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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 – ADDENDUM

BLA/Serial Number #: NDA 205353 / 00

Supplement #: Original New Drug Application

Drug Name: Panobinostat (LBH589, Farydak[®]) Capsules

Indication(s): In combination with bortezomib and dexamethasone for the treatment of patients with previously treated multiple myeloma

Applicant: Novartis Pharmaceuticals

Date(s): Submission date: 22 March 2014
PDUFA date: 24 November 2014

Review Priority: Priority

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Keywords: multiple myeloma, sensitivity analyses, benefit/risk assessment

Statistical Review Addendum

1. Introduction

On November 06 of 2014, an Oncologic Drug Advisory Committee (ODAC) meeting was held to discuss the benefit/risk profile of panobinostat (Farydak[®]) in combination with bortezomib and dexamethasone for the treatment of patients with relapsed multiple myeloma. The discussion on panobinostat focused on the results of the pivotal trial D2308, which is a randomized double-blind trial evaluating the efficacy and safety of panobinostat as an add-on therapy to bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. Trial D2308 showed an improvement in median progression-free survival (PFS) of 3.9 months as assessed by investigators as the primary endpoint analysis. However, large amounts of censored data limited the Agency's confidence in the primary analysis results. Sensitivity analyses for PFS submitted in the NDA application by Applicant showed much shorter improvement in median PFS by panobinostat. In addition, the patients on Trial D2308 panobinostat treatment group had twice the incidence of on-treatment deaths not due to disease progression – 7 percent vs. 3.5 percent – and a high incidence of myelosuppression, hemorrhage, infection, and cardiac toxicity. The high amount of observed toxicity combined with unreliable efficacy results make the benefit/risk assessment of panobinostat in combination with bortezomib and dexamethasone challenging.

In preparation for the ODAC meeting, the statistical reviewer performed evaluations on the Applicant's additional analyses, as well as conducted the Agency's own additional analyses to support the FDA presentation. This addendum is a repository of those evaluations and analyses that were not included in the original statistical review of panobinostat. Please refer to the original statistical review, dated August 26 of 2014, for all other details.

2. Applicant Analyses between the NDA Submission and the ODAC Meeting

Between the initial NDA submission and the ODAC meeting, the Applicant conducted two major analyses: (1) one additional overall survival (OS) interim analysis; and (2) one additional sensitivity analysis of PFS based on Independent Review Committee (IRC) assessment. The additional OS interim analysis was pre-planned and incorporated into protocol amendment #6 in September 2014 in order to generate a more updated OS analysis for the ODAC meeting. The additional sensitivity analysis of IRC-determined PFS, which required a confirmation of disease progression by at least one repeat assessment, *is not pre-planned*. The Applicant submitted the additional IRC-PFS analysis on October 7 of 2014, with an intention to revise and replace their original IRC-PFS analysis in the Applicant Briefing Document.

2.1 Planned additional OS interim analysis of Trial D2308

The additional planned OS interim analysis was conducted after 359 (86.5%) of the target 415 OS events required for the final OS analysis have been observed. The cut-off date for this analysis was August 18, 2014. OS was not statistically significantly different between the two

treatment groups at this interim analysis, as shown in Table 1 and Figure 1, with an estimated hazard ratio of 0.87 and a log-rank p-value of 0.1783. The estimated median OS was 38.2 months and 35.4 months for the panobinostat arm and the placebo arm, respectively.

In total, 409 patients were censored in this analysis:

- 168 patients in the panobinostat group and 151 patients in the placebo group were alive and being followed-up for survival
- 39 patients in the panobinostat group and 28 patients in the placebo group withdrew consent to survival follow-up. The median time from randomization to the last contact in these patients was 3.1 months for the panobinostat group and 4.9 months for the placebo group.
- 11 patients in the panobinostat group and 12 patients in the placebo group were lost to follow-up as recorded by the investigator

Among the patients that were alive and being followed for survival, the follow-up time (time from randomization to the last contact) was comparable between the two treatment groups.

Table 1: Analysis of Overall Survival as of August 18, 2014 (Trial D2308)

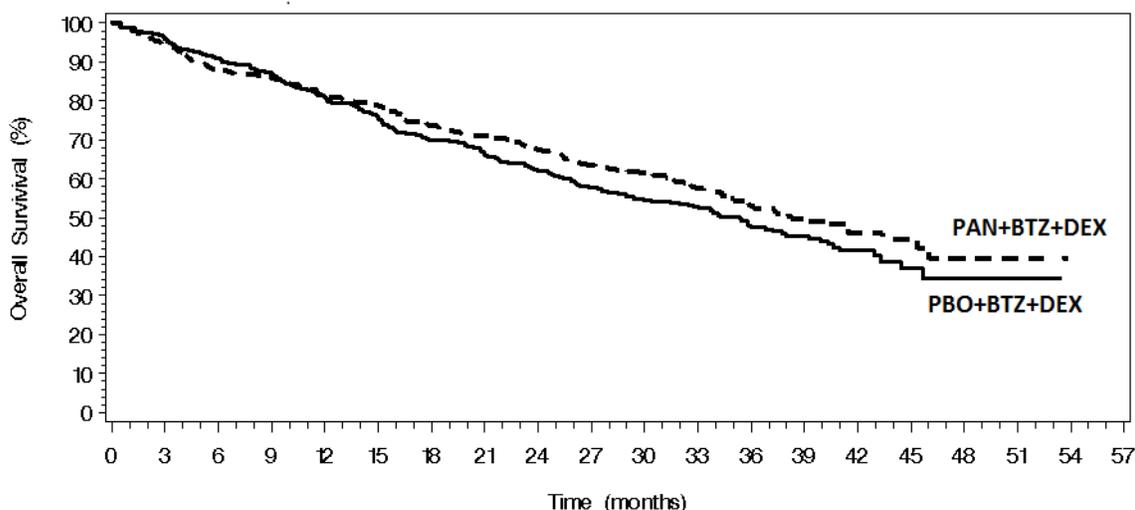
	PAN + BTZ + DEX N = 387		PBO + BTZ + DEX N = 381	
Events / Censored, n (%)	169 (43.7%) / 218 (56.3%)		190 (49.9%) / 191 (50.1%)	
Reason for censoring	n	Median follow-up	n	Median follow-up
Alive	168	36.3 months	151	37.4 months
Withdrawal of consent	39	3.1 months	28	4.9 months
Lost to follow-up	11	27.0 months	12	25.3 months
Median overall survival (95% CI)	38.2 (34.6, 45.4) months		35.4 (29.3, 39.9) months	
Hazard ratio¹ (95% CI)	0.87 (0.70, 1.07)			
p-value²	0.1783			

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo; CI = confidence interval; NE = not estimable

¹For PAN+BTZ+DEX over PBO+BTZ+DEX, estimated using Cox model stratified by randomization factors

²Calculated based on log-rank test, stratified by the randomization factors

Figure 1: Kaplan-Meier plot of OS interim analysis as of August 18, 2014 (Trial D2308)



PAN+BTZ+DEX	387	334	308	286	268	244	228	206	163	101	59	26	10	2	0
PBO+BTZ+DEX	381	345	315	284	251	238	213	187	152	101	60	24	8	3	0

2.2 Revised IRC-determined PFS analysis

During the preparation for the advisory committee meeting, the Applicant submitted a revised IRC PFS analysis. Per Applicant, this revised analysis was based on IRC assessment considering progression, or relapsed from complete response, if confirmed by at least one repeat assessment based on M-protein. Table 2 shows results from this revised analysis in comparison with the original IRC PFS analysis (as submitted in the NDA application). The magnitude of improvement in median PFS by panobinostat increased from 2.2 months to 3.7 months in the revised analysis; however, the amount of censoring increased dramatically as a result of lack of confirmation for IRC-determined progressive disease events.

Table 2: IRC PFS Analyses – Progressive disease without or with confirmation (Trial D2308)

		PAN + BD N = 387	PBO + BD N = 381	Δ in median PFS	Hazard Ratio (95% CI)	Censoring % PAN vs. PBO
Original (without confirmation)	Events	241	283	2.2 months	0.69 (0.58, 0.83)	38% vs. 26%
	Censored	146	98			
Revised (with confirmation)	Events	201	254	3.7 months	0.63 (0.52, 0.76)	48% vs. 33%
	Censored	186	127			

3. FDA Analyses for ODAC Meeting

Evaluations were performed to assess the likelihood of having a positive OS result at the protocol specified final analysis, and to assess any critical issue with the Applicant's revised IRC

PFS analysis. In addition, to consider both efficacy and treatment toxicity together, additional efficacy + safety exploratory analyses were conducted by the Agency.

