint was duration of response (DoR) which was also centrally reviewed. Other secondary endpoints were progression-free survival (PFS), disease control rate (DCR), and patient reported outcomes (PRO). A total of 230 patients were randomized in a 1: 2 allocation (sonidegib 200 mg, n=79; sonidegib 800 mg, n=151).

Patient demographics and baseline disease characteristics for Study A2001 are in the tables below which were copied from Dr. Casey's review:

Study A2001 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 ≥ 65	47 (60)	78 (52)	125 (54)
Age ≥ 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

Study A2001 Baseline 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.

Only the data and analyses for patients with laBCC met the study predefined criteria for point estimates to meet or exceed 30%. In this group of patients, the lower bounds of the associated 95% confidence intervals (CIs) also exceeded 20%, which was the pre-specified threshold for clinical relevance based on the study design operating characteristics.

Specifically, patients with laBCC followed for at least 12 months in the sonidegib 200 mg QD arm demonstrated an ORR of 58% (95% confidence interval [CI]: 45, 70), and consisted of 3 (5%) complete responses (CR) and 35 (53%) partial responses (PR). Patients assigned to the sonidegib 800 mg QD arm demonstrated an ORR of 44% (95% CI: 45, 70), and consisted of 2 (2%) CR and 54 (42%) PR.



(b) (4)

The centrally reviewed median DOR in patients with laBCC was nonestimable for both treatment arms with 87% of responders censored in the 200 mg group and 93% of responders censored in 800 mg group.

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)

As noted by Dr. Chen, without a control arm, statistical inferences cannot be drawn from this study. All statistical summaries presented are descriptive. Furthermore, only data and analyses in for patients with laBCC in study A2201 met the predefined criteria for point estimates to meet or exceed 30% of ORR. The lower bounds of the associated 95% confidence intervals (CIs) for these patients also exceeded 20%, the pre-specified threshold for clinical relevance base upon study design operating characteristics.

[REDACTED] (b) (4)

In addition three Special Government Employees (SGE) were consulted by FDA after undergoing a rigorous clearance process. All three SGEs, two physician, subject matter experts and one Patient Representative, agreed that [REDACTED] (b) (4). This information was conveyed to the Applicant during the PDUFA V Late Cycle Meeting (LCM) [REDACTED] (b) (4).

Also discussed at the LCM was the Applicant's request [REDACTED] (b) (4). Specifically, [REDACTED] (b) (4) were discussed. The applicant was made aware that [REDACTED] (b) (4).

The Applicant was also reminded that [REDACTED] (b) (4).

[REDACTED] (b) (4)

The applicant was reminded that in general, the study they conducted will be the study data that informs the label; however, the team agreed to look at their additional analyses and the rationale behind it before coming to a final decision.

The results observed for patients with laBCC from the trial supporting the application are statistically significant, robust and clinically meaningful to patients. Reviewers are in agreement that the application warrants an approval. I concur with their opinions.

❖ Safety

The following summary was derived from the Clinical Review of Denise Casey, M.D., DOP2, OHOP

The safety of sonidegib was 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 (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, submitted to the NDA and reviewed during the initial review cycle.

The safety databases discussed above are deemed adequate to support the safety of this product in the indicated population.

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.

Study A2201: Overview of safety

	Sonidegib 200 mg N=79 (%)	Sonidegib 800 mg N=150 (%)
Patients who experienced an AE	75 (95)	150 (100)

	Sonidegib 200 mg N=79 (%)	Sonidegib 800 mg N=150 (%)
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)

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 six 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 and reviewed. A summary of these documents and a detailed discussion of the muscle toxicity risk associated with sonidegib treatment can be found in Section 7.3.5 of Dr. Casey's review.

The safety profile of sonidegib is acceptable for patients with laBCC whose disease is not amenable to local therapies. The safety reviewer agrees that the 200 mg dose is the most appropriate for patients. Although ORR was similar between treatment arms, the 200 mg dose was safer and tolerated better allowing patients who were deriving clinical benefit from sonidegib to remain on study treatment longer. Although the risk for musculoskeletal adverse

reactions is of concern, the incidences of muscle-related AEs and SAEs were decreased in patients in the 200 mg group. No risk evaluation and mitigation strategy (REMS) for sonidegib was recommended by the clinical reviewer or DRISK. Recommendations for safe and effective use of sonidegib, including adequate safety monitoring for serum CK elevation and musculoskeletal adverse events, were made in the product label.

❖ Advisory Committee Meeting

No Advisory Committee meeting was held for this application since there were no controversial issues raised by the application that would benefit from an advisory committee discussion. Specifically, the primary efficacy outcome measures are acceptable for the indications sought, the safety profile is acceptable and the application did not raise significant public health questions.

Three Special Government Employees (SGEs) were consulted, two subject matter experts and one patient advocate. Subject matter experts were in agreement that (b) (4)

(b) (4), all SGEs agreed that the benefit: risk profile is favorable for patients with locally advance disease and that the response rates and durations of response observed are clinically meaningful for patients.

