

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205266Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA#:** 205,266

**Drug Name:** Odomzo<sup>®</sup> (Sonidegib)  
Basal Cell Carcinoma

**Indication(s):** Adult patients with locally advanced (b) (4) basal cell carcinoma who are not amenable to curative surgery or radiation therapy

**Applicant:** Novartis Pharmaceuticals Corporation

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## 1 EXECUTIVE SUMMARY

In this original New Drug Application (NDA), the applicant is seeking an approval of Odomzo® (sonidegib or LDE225) for patients with locally advanced basal cell carcinoma (LaBCC) who were not amenable to curative surgery or radiation therapy [REDACTED] (b) (4)

The study CLDE225A2201 (A2001) to support the application was a randomized, double-blinded, non-comparative, parallel, multicenter phase II study evaluating the efficacy and safety of two dose levels of sonidegib (200 mg QD vs. 800 mg QD). The primary efficacy endpoint was objective response rate (ORR) per central review according to the modified RECIST (mRECIST) 1.1 in laBCC patients and RECIST 1.1 in the mBCC patients. The secondary endpoints included duration of response (DoR). A total of 230 patients were randomized in a 1: 2 allocation (sonidegib 200 mg: 79; sonidegib 800 mg: 151).

Only data and analyses in the laBCC patients met the predefined criteria for point estimates to meet or exceed 30%. The lower bounds of the associated 95% confidence intervals (CIs) also exceeded 20%, the pre-specified threshold for clinical relevance as per the study design operating characteristics.

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

[REDACTED] (b) (4)

The two statistical issues are 1) tumor assessment criteria, mRECIST, for the laBCC patients was amended after the majority of laBCC patient enrollment; 2) the algorithm to determine the composite overall response assessment in laBCC patients was finalized after primary analysis data cut-off and less than two months before 12-month analysis data cut-off.

Whether the data and analyses from the current submission in the laBCC patients in two dose levels demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

## 2 INTRODUCTION

In this New Drug Application (NDA), the applicant is seeking an approval of Odomzo® (sonidegib) for the treatment of patients with locally advanced basal cell carcinoma (laBCC) who were not amenable to curative surgery or radiation therapy [REDACTED] (b) (4)

[REDACTED] This submission was primarily supported by results from a randomized, double-blinded, non-comparative, parallel, multicenter phase II study A2201 (CLDE225A2201) under Investigational New Drug (IND) 102,961.

### 2.1 Overview

#### 2.1.1 Class and Indication

As stated by the applicant and the reviewer's literature review, basal cell carcinoma (BCC) is the most common human malignancy (Pfeiffer et al 1990, Spates et al 2003) for approximately 80% of non-melanoma skin cancer (NMSC) (American Cancer Society 2012, Lomas et al 2012). Distinguishing between histological BCC subtypes is important due to the variance in propensity for growth (aggressive vs less aggressive disease) (Goldenberg and Hamid 2013). There are an estimated 2.2 million NMSC cases diagnosed annually in the United States (US) (American Cancer Society 2012). The observation that approximately 80% of BCC cases occur on the head or neck (Wong et al 2003) support the role of sun exposure and UV light as key etiological factors.

A small proportion of BCCs may progress to an advanced state that is no longer amenable to available treatments. In these cases, progressive disease results in considerable morbidity from local tissue invasion and destruction particularly on the face, head, and neck, causing severe disfigurement (Wong et al 2003). These lesions include both laBCCs, that are either inoperable or in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or very rarely, metastatic BCC (mBCC), for patients whose BCC has spread to distant sites (von Domarus and Stevens 1984, Lo et al 1991, Wadhera et al 2006).

Published data on the prevalence and life expectancy for laBCC are unavailable. The incidence of mBCC is extremely rare (0.0028% to 0.55%, Wadhera et al 2006). Median survival has been reported to be 8-14 months with a 5-year survival rate of approximately 10% (von Domarus and Stevens 1984, Lo et al 1991, Spates et al 2003). Based on a recent review of 100 cases of mBCC, median survival was 54 months, with shorter survival in patients with distant metastases relative to those with regional metastases (24 vs. 87 months) (McCusker et al 2014).

Vismodegib is the only approved systemic treatment of patients with laBCC and mBCC based on the results of independent assessed objective response rates (ORRs) per (LaBCC: 43% vs. mBCC 30%), There is thus still an unmet need for systemic treatments for patients with laBCC who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4).

According to the applicant's report, sonidegib is an oral bioavailable small molecule inhibitor of that binds and inhibits smoothed, a G-protein-coupled receptor in the hedgehog (Hh) signaling pathway. It is derived from a novel structural class N-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-1,1'-[biphenyl]-3-carboxamide diphosphate.

In the current NDA submission, the proposed indication is for the treatment of patients with inoperable laBCC (b) (4). This indication was supported by a randomized, double-blind, parallel-group, multicenter phase II study.

## 2.1.2 Regulatory History

The following list summarizes the key statistical related regulatory history for study A2201:

- September 27, 2011: The applicant submitted the modified RECIST (mRECIST) guidelines for FDA review.
- November 17, 2011: The applicant submitted Protocol (Amendment 2):
  - Implementation of the mRECIST criteria for laBCC patients when associated with ulceration, cysts, and scarring/fibrosis were not adequately covered by RECIST 1.1.
  - Sample size increased from 80 to 100 in 800-mg arm and from 40 to 50 in the 200-mg arm.
  - Implementation of central reading for determination of primary endpoint to obtain more robust conclusions.
- June 28, 2012: The applicant submitted Protocol Amendment 4
  - Defined the primary efficacy analysis set (pEAS), a subset of treated population.
  - Sample size was expanded to approximately 210 patients to ensure sufficient patients in the pEAS (50 on 200mg and 100 on 800 mg).
- April 3, 2013: The applicant submitted a briefing package to get input on the planned analyses in preparation for an NDA submission. FDA recommended that the primary analysis of objective response rate (ORR) be performed in the intent to treat population (ITT the same as full analysis set).
- June 12, 2013: The applicant submitted a revised Protocol Amendment 5
  - Updated Statistical analysis for secondary endpoints, which allowed ORR according to RECIST 1.1 to be derived for central review data by MRI and photography (b) (4)
  - FDA stated that (b) (4) 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 an 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 the 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: The applicant submitted a revised Protocol Amendment 6
  - 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 was reached on the proposal for submission of electronic datasets and the proposed contents for the NDA.
- September 26, 2014: NDA 205266 for sonidegib was submitted.

### **2.1.3 Study Reviewed**

Study A2201 was a randomized, double-blinded, non-comparative, multicenter phase II study of sonidegib in 230 patients (sonidegib 200 mg QD: 79; sonidegib 200 mg QD: 151) with laBCC and mBCC. This study was conducted at 58 centers within 12 countries (21 U.S. sites) from July 20, 2011. The planned primary endpoint was ORR. The secondary endpoints included duration of response (DoR) and patient reported outcomes.

The clinical data cut-off for the pre-specified primary efficacy analysis was when all patients had been treated for 24 weeks or discontinued treatment (June 28, 2013). The clinical data cut off for the 12-month amendment was December 31, 2013, which provided longer follow-up data, 50 weeks following enrollment of the last patient.

## **2.2 Data Sources**

The electronic submission including protocols, SAP, clinical study reports (CSR), and analysis datasets for this NDA submission are located on the network with network path: \\cdsub1\evsprod\nda205266\0000\m5.

## **3 STATISTICAL EVALUATION OF STUDY A2201**

Part of the text, tables, and figures presented in this section are adapted from the applicant's CSR.

### **3.1 Data and Analysis Quality**

The data and analysis quality were acceptable. This reviewer was able to duplicate the analysis variable derivation and summary statistics.