3.1 Projected Likelihood for a Statistically Significant Final OS Result

This reviewer calculated the conditional power to evaluate how likely Trial D2308 is to demonstrate an overall survival benefit for panobinostat at the protocol-specified final OS analysis. The conditional power is the probability that the final OS result will be statistically significant, given the data observed thus far and a specific assumption about the pattern of the data to be observed in the remainder of the study.

Based on the observed hazard ratio of 0.87 in OS data so far, if it is assumed that the trend of event occurrence continues, the calculated conditional power would be only 7%. If it is assumed that an event occurrence trend towards the protocol-specified hazard ratio of 0.73 for events after the last interim analysis, then the calculated conditional power would be 20%. Thus, the likelihood of demonstrating a survival benefit for panobinostat at the final analysis is not expected to be high given the observed data thus far.

3.2 Critical Issue with the Applicant’s Revised IRC PFS Analysis

As shown in Table 2, the Applicant’s revised IRC PFS analysis increased the amount of censoring for requiring confirmation in progressive disease (PD) events. This revision led to an estimated median improvement in PFS and percent of censoring by IRC assessment close to the ones by investigators assessment (median improvement in PFS: investigators 3.9 months, revised IRC 3.7 months; percent of censoring: investigators 47% versus 32% for panobinostat arm versus placebo arm, revised IRC 48% versus 33% for panobinostat arm versus placebo arm).

This reviewer compared the revised IRC PFS data with the original IRC PFS data, and identified as high as 24.6% of the original IRC-determined PD event observations were changed. Table 3 shows the amount of changes made in this revised analysis to be disproportional between the two study arms, with 30.7% of the PD event data were changed in the panobinostat arm versus 19.7% of the PD event data were changed in the placebo arm.

Table 3: Changes to the original IRC PD events in Applicant’s revised IRC-PFS analysis

	Original PD events panobinostat arm N = 218	Original PD events placebo arm N = 269	Original PD events total N = 487
PD event data changed	67 (30.7%)	53 (19.7%)	120 (24.6%)
Changed to censored	40 (18.3%)	30 (11.2%)	70 (14.4%)
Changed to later time	27 (12.4%)	23 (8.6%)	50 (10.3%)

The changes to censor PD events for lacking a confirmation in the next visit were likely to be informative, because some patients did not have data available from the next visit to confirm their PD status due to withdrawal of consent to disease follow-up. The percentage of patients that were censored due to withdrawal of consent in the revised IRC-PFS analysis was 18.3% versus 10.5% for the panobinostat arm versus the placebo arm (71 patients in the panobinostat

arm and 40 patients in the placebo arm, respectively, according to data provided by the Applicant at the Late Cycle Meeting on October 23, 2014). In comparison, the percentage of patients that were censored due to withdrawal of consent in the investigator-assessed PFS analysis was 19.1% versus 11.8% for the panobinostat arm versus the placebo arm (74 patients in the panobinostat arm and 45 patients in the placebo arm, respectively, according to data in the NDA submission). The revised IRC-PFS analysis increased the amount of censoring and some of the censoring are likely to be informative, and therefore cannot be considered as a more valid analysis than the original IRC-PFS analysis in the NDA submission.

3.3 Efficacy + Safety Exploratory Analyses

Table 4 gives the number of patients that had an adverse event (AE) that led to discontinuation of study treatment. Overall, 36% (n=139) of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20% of patients (n=76) in the control arm.

Table 4: AE as a reason for discontinuation of therapy (Trial D2308)

Last treatment cycle	PAN+BTZ+DEX treatment group, as treated (N=386)			PBO+BTZ+DEX treatment group, as treated (N=372)		
	Discontinued from treatment due to AEs (n = 139)	%	Cumulative %	Discontinued from treatment due to AEs (n = 76)	%	Cumulative %
1	14	3.6	3.6	7	1.9	1.9
2	20	5.2	8.8	13	3.5	5.4
3	21	5.4	14.2	11	3.0	8.3
4	19	4.9	19.2	13	3.5	11.8
5	16	4.1	23.3	8	2.2	14.0
6	14	3.6	26.9	5	1.3	15.3
7	7	1.8	28.8	10	2.7	18.0
8	10	2.6	31.3	3	0.8	18.8
9	9	2.3	33.7	2	0.5	19.4
10	4	1.0	34.7	1	0.3	19.6
11	1	0.3	35.0	2	0.5	20.2
12	4	1.0	36.0	1	0.3	20.4

Given the significant number of treatment discontinuations due to adverse events, this reviewer performed two exploratory analyses that incorporated both PFS and treatment toxicity information to provide overall assessments about the treatment risk-benefit profile. One exploratory analysis was a time to treatment failure analysis, which considered death, disease progression as assessed by investigators, and any premature treatment discontinuations as events. The other exploratory analysis was a PFS + toxicity analysis with death, disease progression as assessed by investigators, and any premature treatment discontinuations *due to adverse event* as events. These exploratory analyses were conducted in the safety population as treated.

Results from the exploratory analyses are shown in Table 5. The time to treatment failure analysis resulted in a median time to progression of 6.2 months in the panobinostat and placebo arms. There was no difference between the arms with regards to the median time to event or the hazard ratio. The second exploratory analysis resulted in a median time to progression of 6.8

months in the panobinostat arm and 6.9 months in the placebo arm. Figure 2 and Figure 3 corresponds to the first and the second exploratory analyses, respectively. As seen in the graphs, the two curves overlapped and there was no apparent difference between the two treatment arms.

Table 5: Efficacy + Toxicity exploratory analyses (Trial D2308, as treated population)

	Panobinostat + BD (N=386)	Placebo + BD (N=372)
Time to treatment failure analysis		
Events / Censored, n (%)	268 (69%) / 118 (31%)	294 (79%) / 78 (21%)
Median time to event (95% CI)	6.2 (5.2, 7.4) months	6.2 (5.1, 7.2) months
Hazard ratio (95% CI)	0.89 (0.75, 1.05)	
PFS efficacy + toxicity analysis		
Events / Censored, n (%)	255 (66%) / 131 (34%)	279 (75%) / 93 (25%)
Median time to event (95% CI)	6.8 (5.7, 8.1) months	6.9 (5.6, 7.8) months
Hazard ratio (95% CI)	0.87 (0.73, 1.03)	

Figure 2: Kaplan-Meier plot of time to treatment failure analysis (Trial D2308, as treated population)

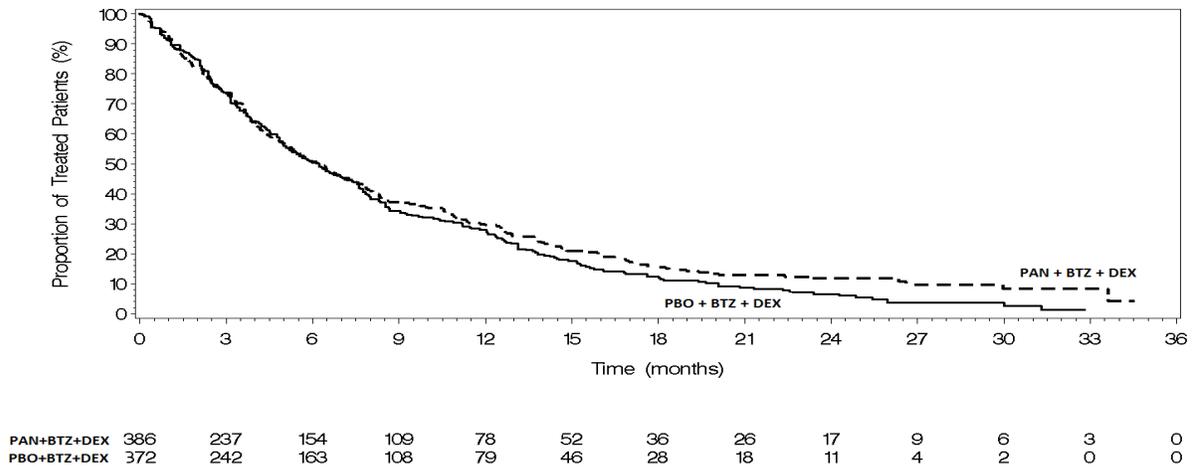
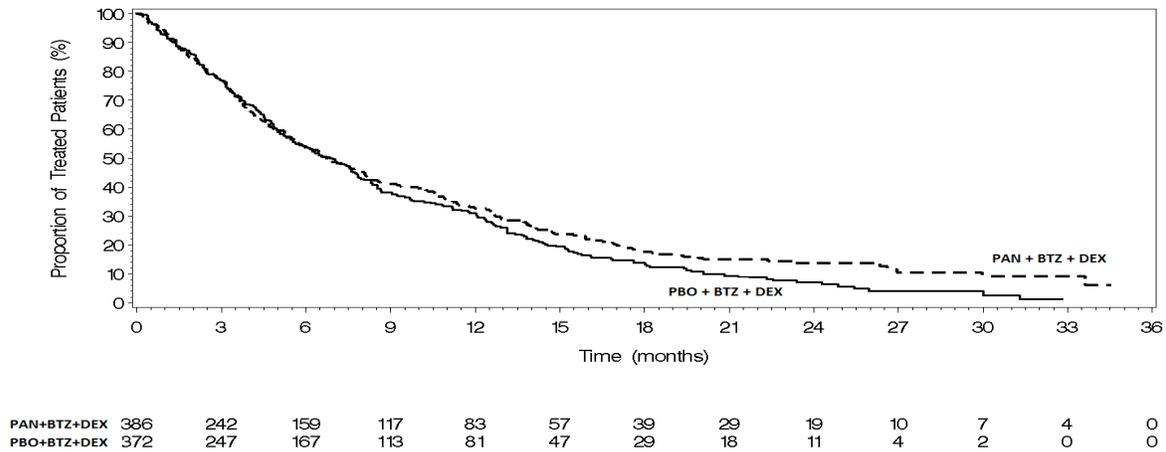


