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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	NDA
Application	205353
Received	March 24, 2014
Review Extension	Major Amendment
Amendment Received	October 7, 2014
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Division / Office	Hematology Products / OHOP
Reviewers	Barry W. Miller, MSN, CRNP Nicole Gormley, MD
Division / Office	Biometrics 5 / Biostatistics
Reviewer	Chia-Wen Ko, PhD
Review Completion	January 14, 2015
Established Name	Panobinostat
Proposed Trade Name	Farydak
Therapeutic Class	Histone Deacetylase inhibitor
Applicant	Novartis Pharmaceuticals, Corp.
Formulations	10 mg, 15 mg, 20 mg capsules
Dosing Regimen	20 mg orally, once daily, 3 times a week for 2 weeks of eight repeated 3-week cycles, followed by eight additional cycles for patients with clinical benefit.
Indication	In combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent.
Intended Population	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review team recommends approval of panobinostat under Subpart H (21 CFR 314.510), in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent (b) (4). Accelerated approval is based on the finding of prolonged progression-free survival in a subgroup population of patients from Trial 2308. Confirmation of clinical benefit is required.

Approval for this indication is supported by the results of Trial 2308, a randomized, controlled trial of panobinostat, intravenous bortezomib, and dexamethasone compared to placebo, bortezomib and dexamethasone in patients with relapsed multiple myeloma who had received 1 to 3 prior therapies. The applicant proposed that panobinostat should be used in all patients with relapsed multiple myeloma, but the benefit-risk assessment does not support approval for that indication. Despite a statistically significant primary endpoint of PFS in the single randomized controlled trial, poor trial conduct resulting in a large amount of missing data limited confidence in the trial results, and significant risks contributed to an overall negative benefit-risk determination for the proposed indication.

In a pre-specified subgroup analysis of patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median number of two prior treatments, a favorable benefit-risk assessment sufficient for accelerated approval was attained. It remains to be confirmed in post-marketing studies that panobinostat is efficacious, safe, and tolerable in patients with multiple myeloma.

1.2 Benefit-Risk Assessment

For the approximately 24,000 patients diagnosed with multiple myeloma in the United States this year, several treatment options are available. Cure is rare and even though many patients can live years with multiple myeloma, relapses are common, serious, and life-threatening. Novel agents are needed to manage this disease. Although there are several active combinations of cytotoxic and immunochemotherapeutics that can be used for treatment of relapsed multiple myeloma, efficacy is variable and the durations of response are limited. Moreover, repeat administration of treatments can be myelosuppressive and cumulative toxicities pose additional challenges.

Results of the analysis of the subgroup of patients who had received prior treatment with both bortezomib and an immunomodulatory agent on Trial 2308, demonstrated that panobinostat, an oral histone deacetylase inhibitor, has activity in combination with bortezomib and dexamethasone in patients with multiple myeloma who received a

median of 2 prior regimens. The safety review, however, revealed substantial hematologic and non-hematological risks, including fatal events. The risks were moderated in part by close monitoring and dose interruption and/or reduction for toxicities, a strategy that would be needed for safe use of the drug in practice. It is not clear that this can be accomplished without explicit instructions to the patients and education of the healthcare providers. With such controls of risk in place, the current measure of clinical benefit outweighs the expected risks for patients with relapsed multiple myeloma who have no other effective therapy available.

1.3 Recommendations for Labeling

The following are recommendations for panobinostat labeling based on this review:

- Limit use to patients who have received at least two prior therapies.
- Limit use to patients who have received both bortezomib and an immunomodulatory agent.
- Include a boxed Warning addressing cardiac events and arrhythmias, and diarrhea. The Warning and Precautions section should also address myelosuppression, hemorrhage, and hepatotoxicity.
- Include instructions for dose interruption and modification for patients who develop myelosuppression, diarrhea, nausea or vomiting, QTc prolongation, and hepatic impairment.
- Include instructions for monitoring for neutropenia and thrombocytopenia, QTc prolongation, and electrolyte abnormalities.
- Display the incidence of laboratory abnormalities rather than reported adverse events for cytopenias and blood chemistries.

1.4 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

The applicant will develop a communication plan to inform healthcare professionals about the risk of cardiac events (EKG changes and arrhythmias) and diarrhea in patients taking panobinostat.

1.5 Recommendations for Post-market Requirements and Commitments

1. Conduct a randomized dose-finding clinical trial sufficient to characterize the safety and efficacy of at least two different doses of panobinostat in combination with subcutaneous bortezomib and dexamethasone. Eligible patients will include

patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The primary objective is to assess the overall response rate (ORR) in both treatment arms according to IMWG criteria by investigator assessment. Trial results will inform the dose selection for a randomized Phase 3 confirmatory trial. Submit a complete study report with data.