## 3.2 Evaluation of Efficacy in Study A2201

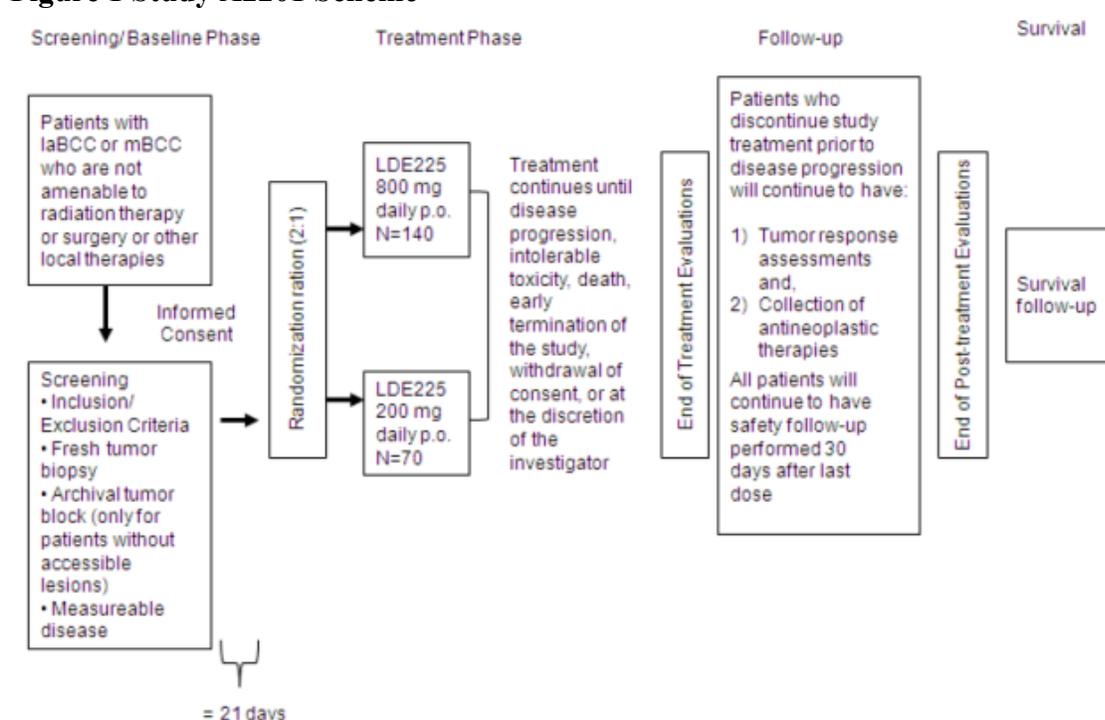
### 3.2.1 Objective

The primary efficacy objective of the study A2201 was to assess the efficacy of ORR per central review, according to mRECIST in patients with laBCC and RECIST 1.1 in patients with mBCC. The key secondary efficacy objectives included DoR per central review.

### 3.2.2 Study Design

The study A2201 was designed to evaluate the efficacy of sonidegib in 210 patients with laBCC and mBCC. Patients were randomized 2:1 to receive sonidegib at either 800 mg (140) or 200 mg (70) QD. The randomization was centralized and stratified by stage of disease (locally advanced vs. metastatic), histological classification of initial diagnosis or subsequent analysis at recurrent in laBCC patients (aggressive vs. non-aggressive), and geographic region (Australia, Europe, vs. North America). Figure 1 presents a schematic of the study A2201 design. Patients continued treatment until disease progression, intolerable toxicity, withdrawal of consent, or death.

**Figure 1 Study A2201 Scheme**



Source: CSR Figure 9-1

Tumor assessment was assessed using RECIST 1.1 for patients with mBCC. However, a set of protocol-specific composite criteria, termed modified RECIST, incorporating response assessments using MRI, color photographs and histology, were used to adequately capture tumor response in the la-BCC patients, especially when the disease was associated with post-treatment morphological changes, such as ulceration, cyst formation or scarification/fibrosis formation.

LaBCC patients were assessed with localized/soft tissue MRI scans, color photography and histology at baseline and follow-up visits. Only the most representative or most suitable localized/soft tissues were evaluated by MRI scans when all lesions present (both measurable and non-measurable) were also evaluated by color photography.

For the evaluation of lesions at baseline and throughout the study, the lesions were classified as target or non-target lesions (separately for each modality). Any lesion that had been previously treated with radiotherapy were considered as a non-target lesion, unless it is measurable and had shown clear progression since the radiotherapy, in which case, it was considered as a target lesion.

In the event the localized/soft tissue MRI scan captured more than one measurable lesion adequately (up to 2 lesions) were selected as target lesions. Any lesions captured on the MRI scan that were not selected as target lesions, were documented as non-target lesions. For photographic assessments, up to two target lesions may be identified.

In the new m-RECIST, a target lesion was defined as the largest affected area, including both visible and palpable components of the lesion. Any remaining lesions documented by color photography, whether measurable or not, were documented as non-target lesions. If a patient had numerous lesions, up to 4 non-target lesions were evaluated individually and the rest of the lesions were grouped together by anatomical location/region and reported as additional non-target lesions.

Post baseline radiographic, photographic, and histological data were each independently reviewed by a separate central Contract Research Organization (CRO) and an independent review committee (IRC, two independent oncologists and one independent radiologist). Tumor assessments were conducted at baseline, week 5, week 9, week 17, and then every eight weeks during the first year of treatment and once every twelve weeks thereafter.

When overall lesion response assessments for all modalities (MRI, photography, and tumor biopsy) were available, the methodologies were to be prioritized in the following order: histopathology, clinical photographs, and MRI.

The main inclusion criteria included patients:

- Age 18 years or older.
- Patient with locally advanced BCC or metastatic BCC that was amenable to radiation therapy, curative surgery, or other local therapies:
- WHO performance status  $\leq 2$
- Adequate bone marrow, liver and renal functions

The main exclusion criteria included patients:

- Previous treatment with Hedgehog pathway inhibitors

- Concurrent neuromuscular disorder or concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, that cannot be discontinued at least two weeks prior to starting study treatment (patients who require a statin were permitted to take pravastatin).

### 3.2.3 Efficacy Measures

**ORR** was defined as the proportion of randomized patients achieving a confirmed best overall response (determined on repeat assessments  $\geq 4$  weeks apart) of complete response (CR) or partial response (PR), per central view. Objective response was assessed in accordance with the following:

- Patients with laBCC: protocol-specified mRECIST, using an integrated composite response based on all radiographic (MRI), photographic (digital clinical photography), and histological (histopathology) data
- Patients with BCC: RECIST 1.1
- Patients with a best overall response of 'Unknown' (UNK) will be treated as non-responders in estimating the ORR.

Table 1 presents the composite overall response assessment per mRECIST in patients with laBCC.

**Table 1 Composite Overall Response Assessment per mRECIST in patients with laBCC**

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

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

<sup>a</sup> Disease unevaluable by photography at baseline; also includes scenarios where photographic data are unavailable

<sup>b</sup> Disease unevaluable by MRI scan at baseline; also includes scenarios where MRI data are unavailable

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

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

**DoR** was defined for responders (CR or PR) per central review, according to mRECIST for patients with laBCC and RECIST 1.1 for patients with mBCC, and was calculated from the date of the first documentation of response (CR, or PR) to the date of first documentation PD or death due to the underlying cancer, whichever occurs first.

**PROs** included assessments based on health-related quality of life questionnaires (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and its associated head and neck cancer-specific module [H&N35]), and SF-36.

Reviewer's Comments:

1. *Without a comparative arm, this randomized two arms study's hypothesis and analysis should be evaluated as a single arm study. Any time-to-event analysis in the single arm study is uninterpretable and considered descriptive.*

- 2. The algorithm to determine the composite overall response assessment per mRECIST in patients with laBCC was finalized after primary analysis data cut-off and less than two months before 12-month analysis.*

### **3.2.4 Analysis Sets**

**Full analysis set** (FAS or ITT) was defined as all randomized patients who were assigned study treatment irrespective of receiving it. The FAS was the primary analysis population for the efficacy analyses.

**pEAS** was a subset of FAS including patients with laBCC with tumors that were adequately assessed according to mRECIST by MRI or photography or both, and including all patients with mBCC included in the FAS. For patients with laBCC, adequate assessment by photography was defined as those with annotated photographs or those without annotated photographs and documentation of the absence of palpable sub-dermal components outside the margins of the photographed lesion(s). The pEAS was planned to be the primary analysis population for the efficacy analyses.