❖ Pediatrics

This application included a request for waiver of pediatric studies for the indication sought. The request was granted on January 28, 2015, after review by the Pediatric Review Committee (PeRC).

❖ Other Relevant Regulatory Issues

Patents and exclusivity: No exclusivity or patent issues were identified during the review of this application.

Financial disclosures: Financial disclosures were provided in the application. The clinical reviewer noted that even in cases where investigators disclosed a financial interest in the applicant company, the disclosures had no effect on the outcome of the clinical trial supporting the application for this drug.

Proprietary name: The proprietary name, Odomzo, was granted on November 26, 2014.

DSI audits: Four BIMO inspections were conducted at two clinical sites. One site had compliance issues identified, in particular a large number of protocol deviations relative to other clinical sites, and missed laboratory assessments and ECGs. A detailed review of these inspectional observations determined that they did not affect the study outcome or subject safety. The second clinical study site had no major inspectional issues. Two Clinical Research

Organizations (CRO) were also inspected, [REDACTED] ^{(b) (4)}, based upon their roles in the determination of efficacy outcomes. There were no major issues revealed during the inspections of either CRO.

❖ Labeling

Sonidegib was given the proprietary name Odomzo.

Physician labeling continues to be negotiated as of the filing of this review. A full discussion of labeling negotiations and final outcomes can be found in the primary clinical review and any addenda thereto.

❖ Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval

Risk Benefit Assessment

The recommendation for approval of sonidegib is based on the results of a single trial demonstrating statistically significant, clinically meaningful and durable objective response rates for patients with locally advanced basal cell carcinoma (laBCC). The clinical benefit observed was unequivocal in the number of patients treated and since there is only one other FDA-approved drug for the indication, there is a clear need for other effective therapies for this uncommon and serious disease.

For patients with laBCC followed for at least 12 months who received sonidegib at the dose recommended for the label, 200 mg daily, the ORR was 58% (95% CI: 45, 70). Patients who received sonidegib 800 mg daily demonstrated an ORR of 44% (95% CI: 45, 70). In these same patients, the median duration of response was non-estimable for patients receiving 200 mg and 15.7 months (95% CI: NE) for patients receiving 800 mg. The evidence of overall response and the durability of the responses were confirmed by central review and are, as such, deemed to be robust.

The safety profile of sonidegib is notable for mild to moderate muscle toxicity, which appears to be a class effect of hedgehog inhibitors, alopecia, dysgeusia, nausea, fatigue, increased serum CK, decreased weight, and diarrhea. These risks led to discontinuation of the drug in less than one quarter of patients treated at the dose to be labeled.

The major risk of sonidegib appears to be to the embryo and fetus of a woman exposed during pregnancy. This risk also appears to be a class effect. A clinical postmarketing pregnancy pharmacovigilance trial will be required of the applicant under FDAAA to better define the

risk and risk minimization through contraception for women and barrier methods for men are included in the product label.

Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)

No REMS was recommended by any discipline or consulting review team. I fully agree with these recommendations and decisions.

Recommendation for other Postmarketing Requirements

The following postmarketing requirements will be required of the applicant.

Clinical:

1. A postmarketing pregnancy pharmacovigilance trial will be required of the applicant under FDAAA because long term data is needed to assess a known serious risk related to the drug and drug class. Sonidegib is a teratogen which interrupts hedgehog pathway signaling and interferes with normal embryo-fetal development. The registration trial did not contain any cases of sonidegib exposure to pregnant women. The rarity of the indicated disease in women of childbearing potential and standard pregnancy precautions make fetal exposure a rare event not likely to be captured in a standard premarketing safety database. In animal studies, sonidegib was embryotoxic and fetotoxic as evidenced by abortion or complete resorption of fetuses, and teratogenic resulting in severe malformations. Fetotoxicity was observed even at low maternal doses where maternal exposure was below the limit of detection. The goal of the pregnancy pharmacovigilance trial is to assess the outcomes of developing embryos and pregnancy after exposure to sonidegib.

Clinical Pharmacology:

2. Completion of an ongoing postmarketing hepatic impairment pharmacokinetic trial will be required of the applicant under FDAAA. Because of the small subpopulation that would be affected, a pre-approval trial of this nature was not practical, therefore, was not required. The mass balance study submitted as part of the NDA 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. The goal of the clinical pharmacokinetic trial is to determine appropriate sonidegib dose in patients with moderate or severe hepatic impairment.
3. Submission of a final study report for a completed clinical pharmacokinetic (drug interaction) trial will be required under FDAAA. Because of the altered pharmacokinetics observed when acid-reducing agents are administered concomitantly with sonidegib, the appropriate dosing regimen for patients being treated with acid-reducing drugs is unknown.

Additional Comments to Applicant

None.

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/s/

SUZANNE G DEMKO
06/12/2015