Figure 3: Kaplan-Meier plot of PFS + toxicity analysis (Trial D2308, as treated population)



These exploratory analyses are conducted to allow for further clarification of the safety profile of panobinostat. Specifically, they offer the opportunity to look at both efficacy and safety together. In resultant analyses, the hazard ratios and medians are not different and the curves cross, primarily due to early toxicity, suggesting that the efficacy of the addition of panobinostat to bortezomib and dexamethasone may be offset by the toxicity.

4. ODAC Vote and Discussion

The ODAC was asked to vote: “Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?” The results of the vote were: 2 Yes, 5 No, and 0 Abstain. The major concerns with panobinostat of the ODAC were: (1) treatment in-tolerability and subsequent therapy options, particularly the issue of potential treatment withdrawals and on-treatment deaths due to adverse events; (2) uncertainty about treatment benefit: the observed improvement in PFS was marginal and did not transfer into a survival or quality of life benefit in the study patients.

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/s/

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number #: NDA 205353 / 00

Supplement #: Original New Drug Application

Drug Name: Panobinostat (LBH589, Farydak[®]) Capsules

Indication(s): In combination with bortezomib and dexamethasone for the treatment of patients with previously treated multiple myeloma

Applicant: Novartis Pharmaceuticals

Date(s): Submission date: 22 March 2014
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Biometrics Division: Division of Biometrics 5 (HFD-711)

Statistical Reviewer: Chia-Wen Ko, Ph.D.

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Medical Division: Division of Hematology Products

Clinical Team: Barry Miller, R.N., M.S. (Primary reviewer for efficacy)
Adam George, M.D. (Primary reviewer for safety)
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Project Manager: Diane Hanner

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1 EXECUTIVE SUMMARY

This is an initial New Drug Application (NDA) seeking the approval of oral panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with previously treated multiple myeloma.

The pivotal study D2308 supporting this application is a phase 3, randomized, double-blind, placebo-controlled study in 768 patients with relapsed multiple myeloma to assess the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone (n=387) compared with placebo in combination with bortezomib and dexamethasone (n=381). Patient randomization was stratified by number of prior lines of anti-myeloma therapy (1 vs. 2 or 3) and prior use of bortezomib (yes vs. no). The primary efficacy endpoint of the study was progression-free survival as assessed by investigators based on modified European Bone Marrow Transplant criteria. Overall survival was the key secondary endpoint with a pre-specified hierarchical testing procedure. A total of 758 patients received a study treatment.

The table below summarizes the key efficacy and safety results from the pivotal study. These results did not provide a definitely positive benefit-risk conclusion for the treatment of panobinostat in combination with bortezomib and dexamethasone. They suggested that the addition of panobinostat may improve efficacy outcomes. But on the other hand, they also showed that panobinostat treated patients had experienced adverse outcomes more frequently as compared to patients who did not receive panobinostat. Particularly concerning are the much smaller estimated improvement in progression-free survival according to an independent review committee, and the imbalance in on-treatment death between the study arms.

	PAN +BTZ+DEX	PBO +BTZ+DEX	Δ	Hazard ratio (95% CI)	P-value
Efficacy outcome	n = 387	n = 381			
Median PFS by INV in month	12.0	8.1	3.9	0.63 (0.52, 0.76)	< 0.0001
Median PFS by IRC in month	9.9	7.7	2.2	0.69 (0.58, 0.83)	< 0.0001
Median OS in month	33.6	30.4	3.2	0.87 (0.69, 1.10)	0.2586
Safety outcome	n = 386	n = 372			
On-treatment death	7.8%	4.8%	3.0 %		
Adverse events (AEs) of grade 3/4	95.1%	82.5%	12.6%		
Serious adverse events	59.6%	41.7%	17.9%		
AEs leading to treatment discontinuation	36.0%	20.4%	15.6%		
AEs leading to dose change/interruption	88.6%	75.5%	13.1%		

P-value calculated for the efficacy outcomes only based on the log-rank test, stratified by the randomization factors PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo; CI = confidence interval
PFS = progression-free survival; OS = overall survival; INV = investigator; IRC = independent review committee

This reviewer does not have a definite recommendation on whether or not this product should be approved for the proposed indication based on data submitted for this application.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

Panobinostat (Farydak[®]) is a pan-deacetylase inhibitor. The proposed indication is: “FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.”

Disease Overview

Multiple myeloma (MM) is a malignant proliferation of plasma cells. The diagnosis of MM is based on the International Myeloma Working Group 2003 definitions considering monoclonal immunoglobulin, bone marrow plasma cells, and disease-related organ or tissue impairment. Newly diagnosed patients receive bortezomib-based regimen, followed by stem cell transplant if eligible for transplantation. Relapsed or refractory patients typically receive salvage therapy until relapse or toxicity. The Applicant studies panobinostat in combination with bortezomib because of observation from preclinical studies that panobinostat may synergize with bortezomib to inhibit both the aggresome and proteasome pathways of the disease.

Clinical Studies

Table 1 summarizes the Applicant’s clinical studies supporting this application. The main study D2308 is a randomized double-blind Phase 3 study having panobinostat in combination with bortezomib and dexamethasone (PAN+BTZ+DEX) compared with placebo in combination with bortezomib and dexamethasone (PBO+BTZ+DEX) in 768 patients with previously treated MM. The supportive studies include a single-arm dose escalation/expansion study and a Phase 2 single-arm study. The supporting studies will not be discussed in this review, because they are not randomized studies to allow for assessment of the contribution from panobinostat.

Table 1: Overview of clinical studies

	Pivotal Study	Supportive Study	
	D2308	B2207	DUS71
No. of patients enrolled	768 (PAN+BTZ+DEX 387, PBO+BTZ+DEX 381)	62 (15 in dose expansion phase)	55
Study location	194 study centers in 34 countries, including US	19 study centers in 6 countries, including US	12 study centers in US
Phase of study	3	1b	2
Study population	Patients with relapsed or refractory MM	Patients with relapsed or refractory MM	Patients with relapsed and BTZ-refractory MM
Study design	randomized, double-blind, placebo-controlled	non-randomized, dose escalation/expansion	Open-label single-arm
Main eligibility criteria	Relapsed and not primary refractory to BTZ; $\geq 1 \leq 3$ prior lines of therapy	≥ 1 prior line of therapy	≥ 2 prior lines of therapy
Dosing regimen	Every 21-day cycle PAN: 20 mg 3 days a week for 2 weeks BTZ: Bolus iv, 1.3 mg/m ² twice a week for 2 weeks DEX: 20 mg oral on D1 and after each BTZ injection four times a week for 2 weeks		
Duration of treatment	Maximum of 48 weeks	24 weeks (8 cycles)	Maximum of 48 weeks
Primary endpoint	Progression-free survival	Maximum tolerable dose	Overall response rate

2.2 Data Sources

Material reviewed for this application: protocol, statistical analysis plan, study report, and submitted datasets for the pivotal study D2308.