#### Reviewer's Comments:

- 3. The mRECIST criteria was implemented in protocol amendment 2. The majority of patients with laBCC enrolled prior to this amendment were not evaluable for response according to mRECIST due to lack of baseline MRI or annotated photography. Protocol amendment 4 introduced the primary efficacy analysis subset (pEAS) of the intent to treat population. All laBCC patients in the pEAS were evaluable using mRECIST. The Applicant performed the primary endpoint efficacy analysis for both the pEAS and FAS.*
- 4. In response to the applicant briefing package (submitted on April 3, 2013), FDA stated that the primary analysis of ORR should be performed in the FAS.*
- 5. This reviewer focuses on the evaluation of efficacy results in the FAS.*

### **3.2.5 Sample Size Considerations**

This study was designed to have 80% power to detect an ORR of 30% or higher on any treatment arm relative with a two-sided alpha of 0.003 for 800 mg arm and 0.024 for the 200 mg arm in a 2:1 randomization ratio, assuming 20% or less true ORR on either arm in the pEAS. It was estimated that 150 patients were needed at the final ORR analysis, which could be expected from a total accrual of 210 patients in FAS. If 800 mg arm was terminated, the 200 mg arm would be continued to enroll 100 patients in the pEAS with a two-sided alpha of 0.005.

A high degree of concordance was assumed between the primary endpoint for the interim analysis (ORR per RECIST 1.1 as determined by local investigators) and the primary analysis of the study (ORR per mRECIST in laBCC patients and RECIST 1.1 in mBCC patients as determined by central review, in the pEAS). The same true ORR was used when calculating the probabilities at interim analysis and at primary analysis.

**Table 2 Decision operating characteristics for the ORR Analysis in pEAS**

True ORR	Probability of observing an ORR $\geq$ 30%		
	800 mg arm with 100 patients in pEAS at the primary analysis	200 mg arm with 50 patients in pEAS at the primary analysis	200 mg arm with 100 patients in pEAS at the primary analysis
0.20	0.003	0.024	0.005
0.25	0.085	0.150	0.089
0.30	0.424	0.417	0.405
0.35	0.805	0.703	0.759
0.40	0.961	0.884	0.921
0.45	0.993	0.962	0.971

Source: Protocol Table 9-1

### 3.2.6 Interim Analysis

An interim analysis (IA) for futility purpose on ORR according to RECIST 1.1 per local investigator assessments in the FAS was planned when the first 48 patients randomized completed 16 weeks of treatment or discontinued treatment. Patients who completed 16 weeks of treatment were expected to have at least 2 tumor response evaluations. Futility was based on the interim results (predictive probability  $<$  0.2) on either treatment arm that the observed ORR on respective treatment arm would exceed 30% at the time of primary analysis.

### 3.2.7 Statistical Methodologies

#### Efficacy Analysis Method for ORR

No statistical test of hypothesis comparing the two treatment arms was planned and was not required to observe a statistically significant difference in ORR between the two treatment arms. Treatment with sonidegib would be considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study was 30% or higher. The point estimate of ORR of each arm and its 95% exact CI would be provided as well as the difference in ORR between the two treatment arms. If the lower bounds of the associated 95% CIs of ORR in either treatment arm exceeded 20%, then it would be considered clinical relevance.

Unless both treatment arms were terminated at the interim futility analysis, the primary analysis of study data would be conducted 24 weeks after the last patient is enrolled. A final analysis of safety and efficacy would be performed at 78 weeks (18 months) following enrollment of the last patient.

#### Efficacy Analysis Method for PROs

No formal inferential statistical analysis was planned for PROs. Summary scores were generated by summing the item responses on the questions for each domain in accordance with the respective scoring manual provided by the developers. Time to deterioration for PRO outcomes, defined as the first time from the date of randomization that the patient's score hit a threshold of 10 points or more worsening from their baseline score with no later improvement

above this threshold observed during the course of the study, was analyzed for the summary scores in EORTC QLQ-C30 and H&N35 using Kaplan-Meier methodology.

### 3.2.8 Applicant’s Results and FDA Statistical Reviewer’s Findings / Comments

#### 3.2.8.1 Patient Population and Disposition

A total of 230 patients were randomized in a 2:1 allocation (sonidegib 200 mg: 79; sonidegib 800mg: 152). Table 3 presents the study populations and stratification factors by BCC subtypes and treatment arms.

**Table 3 Patient Population in the Randomized Patients**

	LaBCC		mBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)	Sonidegib 200 mg (N=13)	Sonidegib 800 mg (N=23)
FAS (FAS)	66 (100%)	128 (100%)	13 (100%)	23 (100%)
pEAS	42 (64%)	93 (72%)	13 (100%)	23 (100%)
Untreated	0	1 (<1%)	0	0
Ongoing up to 6/28/13	33 (50%)	37 (29%)	6 (46%)	9 (39%)
Ongoing up to 12/31/13	19 (29%)	25 (20%)	2 (15%)	4 (17%)
Aggressive: Yes	37 (56%)	75 (59%)	0	0
No	29 (44%)	53 (41%)	0	0
Region AUS	2 (3%)	4 (3%)	3 (23%)	3 (13%)
EU	42 (64%)	78 (61%)	3 (23%)	5 (22%)
NA†	22 (33%)	46 (36%)	7 (54%)	15 (65%)

† NA: North America

Reviewer’s Comments:

1. A patient with aggressive laBCC (CLDE225A2201\_1150002) randomized to the sonidegib 800 mg arm did not receive allocated treatment. Due to inconsistent number of total patients in the dataset and CSR, the applicant clarified this patient’s status in the FAS population in the response to the statistical reviewer’s information request dated March 10, 2015.
2. Relative to primary analysis data cut off, the 12-month analysis data cut-off have more patients completed study treatment with more tumor assessments. This reviewer focuses on 12-month analysis results.
3. In the CSR, efficacy analysis results were reported by treatment arms. This review presents efficacy analysis results for the respective laBCC (b) (4) patient populations at both dose levels respectively.

### 3.2.8.2 Baseline and Demographic Characteristics

Table 4 presents the patient baseline demographic characteristics.

**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%)

Reviewer's Comments:

4. Baseline demographic characteristics were similar and balanced.
5. The sample size in the mBCC patient sub-population is small.

Table 5 presents the primary reason for treatment discontinuations in the FAS at 12-months analysis.

**Table 5 Primary Reason for Treatment Discontinuations at 12-months Analysis (FAS)**

	LaBCC		mBCC	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)	Sonidegib 200 mg (N=13)	Sonidegib 800 mg (N=23)
Adverse event (AEs)	17 (26%)	48 (38%)	3 (23%)	4 (17%)
Death	0	4 (3%)	0	1 (4%)
Lost to follow-up	1 (2%)	4 (3%)	0	0
Non-compliance with study treatment	0	2 (2%)	0	2 (9%)
Physician decision	7 (11%)	9 (7%)	0	2 (9%)
Progressive disease	15 (23%)	8 (6%)	8 (62%)	7 (30%)
Protocol violation	0	1 (<1%)	0	0
Withdrawal by subject	7 (11%)	26 (20%)	0	3 (13%)

Reviewer's Comments:

6. Disease progression and AEs were the primary reasons for treatment discontinuation, which were imbalanced in the four reported subpopulation in Table 4.

Table 6 presents the important baseline disease characteristics and prior treatments in the FAS population.

**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%)
Tumor Assessment				
MRI & Photo	49 (74%)	99 (77%)	2 (15%)	2 (9%)
MRI	2 (3%)	12 (9%)	2 (15%)	8 (35%)
Photo	13 (20%)	15 (12%)	3 (23%)	3 (13%)
Missing	2 (3%)	2 (2%)	6 (46%)	10 (43%)
Time from initial diagnosis of primary site to first dose (mo)				
<6	15 (23%)	23 (18%)	1 (8%)	3 (13%)
6 to <12	1 (2%)	6 (5%)	1 (8%)	1 (4%)
12 to <24	3 (5%)	5 (4%)	1 (8%)	2 (9%)
>24	45 (68%)	86 (67%)	9 (69%)	15 (65%)
Unknown	2 (3%)	8 (6%)	1 (8%)	2 (9%)
Time from initial diagnosis to first recurrence/relapse (mo)				
<1	7 (11%)	4 (3%)	0	1 (4%)
1 to <2	2 (3%)	4 (3%)	0	0
2 to <3	1 (2%)	1 (1%)	1 (8%)	1 (4%)
>=3	35 (53%)	72 (56%)	9 (69%)	16 (70%)
Unknown	21 (32%)	47 (37%)	3 (23%)	5 (22%)
Time from most recent relapse to first dose (mo)				
<1	7 (11%)	10 (8%)	2 (15%)	4 (17%)
1 to <2	6 (9%)	13 (10%)	0	5 (22%)
2 to <3	9 (14%)	11 (9%)	2 (15%)	4 (17%)
>=3	25 (38%)	54 (42%)	5 (38%)	5 (22%)
Unknown	19 (29%)	40 (31%)	4 (31%)	5 (22%)

***Reviewer's Comments:***

7. Baseline disease characteristics appear imbalanced across the respective laBCC and mBCC patient populations at both dose levels in the FAS. Hence, this reviewer considers the respective laBCC and mBCC patient populations at both dose levels as individual subgroup.