2. Conduct a multicenter, randomized, three-arm, double-blind, placebo controlled phase 3 trial of two different doses of panobinostat in combination with subcutaneous bortezomib and dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The primary objective will be progression-free survival. Submit a complete study report with full data.

2 Introduction

This Application was discussed at an Oncologic Drugs Advisory Committee meeting held on November 6, 2014. FDA review of analysis was presented to the Committee and summarized as follows:

Trial 2308 is a randomized, placebo-controlled, double-blinded trial, with an add-on treatment design using bortezomib and dexamethasone as backbone therapy. Adequate disease response measurements were missing for 25% of patients on trial. The panobinostat treatment arm results included:

- Improvement in median progression-free survival of 3.9 months as assessed by investigators.
- Improvement in median progression-free survival of 1.9 months as assessed by a sensitivity analysis, which included the following as events: death, progression as assessed by investigators, initiation of another antineoplastic therapy, discontinuation of therapy due to disease progression, and disease progression that was documented after 2 or more missing assessments.
- 6% improvement in overall response rate.
- Increased incidence of deaths not due to progressive disease (7% vs. 3.5%) and adverse events of myelosuppression, hemorrhage, infection, and cardiac toxicity.
- No statistically significant difference in overall survival.
- No difference between arms in a time-to-treatment failure sensitivity analysis, which included the following as events: death, disease progression as assessed by investigators, and discontinuations due to adverse events.

Following FDA, Applicant, and Open Public Hearing presentations, the Committee was asked to discuss and vote on the following: Given this benefit to risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

In response, five of the seven committee members voted "No" and two voted "Yes". Those committee members who voted in the negative described unease regarding the lack of additional data, such as improvement in overall survival or quality of life endpoints, to support the observed improvement in progression-free survival (PFS). While these committee members generally agreed that Trial 2308 demonstrated that panobinostat shows activity in patients with myeloma, concerns with the toxicity and uncertain magnitude of PFS improvement were cited as contributing to a negative benefit to risk profile overall.

Some members hypothesized that toxicities exhibited on Trial 2308 may be better managed in the United States as compared to the international sites from the trial, but that the data under consideration does not provide evidence of this. One committee member specifically questioned whether the dose and combination of agents from the trial was ideal for maximizing benefit while minimizing toxicity. With regard to magnitude of improvement in PFS, some committee members referred to the censoring and missing data as raising questions about this magnitude, particularly in light of the lack of supportive data from other assessed endpoints.

Several committee members who voted "No" encouraged the applicant to continue to pursue clinical development of this agent in hopes of better elucidating a population of patients with multiple myeloma who would safely benefit from treatment with panobinostat in combination with other treatment. Committee members who voted "Yes" described a judgment that the demonstrated magnitude of improvement in PFS was sufficient to support a positive benefit to risk profile for the use of panobinostat in this complex and challenging population of patients.

After the Advisory Committee meeting and in consideration of the advice received, the Applicant proposed a modified indication for the use of panobinostat based on a pre-specified subgroup of patients. The Applicant submitted additional subgroup analyses for FDA review; which constituted a major amendment to the Application. Review of the additional analyses relevant to the proposed indication based on the subpopulation is included herein.

This Addendum supplements the Clinical Review by Adam George dated August 27, 2014 and the Clinical Review of Efficacy by Barry Miller dated August 26, 2014.

3 Review of Efficacy

Efficacy Summary

The key efficacy findings based on the complete trial population of 768 patients, as detailed in the primary Clinical Review of Efficacy, follows:

- Investigator-assessed median PFS difference was 3.9 months: 12.0 months in the panobinostat + bortezomib and dexamethasone (BD) arm vs. 8.1 months in the placebo + BD arm. The hazard ratio was 0.63 (95% CI: 0.52, 0.76), *p*-value <0.0001.

- An interim analysis for OS was not mature.

- Overall response rate (ORR) was 61% [11% complete response (CR)] on the panobinostat + BD arm with a median duration of response (DOR) of 13.1 months vs. 55% (6% CR) in the placebo + BD arm with median DOR of 10.9 months.

- A sensitivity analysis of Independent Review Committee-assessed median PFS resulted in a difference of 2.2 months: 9.9 months in the panobinostat + BD arm vs. 7.7 months in the placebo + BD arm. The hazard ratio was 0.69 (95% CI: 0.58, 0.83), *p*-value <0.0001.