Reviewed data were provided electronically with the standard analysis data formats. SAS programs used to create the primary endpoint and key efficacy analyses for the pivotal study were submitted in this application. Study D2308 datasets for this application are located at: <\\cdsesub1\evsprod\NDA205353\0000\m5\datasets\lbh589d2308>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the pivotal study D2308 were provided electronically with standard formats. Documentations on datasets and programming for the derivation of key study endpoints and results were included with sufficient details for verification.

3.2 Evaluation of Efficacy

This section shows Study D2308 key efficacy results with Reviewer's comments and evaluations. The key efficacy results shown in this section have been verified by the Reviewer.

3.2.1 Study Design and Endpoints

The pivotal study supporting this application is Study D2308. Study D2308 was a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to assess the efficacy and safety of panobinostat (PAN) + bortezomib (BTZ) + dexamethasone (DEX) compared with placebo (PBO) + bortezomib (BTZ) + dexamethasone (DEX) in patients with previously treated MM. The study enrolled a total of 768 patients, randomized in a 1:1 ratio to receive panobinostat at 20 mg (n=387) or placebo (n=381) plus bortezomib and dexamethasone. The randomization was stratified by number of prior lines of anti-myeloma therapy (1 vs. 2 or 3) and prior use of bortezomib (yes vs. no). The maximum duration of treatment was 48 weeks, divided into two treatment phases. In treatment phase 1, patients received study treatment until completion of Week 24 (eight 21-day cycles). Patients with clinical benefit in treatment phase 1, as assessed per modified European Bone Marrow Transplant (mEBMT) criteria, could continue onto treatment phase 2 for another 24 weeks. Treatment cross-over was not allowed for either treatment arm.

Assessment of disease status was performed every 3 weeks while on treatment, and every 6 weeks from the end of treatment until documented disease progression/relapse or death. Responses and progressive disease/relapse were determined using the mEBMT criteria, which used the change in monoclonal M-protein level since baseline as the primary parameter for evaluation. To assess the change in monoclonal M-protein level, the initial protocol requires use

of protein electrophoresis method (PEP) to measure the monoclonal M-protein spike in serum and urine according to the mEBMT criteria. The Applicant amended the study protocol in May 2013 to allow for alternative methods other than PEP for measuring M-protein after realizing that not all the study sites had used the protocol-defined method.

The primary efficacy endpoint for Study D2308 was progression-free survival (PFS) as assessed by investigators based on mEBMT criteria. PFS was defined as the time from randomization to the first documented progressive disease, relapse, or death due to any cause. If a patient had not experienced a PFS event by the date of the analysis cut-off or had started another antineoplastic therapy, or had an event after more than two missing adequate assessments, PFS was censored at the date of the last adequate response assessment prior to the cut-off date or start of new antineoplastic therapy.

The following lists the protocol-specified secondary endpoints for Study D2308, starting with overall survival as the only indicated key secondary endpoint:

1. Overall survival (OS), defined as the time from randomization to death due to any cause
2. Overall response rate (ORR), defined as the proportion of patients with complete response (CR), near complete response (nCR) or partial response (PR) per investigator's assessment based on mEBMT criteria
3. nCR/CR rate, as the proportion of patients with CR or nCR per investigator's assessment
4. Time to response (TTR), as the time from randomization to the first documented response
5. Duration of response (DOR), defined as the time from the first documented occurrence of response (CR, nCR or PR) to the first documented progressive disease, relapse, or death due to MM per investigator's assessment based on mEBMT criteria
6. Time to progression to relapse (TTP), defined as the time from randomization to the first documented progressive disease, relapse, or death due to MM per investigator's assessment based on mEBMT criteria

Reviewer Comments:

- *Protocol Amendment #5 was introduced in May 2013, after the study had completed its enrollment, to consider the use of non-PEP M-protein measuring methods as a major protocol deviation, but not to change the primary PFS analysis. This amendment concerned a total of 193 patients (25.1% of study patients). Following the recommendation from Study Steering Committee, the Applicant established an independent review committee (IRC) to perform response assessments and specified additional sensitivity analyses for PFS based on the IRC assessments.*
- *The Agency agreed to have the primary PFS assessment be based on the investigators' assessments, because the study is a double-blind study and the assessment of disease progression is based on laboratory testing.*
- *Several patient-reported outcome instruments (EORTC QLQ-C30, QLQ-MY20, and FACT/GOG-NTX) were administrated in Study D2308;* (b) (4)

3.2.2 Statistical Methodologies of the Pivotal Study

Primary analysis populations

The primary efficacy analysis population for Study D2308 included all randomized patients, to be analyzed as randomized. The primary safety analysis population included all treated patients, to be analyzed as treated.

Sample size determination

The study was sized at 762, with a 1:1 randomization, to detect an increase of 2.7 months in median PFS from 7.5 months in the placebo-control arm to 10.2 months in panobinostat arm (corresponding hazard ratio [HR] = 0.74) with a 2-sided 5% significance level and 90% power. The sample size was planned to have approximately 460 events at the final analysis for the hypothesis testing, accounting for planned sequential testing at interim analyses.

Analysis of the primary endpoint

The primary comparison in PFS between treatment arms was based on a 2-sided stratified (by randomization factors) log-rank test. The HR estimation for the effect of PAN+BTZ+DEX over PBO+BTZ+DEX was based on a proportional hazards model including treatment arm and the randomization factors. The study had several pre-specified sensitivity analyses for PFS with respect to censoring rules, handling of missing M-protein assessments, and impact of prognostic factors. Please refer to Table 5 for the description of the sensitivity analyses.

Analysis of secondary endpoints

OS was the only secondary endpoint with pre-specified testing using stratified log-rank test. For other secondary time-to-event endpoints, the analysis included estimation of median times with 95% confidence intervals using the Kaplan-Meier product-limit method. Secondary response rate endpoints were estimated along with 95% exact confidence intervals as derived by the Clopper-Pearson method for each treatment arm.

Interim analyses

Two interim analyses for PFS were planned after observing 33% and 80% of the 460 events targeted for the final analysis. The first interim analysis was for testing futility, while the second interim analysis was intended to test for treatment efficacy. OS would be tested if the primary endpoint PFS was statistically significant for efficacy.

Type I error control

The Type I error control for multiple testing in PFS was done through the O'Brien-Fleming alpha spending function approach. For the key secondary endpoint OS, a separate pre-planned O'Brien-Fleming function was utilized for alpha spending based on anticipated number of OS events at the planned PFS analyses and the final targeted 415 OS events for the final OS analysis. This strategy, as shown in Glimm et al (2009, Statistics in Medicine) and Tamhane et al (2010, Biometrics), utilized a hierarchical testing procedure allowing for the testing of OS after PFS was statistically significant without inflating the study Type I error, because alpha sharing in OS was done based on a separate alpha spending function for all possible planned interim analyses of OS irrespective of whether the analysis was performed.

Previous communications on statistical design and analyses

Statistical recommendations to the Applicant regarding the pivotal study are summarized below:

- The Agency discourages an early interim analysis of PFS as estimated effects will be less precise with the comparison weighted towards early events, and there may be little follow-up on subjects at an early interim analysis for a risk-benefit assessment.
- Alpha sharing should be done for all possible planned interim analyses of overall survival irrespectively of whether the analysis is performed.
- You should be aware that PFS is subject to ascertainment bias and any imbalance in assessment dates or a substantial amount of missing data could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS. All patients should be followed for PFS until a PFS event has occurred or until the data cutoff. Missing data/assessments of progression should be kept at a minimum. Additionally, you should provide sensitivity analyses to study the impact on the analysis of PFS due to any missing data/assessments, and any loss to follow-up or discontinuation of assessments of PFS not due to an event.