### 3.2.8.3 ORR Analysis

Table 7 presents the results of ORR based on the central review for the FAS at the 12-month and primary analyses for the respective laBCC (b) (4) patients populations at both treatment arms.

In the 12-month analysis, ORRs were 58% (95% CI: 44.8, 69.7), 44% (95% CI: 35.0, 52.8), (b) (4) for patients with laBCC sonidegib 200 mg, laBCC sonidegib 800 mg, (b) (4).

In the primary (6-month) analysis, ORRs were 47% (95% CI: 34.6, 59.7), 35% (95% CI: 26.9, 44.1), (b) (4) for patients with laBCC in sonidegib 200 mg arm, laBCC in sonidegib 800 mg arm, (b) (4).

**Table 7 ORR Results (FAS)**

	LaBCC	
	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)	

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

#### Reviewer's Comments:

8. For the primary and 12-months analyses, ORR results in laBCC patients assigned to both sonidegib 200 mg and sonidegib 800 mg subgroups met the predefined criteria for point estimates to meet or exceed 30%. The lower bounds of the associated 95% CI also exceeded 20%, the pre-specified threshold for clinical relevance as per the study design operating characteristics.
9. (b) (4)
10. The ORR sensitivity analyses based on pEAS, INV assessment, and RECIST 1.1 in laBCC patients provided similar ORR results for the FAS in the range of 42 % - 67%, 38% - 58%, (b) (4) for patients with laBCC in sonidegib 200 mg

arm, laBCC in sonidegib 800 mg arm, (b) (4)

### 3.2.8.4 DoR Analysis

Table 8 presents the median and its 95% CI for DoR based on the central review for the FAS at the 12-month and primary analyses for the respective laBCC (b) (4) patients populations at both treatment arms.

At the 12-month analysis, median DoR was non-estimable for patients with laBCC receiving treatment with sonidegib 200 mg (82% censoring rate) and 15.7 months (95% CI: NE) for the 800-mg arm. (b) (4)

At the primary analysis, median DoR for patients with laBCC was non-estimable for both treatment arms with 87.1% and 93.3% of responders censored in the analysis in the 200 mg and 800 mg arms, respectively. (b) (4)

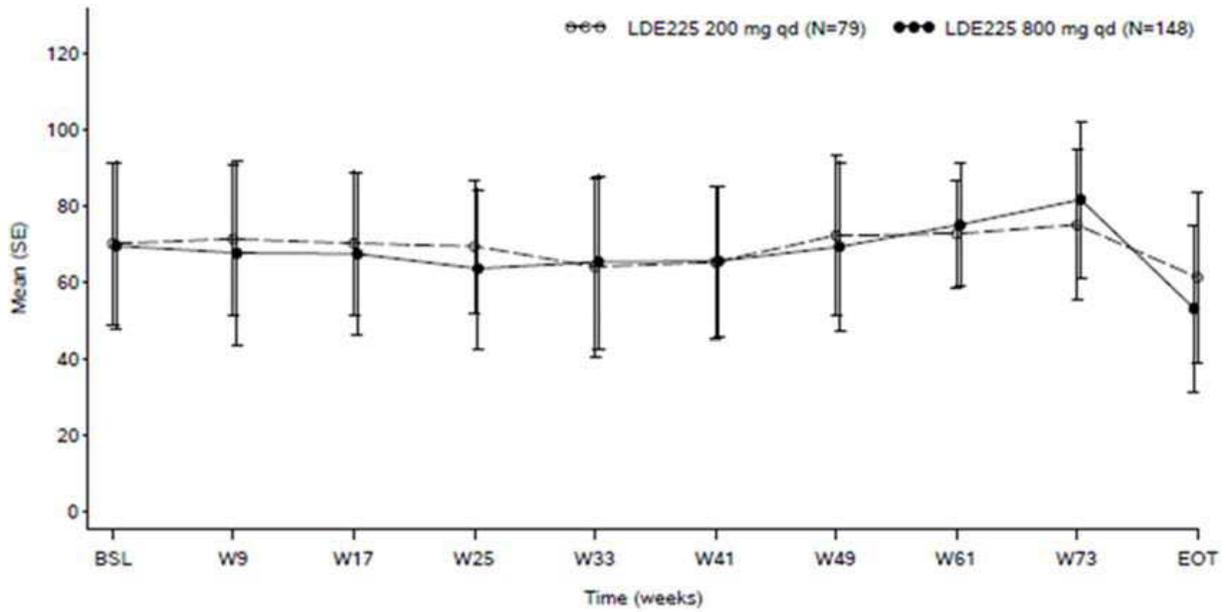
**Table 8 DoR Results**

	LaBCC (b) (4)	
	Sonidegib 200 mg (N=66)	Sonidegib 800 mg (N=128)
12 Months Update		
ORR	38	56
No. of Events	7	11
No. of Censored	31	45
Median (95% CI)	NE	15.7 (NE)
Primary Analysis (6 months)		
ORR	31	45
No. of PD Events	4	3
No. of Censored	27	42
Median (95% CI)	NE	NE

### 3.2.8.5 PROs Analysis

Figures 2-4 present the results of EORTC QLQ-C30. The results of the associated QLQ-H&N35 are presented in Figure 5.

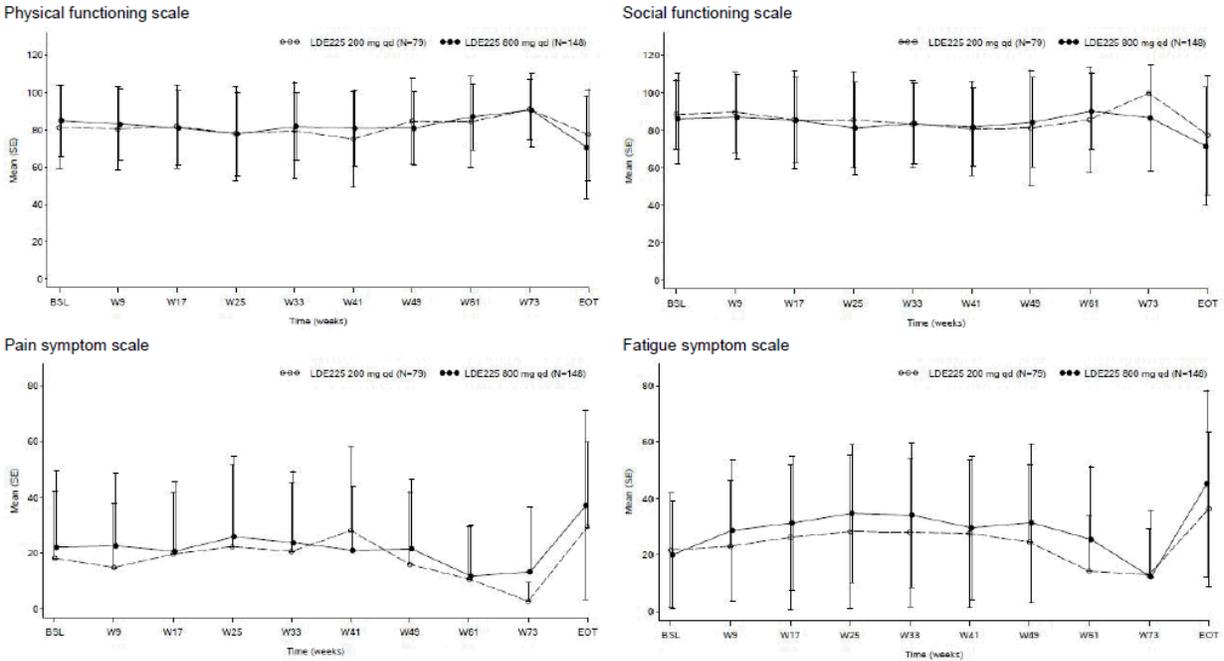
**Figure 2 EORTC QLQ-C30 profiles: QoL or overall health status (FAS)**



Standard error depicted as error bars.

Source: CSR Figure 11-11

**Figure 3 EORTC QLQ-C30 profiles: physical and social functioning and pain and fatigue symptoms (FAS)**

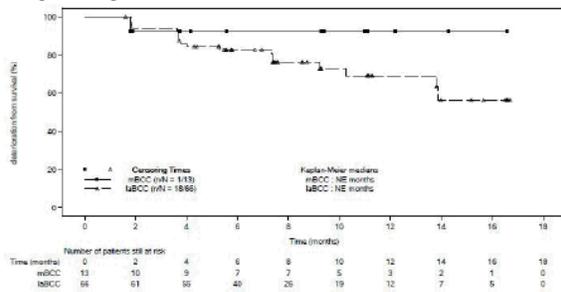


Source: CSR Figure 11-12

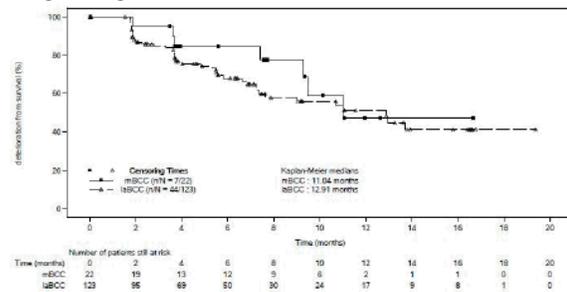
**Figure 4 Kaplan-Meier plots of time to deterioration of EORTC QLQ-C30 scales**

Physical functioning

Sonidegib 200 mg

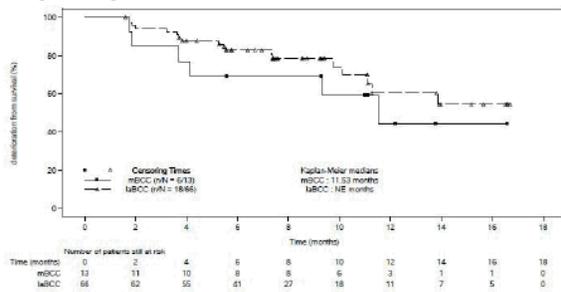


Sonidegib 800 mg

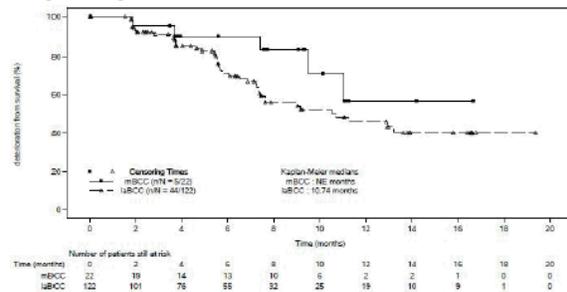


Social functioning

Sonidegib 200 mg



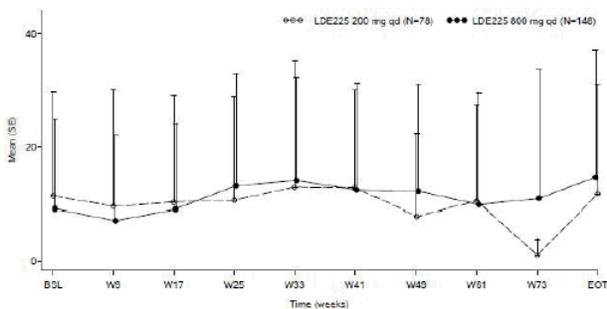
Sonidegib 800 mg



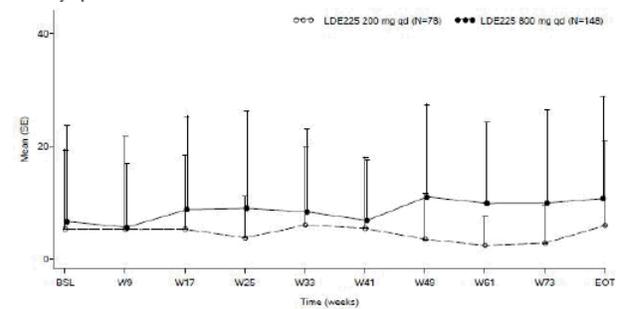
Source: CSR Figure 11-14

**Figure 5 EORTC QLQ-H&N35 profiles: trouble with social contact, and pain and weight loss symptom scales**

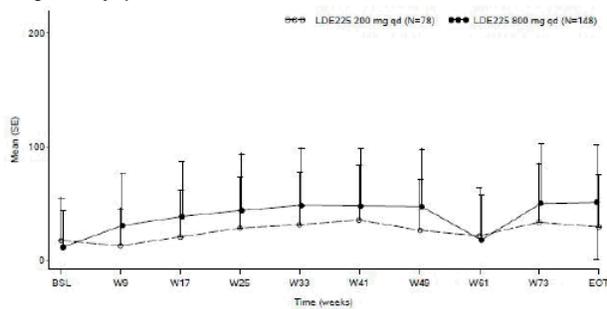
Trouble with social contact



Pain symptom scale



Weight loss symptom item



Source: CSR Figure 11-13

Reviewer's Comments:

11. As part of exploratory endpoints, the review team did not request for PROs results to be reported in the 12-months analysis at the pre-NDA meeting.
12. The PRO results were not included in the proposed label.
13. The applicant only provided PRO dataset and brief summary for the analysis results. Without a define file for PROs data set, analysis data review guide for PRO, SAS programs, and statistical models as well as assumptions in the SAP, this reviewer could not duplicate the applicant PRO results.
14. The SF-36 was ongoing at the time of NDA submission and will be reported in the future.

### 3.3 Evaluation of Safety

Please refer to the clinical review of this application for safety evaluation.

### 3.4 Benefit/Risk Ratio

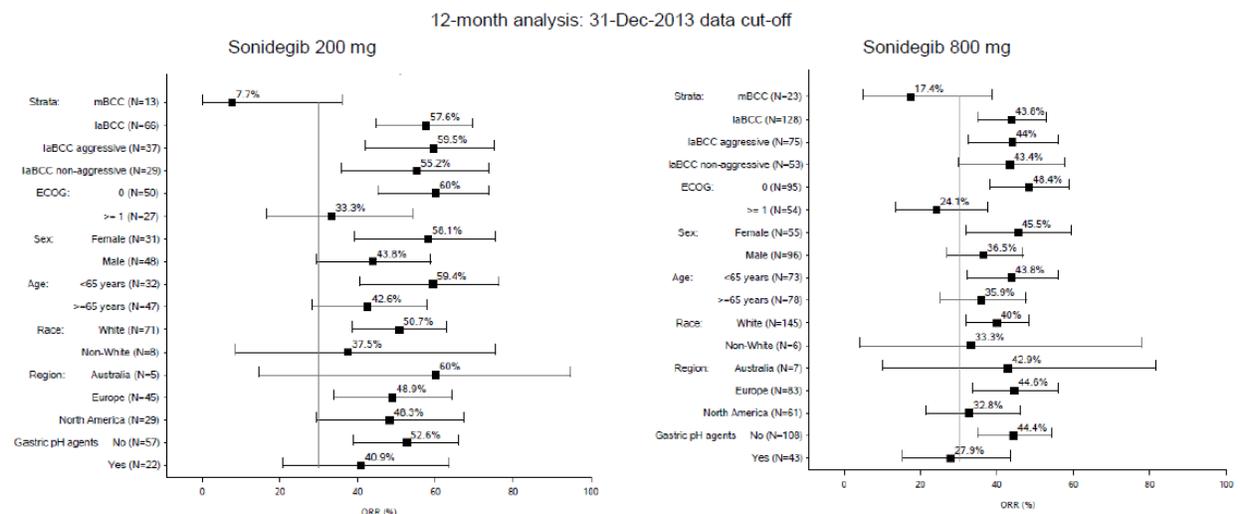
Sonidegib in the laBCC patients met the predefined criteria for point estimates to meet or exceed 30% of ORR. The lower bounds of the associated 95% confidence intervals (CIs) also exceeded 20%, the pre-specified threshold for clinical relevance as per the study design operating characteristics. Whether the submission demonstrated an overall favorable benefit vs. risk profile for sonidegib in the laBCC patients is deferred to the clinical team reviewing this submission.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Country

Figure 6 presents the subgroup analysis of ORR by baseline demographic characteristics for 12-month analysis.