Reviewer Comments:

- *The Sponsor did not perform the second planned PFS interim analysis, because the required 80% of events occurred around the same time as the implementation of protocol amendment #5, which required an IRC to repeat all the response assessments.*
- *The pre-specified significance level for an OS analysis at the final PFS analysis was 0.0193 under the anticipation of 313 events (75% of 415 final OS events) had occurred at that time. The actual number of OS events at the NDA data cut-off of September 10th of 2013 was 286 (69% of 415 events), with the corresponding significance level re-calculated to be 0.0131.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows patient disposition for Study D2308 as of the data cutoff date September 10, 2013. A total of 768 patients enrolled in Study D23080: 387 patients were randomized to receive panobinostat + bortezomib + dexamethasone and 381 patients were randomized to receive placebo + bortezomib + dexamethasone. The percentage of patients received study treatment was the same for both treatment arms; however, one patient was randomized to panobinostat but received placebo instead. No patients were still receiving study treatment as of the data cut-off date. Only 26% of patients, similarly distributed between study arms, had completed protocol planned treatment duration. The most common reasons for treatment discontinuation were disease progression and adverse event. Disease progression was the primary reason for treatment discontinuation in 40% of the patients in the placebo arm compared to 21% of the patients in the panobinostat arm. But on the other hand, occurrence of adverse events was reported to be the primary reason for treatment discontinuation in 34% of the patients in the panobinostat arm compared to 17% of the patients in the placebo arm.

Table 2: Disposition of patients enrolled in Study D2308 as of September 10, 2013

Study Subjects	PAN+BTZ+DEX		PBO+BTZ+DEX	
	n	%	n	%
Randomized	387	100	381	100
Received study treatment	382*	98.7	376*	98.7
Treatment ongoing	0	0	0	0
Discontinued from trial treatment	382	98.7	376	98.7
Primary reason for discontinuation:				
Treatment completed as per protocol	102	26.4	102	26.8
Disease progression	82	21.2	153	40.2
Death	21	5.4	17	4.5
Adverse event(s)	130	33.6	66	17.3
Withdrawal consent	34	8.8	18	4.7
New cancer therapy	4	1.0	7	1.8
Other ¹	9	2.3	13	3.4

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo

* One patient was randomized to PAN but received PBO at start of treatment. This patient was included in the PBO+BTZ+DEX arm for safety analyses.

¹ Other reasons include: abnormal test results, administrative issues, protocol deviation, and loss to follow up

Table 3 gives a summary on demographics and other protocol-specified subgroup analysis factors at baseline. The median age across treatment groups was 63 years. More men than women were enrolled in the study, and the majority of study patients were Caucasians. The treatment groups were balanced with respect to all the baseline factors listed in the table.

Table 3: Demographics and other baseline factors (Study D2308, ITT population)

Factor	PAN + BTZ + DEX (n = 387)	PBO + BTZ + DEX (n = 381)	Total (N = 768)
Demographics			
Age (years)			
<65 / ≥65	225 / 162 (58 / 42 %)	220 / 161 (58 / 42 %)	445 / 323 (58 / 42 %)
mean (SD), median, min-max	62.4 (9.3), 63, 28–84	61.8 (9.4), 63, 32–83	62.1 (9.4), 63, 28–84
Sex			
Female / Male	185 / 202 (48 / 52 %)	176 / 205 (46 / 54 %)	361 / 407 (47 / 53 %)
Race			
Caucasian / Asian / Other	249 / 128 / 10 (64 / 33 / 3 %)	250 / 104 / 27 (66 / 27 / 7 %)	499 / 232 / 37 (65 / 30 / 5 %)
Region			
Americas / Europe / Western Pacific / Other	50 / 194 / 105 / 38 (13 / 50 / 27 / 10 %)	72 / 184 / 90 / 35 (19 / 48 / 24 / 9 %)	122 / 378 / 195 / 73 (16 / 49 / 25 / 10 %)
Other Subgroup Analysis Factors at Baseline			
No. of prior lines of MM therapy[#]			
1 / 2 or 3	178 / 209 (46 / 54 %)	174 / 207 (46 / 54 %)	352 / 416 (46 / 54 %)
Prior use of BTZ			
Yes / No	169 / 218 (44 / 56 %)	167 / 214 (44 / 56 %)	336 / 432 (44 / 56 %)
Clinical staging by ISS			
Stage I / Stage II or III	156 / 181 (40 / 47 %)	152 / 178 (40 / 47 %)	308 / 359 (40 / 47 %)

Factor	PAN + BTZ + DEX (n = 387)	PBO + BTZ + DEX (n = 381)	Total (N = 768)
<i>Renal impairment</i>			
Yes / No	265 / 120 (68 / 31 %)	249 / 129 (65 / 34 %)	514 / 249 (67 / 32 %)
<i>Prior stem cell transplantation</i>			
Yes / No	215 / 172 (56 / 44 %)	224 / 157 (59 / 41 %)	439 / 329 (57 / 43 %)
<i>Prior use of IMiDs and BTZ</i>			
Yes / No	95 / 292 (25 / 75 %)	103 / 278 (27 / 73 %)	198 / 570 (26 / 74 %)
<i>MM characteristics</i>			
Relapsed and refractory / relapsed	134 / 247 (35 / 64 %)	141 / 235 (37 / 62 %)	275 / 482 (36 / 63 %)
<i>Cytogenetic risk</i>			
normal / poor	79 / 24 (20 / 6 %)	88 / 13 (23 / 3 %)	167 / 37 (22 / 5 %)

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo

MM = multiple myeloma; ISS = International Staging System; IMiD = immunomodulatory drug

The frequencies on prior lines of MM therapy listed here are based on the stratification at randomization

3.2.4 Efficacy Results

3.2.4.1 The Primary Efficacy Endpoint

The primary efficacy endpoint for the pivotal study D2308 was progression-free survival (PFS) as assessed by investigators based on mEBMT criteria. PFS was defined as the time from randomization to the first documented progressive disease, relapse, or death due to any cause.

PFS results are shown in sub-sections below for the primary analysis, sensitivity analyses, and subgroup analyses.

3.2.4.1.1 The Primary Analysis

For the protocol-specified primary analysis of PFS, PFS was censored at the date of the last adequate response assessment prior to the data cut-off or start of new antineoplastic therapy if a patient: had not experienced a PFS event by the date of the analysis cut-off, had started another antineoplastic therapy, or had an event after more than two missing adequate assessments.

Table 4 shows the primary analysis result of PFS as per protocol. The improvement by panobinostat over placebo in PFS was statistically significant with an estimated increase of 3.9 months in median PFS and a hazard ratio of 0.63 (95% confidence interval [CI]: 0.52, 0.76). Figure 1 shows the Kaplan-Meier curves for PFS.

Table 4: Primary analysis of PFS (Study D2308)

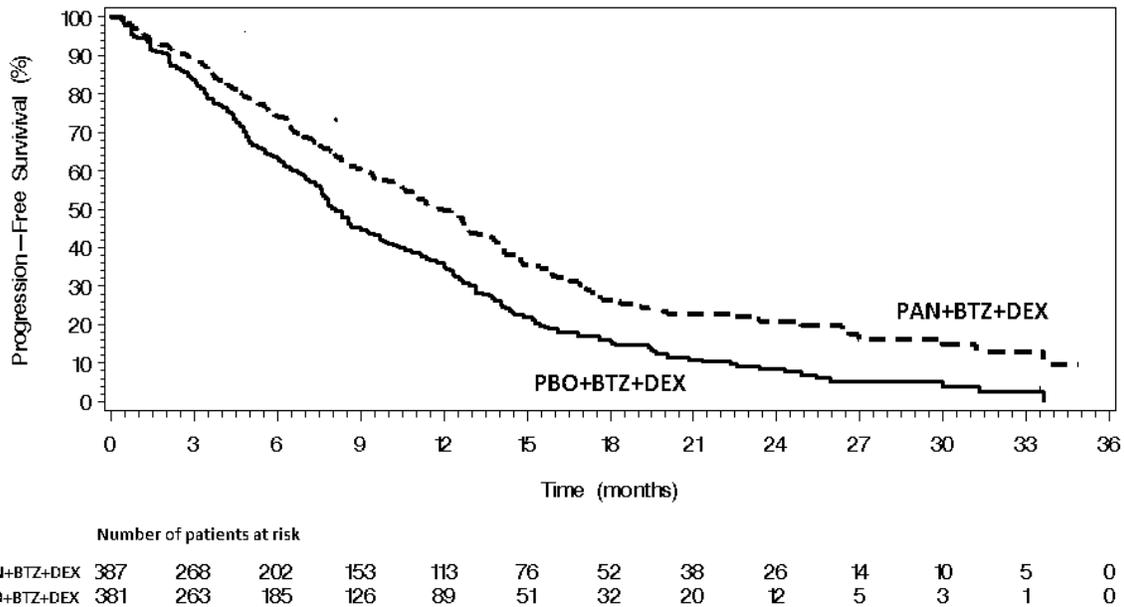
	PAN + BTZ + DEX n = 387	PBO + BTZ + DEX n = 381
Patients with event	207 (53.5%)	260 (68.2%)
Disease progression	164 (42.4%)	231 (60.6%)
Relapse from CR	20 (5.2%)	15 (3.9%)
Death	23 (5.9%)	14 (3.7%)
Patients without event (censored)	180 (46.5%)	121 (31.8%)
Median (95% CI)	12.0 (10.3, 12.9) months	8.1 (7.6, 9.2) months
Hazard ratio¹ (95% CI)	0.63 (0.52, 0.76)	
p-value²	< 0.0001	

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo; CI = confidence interval

¹ For PAN+BTZ+DEX over PBO+BTZ+DEX, estimated using Cox model stratified by randomization factors

² Calculated based on log-rank test, stratified by the randomization factors

Figure 1: Kaplan-Meier plot of PFS as assessed by investigators (Study D2308)



3.2.4.1.2 Sensitivity Analyses

Table 5 specifies the sensitivity analyses used to assess robustness of the primary PFS analysis, with respect to the censoring rule, handling of missing PEP M-protein assessments, protocol violations, potential imbalance in baseline factors, and a possible worse-case scenario.