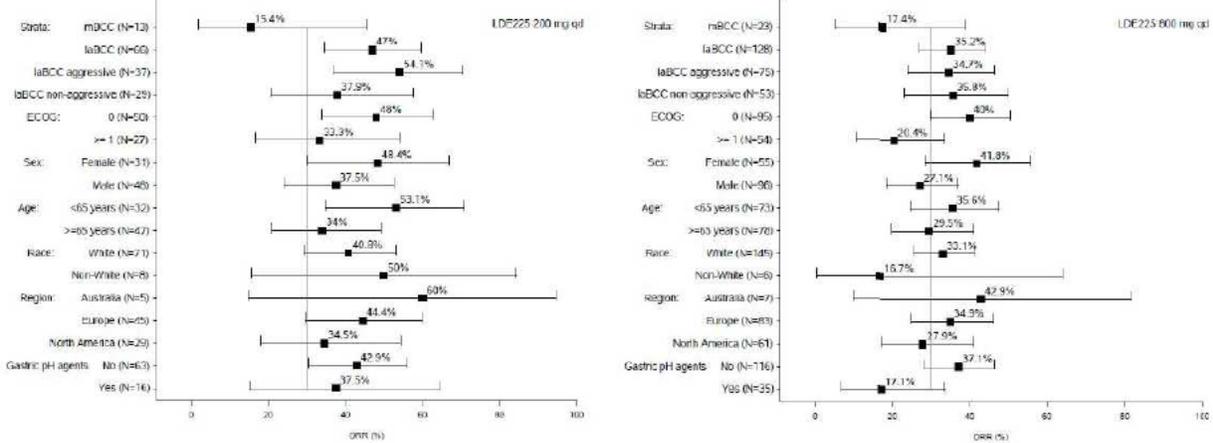
**Figure 6 Demographic Characteristics Subgroup Analyses of ORR per Central Review**



Source: Summary clinical efficacy addendum Figure 2-13

Figure 7 presents the subgroup analysis of ORR by baseline disease characteristics for 12-month analysis.

**Figure 7 Disease Characteristics Subgroup Analyses of ORR per Central Review**



Reviewer's comment:

15. These analyses are exploratory and comparative analyses cannot be conducted. These results should be viewed with caution due to small sample size.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

There are two statistical issues for study A2201. First, major protocol changes on mRECIST for the laBCC patient were submitted after the majority of laBCC patient enrollment. Second, the algorithm to determine the composite overall response assessment in laBCC patients was finalized after primary analysis data cut-off and less than two months before 12-month analysis data cut-off.

### 5.2 Collective Evidence

The data and analyses for laBCC patients followed for at least 12 months in the sonidegib 200 mg QD arm demonstrated an ORR of 58% (95% CI: 45, 70), consisting of 3 (5%) CR and 35 (53%) PR. The sonidegib 800 mg QD arm demonstrated an ORR of 44% (95% CI: 45, 70), consisting of 2 (2%) CR and 54 (42%) PR.



(b) (4)

### 5.3 Conclusions and Recommendations

Without control arm, statistical inference cannot be drawn from this study. All statistical summaries presented are for descriptive purposes only. Furthermore, only data and analyses in the laBCC patients 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) also exceeded 20%, the pre-specified threshold for clinical relevance as per the study design operating characteristics.

Whether sonidegib demonstrated an overall favorable benefit vs. risk profile for laBCC in two treatment arms is deferred to the clinical team reviewing this submission.

#### 5.4 Labeling recommendation

1. The results of ORR analysis in laBCC patients received sonidegib 200mg will be included in the label.
2. [REDACTED] (b) (4). Whether this arm demonstrated an overall favorable benefit vs. risk profile for laBCC is deferred to medical review team reviewing this drug.
3. [REDACTED] (b) (4)

## 6 Reference

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Wong C S M ,Strange R C, Lear J T (2003) Basal cell carcinoma. *BMJ*;327:794–8

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/s/  
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05/28/2015

KUN HE  
05/28/2015

RAJESHWARI SRIDHARA  
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US Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### Biometrics Division: VI

<b>NDA No.:</b>	205266
<b>DATE RECEIVED BY OB:</b>	December 14, 2014
<b>DRUG NAME:</b>	Odmozo (Sonidegib)
<b>INDICATION:</b>	Treatment of patients with locally advanced BCC who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4) [REDACTED]
<b>SPONSOR:</b>	Novartis
<b>REVIEW FINISHED DATE:</b>	January 15, 2015
<b>CMC STATISTICAL REVIEWER:</b>	Zhuang Miao, Ph.D.
<b>PROJECT MANAGER:</b>	Teicher Agosto
<b>CMC REVIEWER:</b>	Ben Stevens

Secondary Reviewer:

Xiaoyu Dong, Ph.D., Mathematical Statistician, DBVI, CDER/OTS/OB/DB VI

Concur:

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Distribution: NDA 205266

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**Stability Analysis of NDA 205266**

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## I. EXECUTIVE SUMMARY

The sponsor's analysis is not appropriate due to the following reasons. (b) (4)

The acceptance criterion (AC) is (b) (4)% for assay. With such a two-sided AC, two-sided 95% confidence limit should be applied based on ICH Q1E guidance. (b) (4)

Based on FDA statistics reviewer's independent analysis on the 18 months long-term stability data of assay with (b) (4) our conclusions are summarized below:

- If there is no significant change at the accelerated storage condition, a shelf life of (b) (4) months for the drug substance with (b) (4) is supported using the pooled data of all three batches as shown in Table 1; however, a shelf life of (b) (4) months for (b) (4) is not supported using by-batch analysis with an estimated shelf life of (b) (4) months as shown in Table 2 ;
- We recommend that the sponsor provides more stability data.

Please note that, the shelf life estimation is performed under the assumption that the time trend beyond 18 months remains the same. The Sponsor's analysis is summarized in Section III. The detailed analyses are provided in Section IV.

**Table 1: Estimated Shelf Life (Months) for (b) (4) based on Long Term Stability Data of Assay using Pooled Data**

Test	Last Obs. Time Point	Acceptance Criterion	Estimated Shelf Life*
Assay	18 Months	(b) (4)%	(b) (4)

\*: shelf life is estimated by the shortest time at which the 95% confidence limits of the mean value intercept with the acceptance criteria using the pooled data.

**Table 2: Estimated Shelf Life (Months) for (b) (4) based on Long Term Stability Data of Assay using By-batch Analysis**

Test	Batch #	Last Obs. Time Point	Acceptance Criterion	Estimated Shelf Life*
Assay	1284036	18	(b) (4)%	(b) (4)
	1284037	18		(b) (4)
	1284038	18		(b) (4)

\*: shelf life is estimated by the shortest time at which the 95% confidence limits of the mean value intercept with the acceptance criteria for each batch separately

## II. INTRODUCTION

On December 14, 2014, Office of New Drug Quality Assessment (ONDQA) requested the CMC statistics team in Office of Biostatistics to review if the sponsor’s “*stability data (proposed (b) (4) supporting a (b) (4) month retest period for the drug substance*” for NDA 205266. The sponsor’s stability data under the long-term storage conditions is provided in Table 3. Based on the above data, FDA statistics reviewer conducted independent stability analyses to estimate the shelf life for the drug substance with (b) (4)

**Table 3: Sponsor’s Stability Data under the Long-term Storage Conditions**

Batch	Package	Initial Month	3 Months	6 Months	9 Months	12 Months	18 Months
1284036	(b) (4)						
1284037							
1284038							
1284036							
1284037							
1284038							

## III. SPONSOR’S STATISTICAL ANALYSES

The sponsor performed poolability test to determine if the stability analysis will be carried out by pooled data or by-batch analysis. Their results are summarized in Table 4 below.

**Table 4: Poolability Testing Results for Stability Data under the Long-term Storage Conditions by the sponsor**

Variables	P-value	Significant Level
Months*Batch*Package	(b) (4)	
Batch		
Months*Batch		
Months*Package		

Based on Table 4, the P-values for Months\*Batch\*Package, Batch, Months\*Batch are larger than the significant level (b) (4) and P-value for Months\*Package is larger than the significant level (b) (4). (b) (4) The estimated intercept and the slope are shown in Table 5, and the estimated shelf life is given in Table 6. Sponsor’s stability plot is provided in Figure 1.

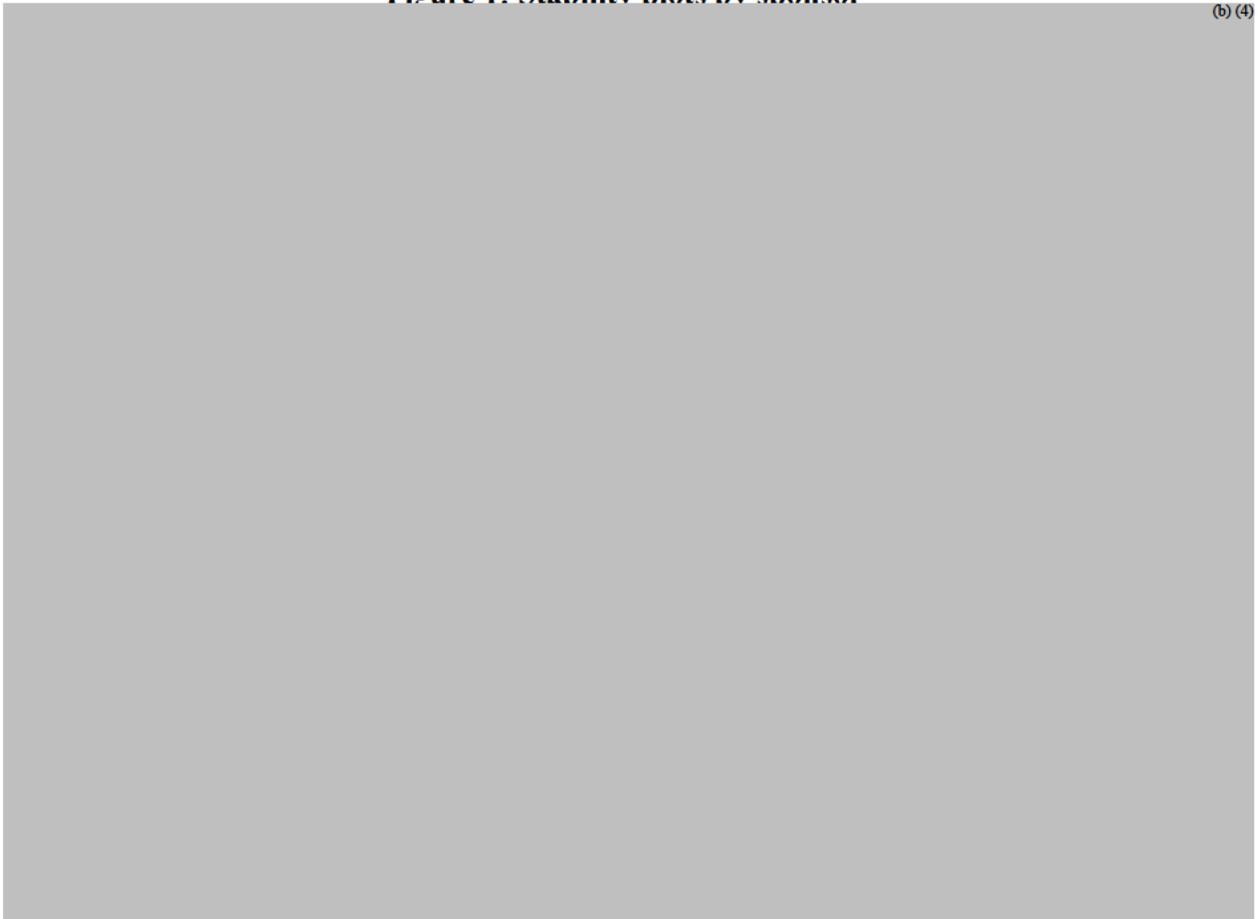
**Table 5: Stability regression model estimation under the Long-term Storage Conditions using pooled data by the sponsor**

BATCH	Parameter	Effect name	Estimate	Standard Error	t Value	Pr> t
1	Intercept	Intercept				(b) (4)
2	Slope	MONTHS				

**Table 6: Shelf life estimation using pooled data by the sponsor**

Batch	Shelf-life (months)
1284036, 1284037, 1284038	(b) (4)

**Figure 1: Stability plots by sponsor**



*Reviewer's Comment on the Sponsor's Analysis:*

1. It is not appropriate to include (b) (4)

2. It is also not appropriate to [REDACTED] (b) (4).  
 [REDACTED] For Assay, the acceptance criterion (AC) is [REDACTED] (b) (4)%.  
 With such a two-sided AC, two-sided 95% confidence limit should be applied based on  
 ICH Q1E guidance. [REDACTED] (b) (4).  
 [REDACTED].

#### IV. FDA STATISTICAL REVIEWER’S ANALYSES

Due to the deficiency of Sponsor’s analysis as pointed out earlier, we performed independent statistical analysis on the long-term stability data of Assay for [REDACTED] (b) (4) only. The shelf life is estimated by the shortest time at which the two-sided 95% confidence limits of the mean value intercept with the acceptance criteria of [REDACTED] (b) (4)%. Both Pooled and By-batch analyses are conducted to evaluate the shelf life in this review.

##### IV.1 Shelf life estimation using pooled data

We conducted the poolability test on [REDACTED] (b) (4) data based on the approach outlined in ICH Q1E guidance. The results are shown in Table 7 below,

**Table 7: Poolability Testing Results for Stability Data of Assay for [REDACTED] (b) (4) under the Long-term Storage Conditions**

Source	DF	Type I SS	Mean Square	F Value	Pr > F
time	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] (b) (4)
batch	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
time*batch	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

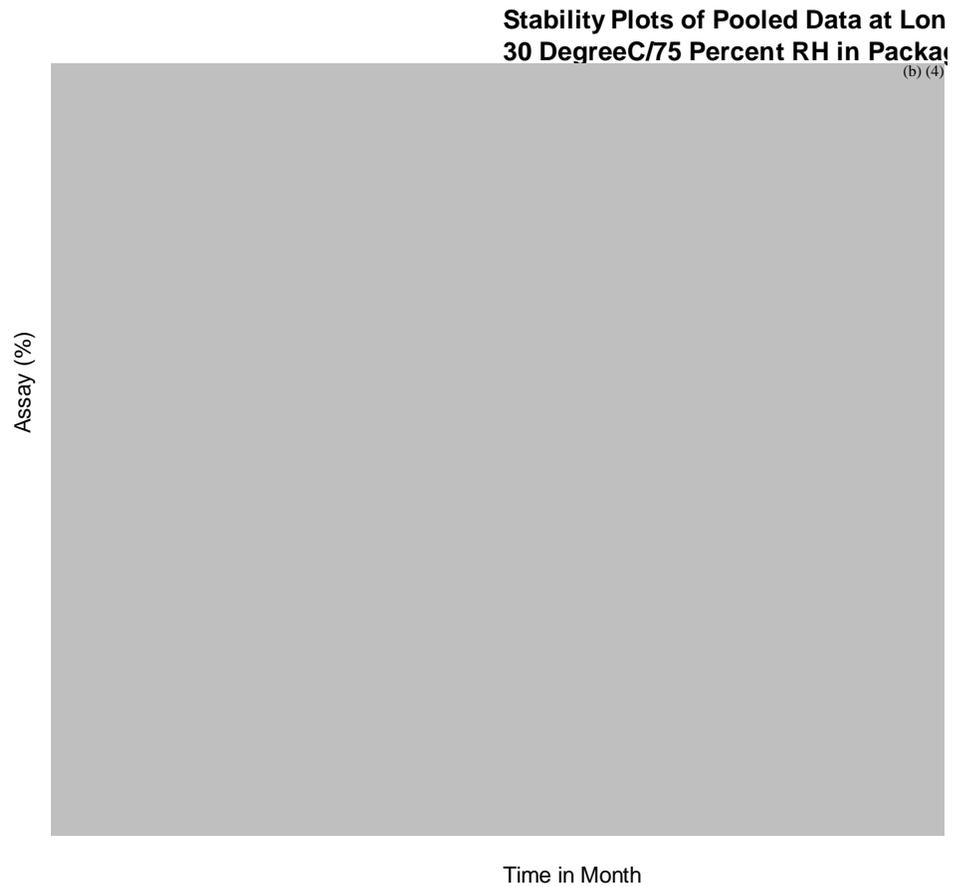
In Table 7, the p-values of batch and the interaction between time and batch are [REDACTED] (b) (4) and [REDACTED] (b) (4), respectively. They are all larger than the [REDACTED] (b) (4). Thus, base on ICH Q1E guidance, the shelf life can be determined by the pooled data of all three batches.