All the sensitivity analyses suggested a statistically significant difference between the treatment arms in PFS distribution (Table 6); however, there was a wide range in the estimated benefit by panobinostat with the estimated improvement in median PFS from some sensitivity analyses to be only half of the one from the primary analysis (Figure 2).

Table 5: Description of sensitivity analyses of PFS

Analysis	Name	With respect to	Description
[1]	Actual event	Censoring rule	Included the event whenever it occurred even after ≥ 2 missing assessments
[2]	Backdating	Censoring rule	Used the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment
[3]	Drop-out	Censoring rule	Considered another neoplastic therapy, disease progression as the primary reason of treatment discontinuation, and disease progression documented after ≥ 2 missing assessments as events
[4]	IRC	M-protein assessments	Used independent review committee (IRC) assessment for all patients
[5]	Composite IRC/INV	M-protein assessments	Replaced INV-PFS with IRC assessment for patients without M-protein measurements by protein electrophoresis (PEP)
[6]	Censored/INV	M-protein assessments	Censored PFS at randomization for non-PEP patients
[7]	INV (PP)	Protocol violations	Excluded patients with protocol violation(s)* from the INV-PFS analysis
[8]	IRC (PP)	Protocol violations	Excluded patients with protocol violation(s) from the IRC-PFS analysis
[9]	Covariate-adjusted	Baseline factors	Adjusted for baseline factors pre-specified for subgroup analyses
[10]	Worse case	Worse-case scenario	Used minimum(INV-PFS, IRC-PFS) for the panobinostat group, and maximum(INV-PFS, IRC-PFS) for the placebo group

INV = investigator; IRC = independent review committee; PP = per protocol; PEP = protein electrophoresis; INV-PFS, IRC-PFS = progression-free survival as assessed by INV and IRC, respectively

* Major protocol violations included missing baseline efficacy assessments and not having a measurable disease confirmed according to the mEBMT criteria using the PEP measuring method

Table 6: Sensitivity analyses of PFS (Study D2308)

Analysis	Event/Censored		Median (months) (95% CI)			HR (95% CI)	p-value
	PAN (n=387)	PBO (n=381)	PAN (n=387)	PBO (n=381)	Difference		
[1]	254/133	299/82	11.3 (9.5, 12.7)	7.9 (7.5, 8.7)	3.4	0.66 (0.56, 0.79)	<0.0001
[2]	254/133	299/82	10.3 (8.3, 11.3)	7.4 (6.4, 8.0)	2.9	0.68 (0.58, 0.81)	<0.0001
[3]	302/85	343/38	9.5 (8.1, 10.9)	7.6 (6.5, 8.1)	1.9	0.71 (0.61, 0.83)	<0.0001
[4]	241/146	283/98	9.9 (8.3, 11.3)	7.7 (6.9, 8.5)	2.2	0.69 (0.58, 0.83)	<0.0001
[5]	218/169	269/112	11.3 (9.9, 12.9)	7.8 (7.4, 8.6)	3.5	0.65 (0.54, 0.78)	<0.0001

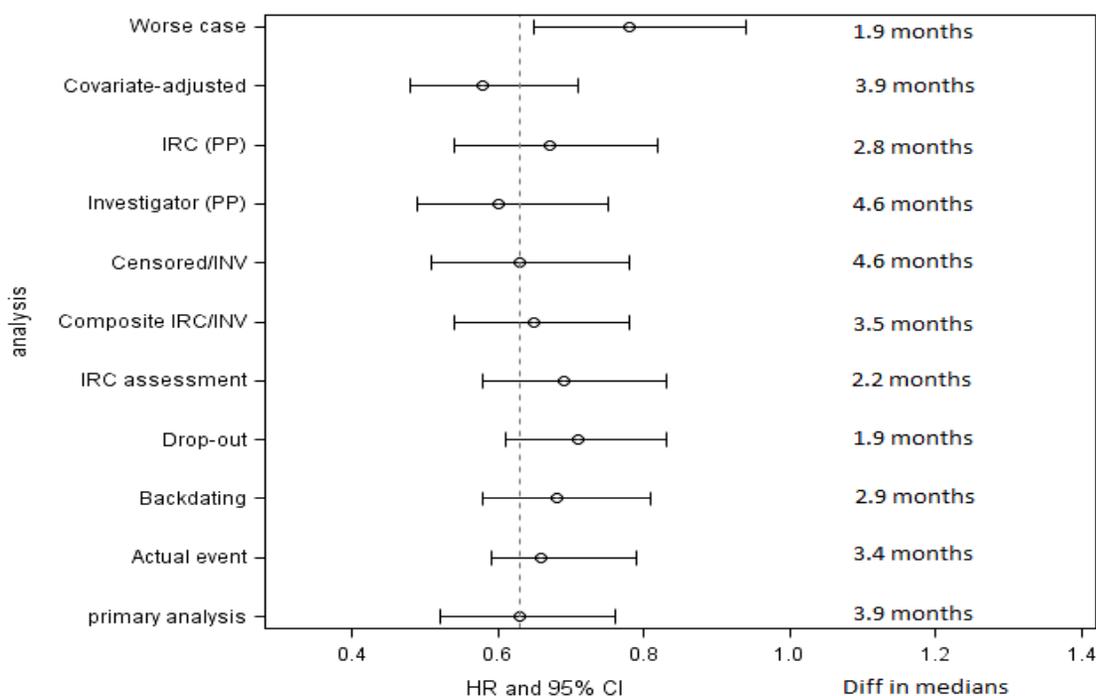
Analysis	Event/Censored		Median (months) (95% CI)			HR (95% CI)	p-value
	PAN (n=387)	PBO (n=381)	PAN (n=387)	PBO (n=381)	Difference		
[6]	154/233	196/185	12.7 (10.6, 14.1)	8.1 (7.1, 9.7)	4.6	0.63 (0.51, 0.78)	<0.0001
[7]	159/130	197/77	12.7 (11.0, 14.1)	8.1 (7.1, 9.7)	4.6	0.60 (0.49, 0.75)	<0.0001
[8]	182/107	208/66	10.5 (8.5, 12.4)	7.7 (6.5, 9.0)	2.8	0.67 (0.54, 0.82)	<0.0001
[9]	207/180	260/121	12.0 (10.3, 12.9)	8.1 (7.6, 9.2)	3.9	0.58 (0.48, 0.71)	<0.0001
[10]	219/168	275/106	10.2 (8.5, 11.8)	8.3 (7.6, 9.3)	1.9	0.78 (0.65, 0.94)	0.0074

PAN represents the panobinostat experimental group; PBO represents the placebo group; CI = confidence interval

¹ Hazard ratio for PAN over PBO, estimated using Cox model stratified by randomization factors

² Calculated based on log-rank test, stratified by the randomization factors

Figure 2: Forrest plot of PFS sensitivity analyses in comparison with the primary analysis (Study D2308)



Reviewer comments:

- Sensitivity analyses [1], [2], [3], [4], [7], [8], [9] were pre-specified in the protocol. Sensitivity analyses [5], [6], [10] were additional analyses performed by the reviewer.
- Because the FDA site inspector identified potential data quality issues at Dr. Hungria site, one additional sensitivity analysis was performed by the reviewer for investigator assessed

PFS excluding the 17 patients studied by Dr. Hungria. Result from this sensitivity analysis, as shown below, was similar to the primary analysis.

	Event / Total	Median PFS (95% CI)	HR (95% CI)	p-value
PAN+BTZ+DEX	200 / 380	12.0 months (10.3, 13.7)	0.63 (0.52, 0.76)	< 0.0001
PBO+BTZ+DEX	250 / 371	8.3 months (7.6, 9.3)		

- The estimated improvement in median PFS using IRC assessments was nearly half of the one estimated according to investigator assessments. The reviewer tabulated the concordance / discordance for IRC versus investigator assessed PFS events, as shown in the table below. This analysis; however, did not suggest an unusually high discordance between the IRC and investigator assessments.

	PAN+BTZ+DEX	PBO+BTZ+DEX
Analysis set: all randomized patients	387	381
Agreement on event status	331 (85.5%)	316 (82.9%)
Event by both IRC and investigator	196 (50.6%)	239 (62.7%)
Complete agreement	112 (28.9%)	147 (38.6%)
Agreement with earlier IRC date	77 (19.9%)	73 (19.2%)
Agreement with later IRC date	7 (1.8%)	19 (5.0%)
No event by either IRC or investigator	135 (34.9%)	77 (20.2%)
Disagreement on event status	56 (14.5%)	65 (17.1%)
Event by investigator but not by IRC	11 (2.8%)	21 (5.5%)
Event by IRC but not by investigator	45 (11.6%)	44 (11.5%)

3.2.4.1.3 Subgroup Analyses

Subgroup analyses as presented in Table 7 did not suggest conflicting results to the primary analysis.

Table 7: Subgroup analyses of PFS (Study D2308)

Subgroup	PAN+BTZ+DEX (n = 387)		PBO+DBTZ+DEX (n = 381)		PAN+BTZ+DEX vs. PBO+BTZ+DEX Hazard ratio (95% CI)
	N	event/censored	N	event/censored	
All patients	387	207/180	381	260/121	0.63 (0.52, 0.76)
Age (years)					
< 65	225	120/105	220	156/64	0.59 (0.46, 0.76)
>= 65	162	87/75	161	104/57	0.72 (0.53, 0.96)

Subgroup	PAN+BTZ+DEX (n = 387)		PBO+DBTZ+DEX (n = 381)		PAN+BTZ+DEX vs. PBO+BTZ+DEX Hazard ratio (95% CI)
	N	event/censored	N	event/censored	
Sex					
Male	202	113/89	205	142/63	0.54 (0.41, 0.70)
Female	185	94/91	176	118/58	0.76 (0.57, 1.00)
Race					
Caucasian	249	139/110	250	169/81	0.69 (0.55, 0.86)
Asian	128	62/66	104	71/33	0.54 (0.38, 0.78)
Other	10	6/4	27	20/7	0.77 (0.27, 2.19)
Geographic region					
Americas	50	32/18	72	50/22	0.75 (0.47, 1.20)
Europe	194	108/86	184	125/59	0.68 (0.52, 0.89)
Western Pacific	105	48/57	90	64/26	0.49 (0.33, 0.73)
Other	38	19/19	35	21/14	1.02 (0.51, 2.03)
No. of prior lines of MM therapy					
1	178	97/81	174	123/51	0.66 (0.50, 0.86)
2 or 3	209	110/99	207	137/70	0.64 (0.50, 0.83)
Prior use of BTZ					
Yes	169	98/71	167	115/52	0.58 (0.44, 0.77)
No	218	109/109	214	145/69	0.68 (0.53, 0.87)
Clinical staging of MM by ISS					
Stage I	156	76/80	152	103/49	0.62 (0.46, 0.85)
Stage II and III	181	104/77	178	127/51	0.61 (0.47, 0.80)
Renal impairment					
Yes	265	144/121	249	178/71	0.65 (0.52, 0.82)
No	120	62/58	129	80/49	0.62 (0.44, 0.87)
Prior stem cell transplantation					
Yes	215	117/98	224	152/72	0.64 (0.50, 0.81)
No	172	90/82	157	108/49	0.64 (0.48, 0.85)
Prior use of IMiDs and BTZ					
Yes	95	56/39	103	73/30	0.53 (0.37, 0.76)
No	292	151/141	278	187/91	0.68 (0.55, 0.85)
MM characteristics					
Relapsed & refractory	134	62/72	141	99/42	0.54 (0.39, 0.75)
Relapsed	247	143/104	235	158/77	0.70 (0.56, 0.89)
Cytogenetic risk					
Normal	79	50/29	88	62/26	0.88 (0.60, 1.29)
Poor	24	12/12	13	9/4	0.47 (0.18, 1.25)

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo

MM = multiple myeloma; ISS = International Staging System; IMiD = immunomodulatory drug

3.2.4.2 The Secondary Endpoints

3.2.4.2.1 The Key Secondary Endpoint – Overall Survival

Table 8 shows the analysis result of overall survival (OS) as of the data cut-off date. At the analysis, 286 events (69% of the 415 planned final OS events) were observed. The estimated median overall survival was longer in the PAN+BTZ+DEX arm as compared to the

PBO+BTZ+DEX arm; however, the difference in overall survival between the study groups was not statistically significant with the p-value to be greater than the pre-specified significance level of 0.0131 and the estimated hazard ratio to be 0.87 (95% CI: 0.69, 1.10) at the analysis. Figure 3 shows the overall survival Kaplan-Meier curves at the data cut-off.

Table 8: Analysis of OS as of September 10, 2013 (Study D2308)

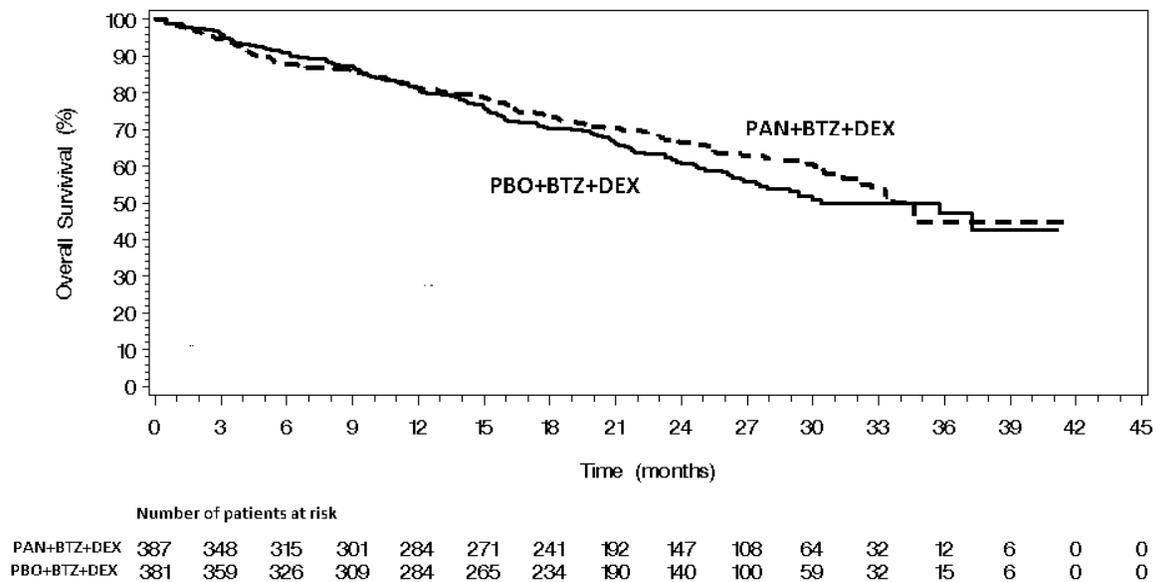
	PAN + BTZ + DEX n = 387	PBO + BTZ + DEX n = 381
Patients with event	134 (34.6%)	152 (39.9%)
Patients without event (censored)	253 (65.4%)	229 (60.1%)
Median (95% CI)	33.6 (31.3, NE) months	30.4 (26.9, NE) months
Hazard ratio¹ (95% CI)	0.87 (0.69, 1.10)	
p-value²	0.2586	

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo; CI = confidence interval; NE = not estimable

¹ For PAN+BTZ+DEX over PBO+BTZ+DEX, estimated using Cox model stratified by randomization factors

² Calculated based on log-rank test, stratified by the randomization factors

Figure 3: Kaplan-Meier curves of OS as of September 10, 2013 (Study D2308)



3.2.4.2.2 Other Secondary Endpoints

Table 9 shows the results of the other secondary efficacy endpoints are in favor of panobinostat over placebo. The results by IRC assessment agree in general with the results by investigator

assessment; however, the complete response rate as determined by IRC is much less than the one determined by investigators.