The stability analysis results from the pooled data of batches 1284036, 1284037 and 1284038 for [REDACTED] (b) (4) are summarized in Table 8. The predicted mean values, 95% confidence limits of mean, and the estimated shelf life are summarized in Figure 2 and Table 9. In Figure 2, the predicted mean values obtained by linear regression are shown in solid line and the corresponding two-sided 95% confidence limits of the mean values are shown in dashed lines. The specified control limits are [REDACTED] (b) (4)% and [REDACTED] (b) (4)%. As Figure 2 and Table 9 show, the lower and upper 95% confidence limits are within the acceptance criteria (AC) of [REDACTED] (b) (4)% at [REDACTED] (b) (4) months. Although the confidence limits intercept with the AC at [REDACTED] (b) (4) months, the shelf life can only be extrapolated up to 12 months beyond the last observed months if there are no significant changes

**Stability Analysis of NDA 205266**

under the accelerated conditions based on ICH Q1E. Thus, the stability analysis supports a shelf life of (b) (4) months for (b) (4) using the pooled data.

**Figure 2: Stability Plots of Assay for (b) (4) under the Long-term Conditions of the pooled data APPEARS THIS WAY ON ORIGINAL**



**Table 8: Stability regression model estimation for (b) (4) under the Long-term Storage Conditions using pooled data**

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr >  t	95% Confidence Limits
Intercept	Intercept						
time	time						

**Table 9: Stability Analysis Results of Assay (%) at (b) (4) Months (LCL = Lower Confidence Limit of Mean, UCL = Upper Confidence Limit of Mean, Est. = Estimated)**

Batch	Acceptance Criterion	At (b) (4) Months			Est. Shelf Life
		Prediction	95% LCL	95% UCL	
1284036, 1284037, 1284038					(b) (4)

**IV.2 Shelf life estimation using by-batch analysis**

We also notice that the assay value at (b) (4) months for Batch 1284038 is (b) (4)%, which is much higher than other assay values. In order to assess the worst case scenario, we also performed by-batch analysis. The estimated slope and its p-value from each batch are given in Table 10. The predicted mean values, 95% two-sided confidence limits of mean and the estimated shelf life are summarized in Table 11 and Figures 3 – 5 for each batch. From the analysis results, we can see that the shortest shelf life among the three batches is only (b) (4) months. Thus a shelf life of (b) (4) months is not supported by the by-batch analysis.

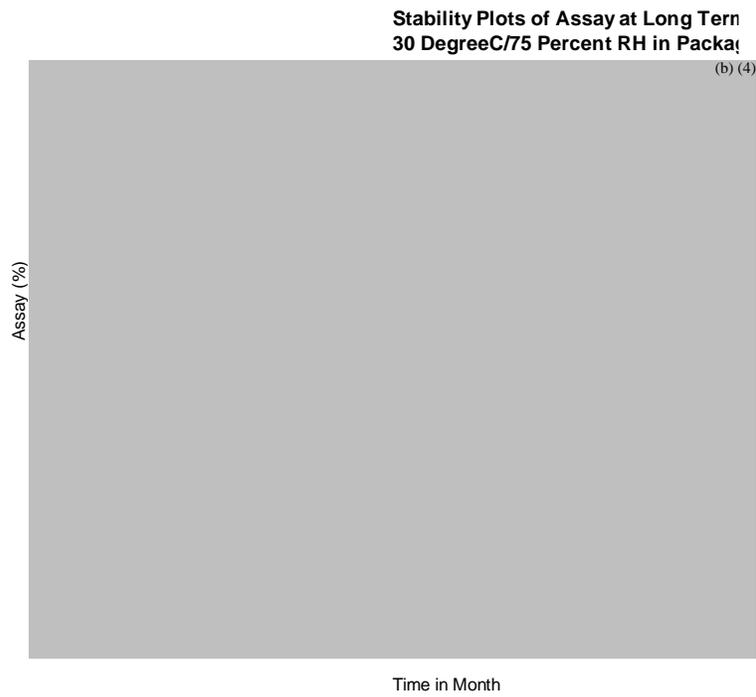
**Table 10: Stability regression model estimations for NDA 205266 for (b) (4) under the Long-term Storage Conditions using by-batch analysis**

Batch	Estimated Slope	P-value
1284036		(b) (4)
1284037		
1284038		

**Table 11: By-batch Stability Analysis Results of Assay (%) at (b) (4) Months (LCL = Lower Confidence Limit of Mean, UCL = Upper Confidence Limit of Mean, Est. = Estimated) for Packaging K**

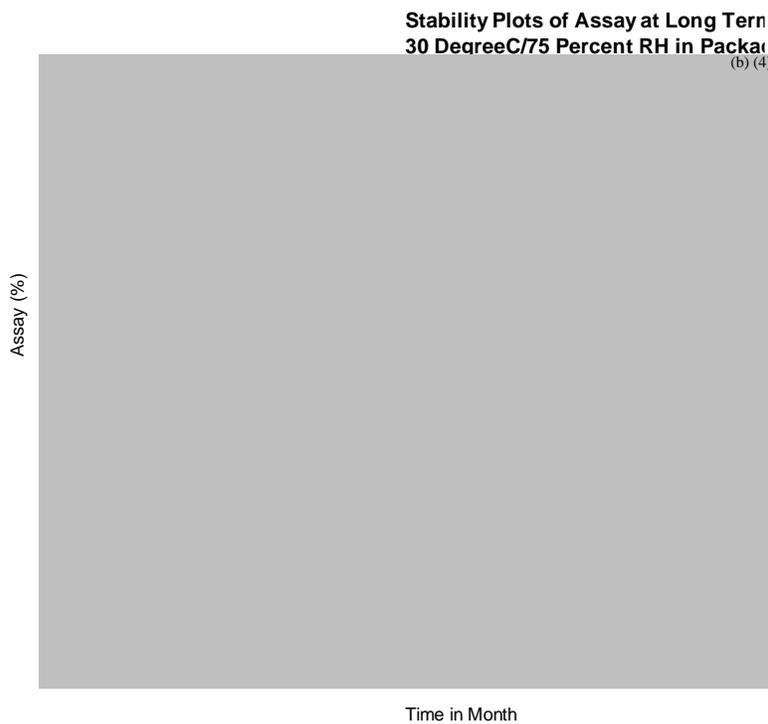
Batch	Acceptance Criterion	At (b) (4) Months			Est. Shelf Life
		Prediction	95% LCL	95% UCL	
1284036					(b) (4)
1284037	(b) (4) %				
1284038					

**Figure 3: Stability Plot of Assay for (b) (4) under the Long-term Conditions of batch 1284036**



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**Figure 4: Stability Plot of Assay for (b) (4) under the Long-term Conditions of Batch 1284037**



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Figure 5: Stability Plot of Assay for (b) (4) under the Long-term Conditions of Batch 1284038



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/s/  
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ZHUANG MIAO  
01/15/2015

XIAOYU DONG  
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01/16/2015

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 205266**

**Applicant: Novartis**

**Stamp Date: 9/26/2014**

**Drug Name: Odomzo**

**NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes**

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

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

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.	√			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

File name: Statistics Filing Checklist for NDA 205266

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/s/  
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HUANYU CHEN  
11/24/2014

KUN HE  
11/24/2014