Table 9: Results of secondary endpoints (Study D2308)

Endpoint	PAN + BTZ + DEX (n = 387)	PBO + BTZ + DEX (n = 381)
Overall response rate – n, % (95% CI)		
Investigator assessment	235, 60.7 (55.7, 65.6)%	208, 54.6 (49.4, 59.7)%
IRC assessment	248, 64.1 (59.1, 68.9)%	205, 53.8 (48.7, 58.9)%
Complete/near complete response rate – n, % (95% CI)		
Investigator assessment	107, 27.6 (23.2, 32.4)%	60, 15.7 (12.2, 19.8)%
IRC assessment	49, 11.9 (8.8, 15.5)%	26, 6.8 (4.5, 9.8)%
Time to response - median (95% CI)		
Investigator assessment	1.5 (1.4, 1.6) months	2.0 (1.6, 2.8) months
IRC assessment	1.4 (1.4, 1.5) months	2.2 (1.7, 3.2) months
Duration of response¹ - median (95% CI)		
Investigator assessment	13.1 (11.8, 14.9) months	10.9 (9.2, 11.8) months
IRC assessment	11.8 (10.2, 12.5) months	9.7 (8.8, 10.6) months
Time to progression or relapse - median (95% CI)		
Investigator assessment	12.7 (11.3, 14.1) months	8.5 (7.7, 9.7) months
IRC assessment	10.9 (9.3, 12.5) months	7.8 (7.1, 9.0) months

PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; IRC = independent review committee; CI = confidence interval

¹ Only patients with partial, near complete or complete response are included in the analysis.

3.3 Evaluation of Safety

There were a total of 758 patients treated in Study D2308. The Applicant reported 381 patients were treated with panobinostat in combination with bortezomib and dexamethasone, but the Agency determined that 386 patients were exposed to panobinostat.

More on-treatment deaths were reported in the PAN+BTZ+DEX treatment arm as compared to the PBO+BTZ+DEX arm. In addition, a much higher proportions of panobinostat treated patients had grade 3/4 adverse events, serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose adjustment or interruption.

Please refer to the review by Dr. George for the Agency determined treatment assignment, and the interpretation of safety findings.

Table 10: Summary of adverse event outcomes (Study D2308)

Adverse outcome	Applicant		FDA	
	PAN+BTZ+DEX n = 381 n (%)	PBO+BTZ+DEX n = 377 n (%)	PAN+BTZ+DEX n = 386 n (%)	PBO+BTZ+DEX n = 372 n (%)
On-treatment death	30 (7.9)	18 (4.8)	30 (7.8)	18 (4.8)
Due to progressive disease	4(1.0)	6 (1.6)	4 (1.0)	6 (1.6)
Reasons other than PD	26 (6.8)	12 (3.2)	26 (6.7)	12 (3.2)

Adverse outcome	Applicant		FDA	
	PAN+BTZ+DEX n = 381 n (%)	PBO+BTZ+DEX n = 377 n (%)	PAN+BTZ+DEX n = 386 n (%)	PBO+BTZ+DEX n = 372 n (%)
Adverse events of grade 3 or 4	364 (95.5)	310 (82.2)	367 (95.1)	307 (82.5)
Serious adverse events	228 (59.8)	157 (41.6)	230 (59.6)	155 (41.7)
Adverse events leading to				
Treatment discontinuation	138 (36.2)	77 (20.4)	139 (36.0)	76 (20.4)
Dose change/interruption	338 (88.7)	285 (75.6)	342 (88.6)	281 (75.5)

Adverse events occurred more than 28 days from study treatment discontinuation are not included in the summary
PAN = panobinostat; BTZ = bortezomib; DEX = dexamethasone; PBO = placebo; PD = progressive disease

3.4 Benefit-Risk Assessment

The efficacy and safety findings from the pivotal study D2308 did not provide a definitely positive benefit-risk conclusion for the treatment of panobinostat in combination with bortezomib and dexamethasone. The study suggested that the addition of panobinostat may improve efficacy outcomes, but on the other hand, it also showed that panobinostat treated patients had experienced adverse outcomes more frequently as compared to the patients who did not receive panobinostat. The observations of a much smaller PFS benefit by IRC assessment and the imbalance between study arms in on-treatment death are particularly concerning.

To give an exploratory benefit-risk assessment, the reviewer calculated the number needed to treat using the PFS event rates and the number needed to harm using the on-treatment death event rates as observed in Study D2308. The number needed to treat (NNT) represents the number of patients who need a treatment in order to prevent one additional bad outcome, and is calculated as the inverse of absolute risk reduction by the treatment. The number needed to harm (NNH) indicates how many patients need to be exposed to treatment in order to cause harm in one patient who would not otherwise have been harmed, and is calculated as the inverse of absolute risk increase by the treatment.

The NNT can also be calculated for PFS as a time-to-event endpoint using the Kaplan-Meier estimated PFS probability at a chosen time point, as proposed by Altman and Andersen (1999, BMJ). The Kaplan-Meier estimated PFS probabilities at 18 months (73.6% vs. 83.9% by investigator assessment, and 78.8% vs. 87.1% by IRC assessments, for panobinostat group vs. placebo group) are also used for the NNT calculation. The 18-month time point is chosen because it is approximately 6 months beyond the treatment duration of 48 weeks.

The calculated NNT in order to avoid a PFS event is 7 and 9 based on PFS observed event rate as assessed by the investigator and IRC, respectively. The calculated NNH with respect to on-treatment death is 33. Combining the information on NNT and NNH, the benefit/harm ratio in terms of reduction in disease progression versus occurrence of on-treatment death is 4.7:1 according to the investigators and 3.7:1 according to the IRC. Using the 18-month PFS event rates, the NNT is calculated to be 10 and 13, with the corresponding benefit/harm ratio to be 3.3:1 and 2.5:1 based on the investigator and IRC assessments, respectively. Whether or not these benefit/harm ratios are adequate for recommending the addition of panobinostat to bortezomib and dexamethasone as a treatment regimen for relapsed multiple myeloma is subject to clinical interpretations.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 7 for Study D2308 primary endpoint results by gender, race, age, and geographic region.

4.2 Other Special/Subgroup Populations

Please refer to Table 7 for Study D2308 primary endpoint results by other protocol-specified subgroup analysis factors, including: prior therapies, renal impairment, clinical staging, disease characteristics, and cytogenetic risk.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The clinical efficacy and safety evaluation of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with previously treated MM was based on Study D2308, a randomized double-blind placebo-controlled study in 768 patients with relapsed MM. The primary efficacy endpoint of the study was PFS as assessed by investigators based on the mEBMT criteria.

The major statistical issue with the efficacy evaluation was that some study sites did not follow the mEBMT criteria and used non-PEP M-protein measuring methods for the determination of responses and disease/relapse. This protocol violation concerned a total of 193 patients (25.1% of the study participants). As a result, the Applicant established an IRC to perform response assessments and specified additional sensitivity analyses for PFS by IRC assessment.

5.2 Collective Evidence

The pivotal study has not provided a convincing evidence to support the addition of panobinostat to bortezomib and dexamethasone as the treatment of patients with relapsed multiple myeloma. The primary analysis of PFS based on investigator assessment showed an improvement of 3.9 months in median PFS by panobinostat (HR [95% CI]: 0.63 [0.52, 0.76]), but the sensitivity analysis of PFS by IRC assessment had the estimated improvement reduced to 2.2 months (HR [95% CI]: 0.69 [0.58, 0.83]). In addition, it was much more frequent for panobinostat treated patients to experience important adverse outcomes, including: on-treatment death (7.8% vs. 4.8%), grade 3 or 4 adverse events (95.1% vs. 82.5%), serious adverse events (59.6% vs. 41.7%), adverse events leading to treatment discontinuation (36.0% vs. 20.4%), and adverse events leading to dose modification or interruption (88.6% vs. 75.5%).

5.3 Conclusions and Recommendations

Efficacy and safety results included in this application are not sufficient for this reviewer to derive a definite conclusion and recommendation.

References

1. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* 2009; 29: 219-228.
2. Tamhane AC, Mehta CR, Liu L. Testing a primary and a secondary endpoint in a group sequential design. *Biometrics* 2010; 66: 1174-1184.
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