Limitations to confident interpretation of the randomized controlled trial include:

- Young age of enrolled patients compared to the U.S. myeloma population
- Few Blacks/African Americans compared to the U.S. myeloma population
- Fewer than 30% of patients completed treatment
- Missing baseline or response data for 25% of patients
- Missing patient reported outcome data for >70% of patients

Missing data contributed to the high proportion of censored events in the analysis of PFS; 47% of events were censored in the panobinostat + BD arm compared to 32% in the placebo + BD arm.

In the trial subpopulation of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent, the median number of prior treatments was two. A summary of the key efficacy findings follows:

- Investigator-assessed median PFS difference was 4.8 months: 10.6 months in the panobinostat + BD arm vs. 5.8 months in the placebo + BD arm. The hazard ratio was 0.52 (95% CI: 0.36, 0.76).

- ORR was 55% on the panobinostat + BD arm with a median DOR of 12.0 months vs. 41% in the placebo + BD arm with median DOR of 8.3 months.

This subpopulation better represents how patients with multiple myeloma are treated in the U.S., though the median age of patients is even younger than in the entire trial population (60 years). This subgroup will better inform patients and prescribers of the risk and benefit of treatment with panobinostat in combination with bortezomib and dexamethasone.

3.1 Methods

A protocol specified subgroup analysis of patients enrolled on Trial 2308 who had received prior treatment with both bortezomib and an immunomodulatory agent was identified by the Applicant as supporting a more favorable benefit-risk determination. This patient subgroup more closely aligns with the current multiple myeloma treatment paradigm for patients treated in the U.S. compared to the overall trial population. Bortezomib, thalidomide, and lenalidomide form the foundation of current standard treatments for primary, maintenance, and relapsed multiple myeloma. Two- and three-agent combinations are preferred regimens. Other agents commonly used include corticosteroids and alkylating agents.

3.2 Subpopulation: Prior bortezomib and an immunomodulatory agent

Efficacy analyses were performed on the subpopulation of 193 patients on Trial 2308 who had received prior treatment with bortezomib and with lenalidomide or thalidomide. This subgroup of 193 patients was defined using the patient treatment history dataset.

3.2.1 Demographics

Compared to the overall trial population, this subgroup was comprised of a larger percentage of patients from the United States (15%). The median age of 60 years is even younger than the overall trial population (63 years) and 9 years younger than the median age (69 years) at myeloma diagnosis in the U.S.

Table 1 Demographic characteristics of patients in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
Age, years		
Mean (SD)	59 (10)	61 (9)
Median	60	61
Range	28-79	32-77
Groups		
<40	5 (5.3%)	3 (3.0%)
40-64	60 (63.8%)	58 (58.6%)
≥65	29 (30.9%)	38 (38.4%)
Sex		
Male	52 (55.3%)	49 (49.5%)
Female	42 (44.7%)	50 (50.5%)
Race		
White or Caucasian	59 (62.8%)	63 (63.6%)
Asian	34 (36.2%)	29 (29.3%)
Black or African American	1 (1.1%)	5 (5.1%)
Other	0	2 (2.0%)
U.S.	13 (13.8%)	16 (16.2%)

BD = bortezomib + dexamethasone, SD = standard deviation

Prior exposure to individual agents is provided in Table 2. The median number of prior treatments is 2 compared to a median of 1 for the whole trial population. The immunomodulatory agent most often used was thalidomide. Treatments differed between arms by approximately 10% for three agents: patients on the panobinostat + BD arm had been treated with more thalidomide and cyclophosphamide than patients on the placebo + BD arm, and more patients on the placebo + BD arm had been treated with lenalidomide compared to patients on the panobinostat + BD arm.

Table 2 Treatment history of patients in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
Number of prior antineoplastic regimens		
Mean (SD)	2.2 (0.8)	2.2 (0.8)
Median	2	2
Range	1-4	1-3
Prior chemotherapy		
Bortezomib	94 (100%)	99 (100%)
Immunomodulatory agent	94 (100%)	99 (100%)
Thalidomide	78 (83.0%)	69 (69.7%)
Lenalidomide	34 (36.2%)	45 (45.5%)
Corticosteroids[1]	92 (97.9%)	95 (96.0%)
Melphalan	80 (85.1%)	80 (80.8%)
Cyclophosphamide	49 (52.1%)	40 (40.4%)
Doxorubicin	37 (39.4%)	36 (36.4%)

BD = bortezomib + dexamethasone, SD = standard deviation
[1] Includes Preferred Terms: betamethasone, dexamethasone, methylprednisolone, prednisolone, and prednisone

3.2.2 Results

For the subgroup of 193 patients on Trial 2308 who had received prior treatment with bortezomib and an immunomodulatory agent, the difference in median PFS was 4.8 months favoring the panobinostat + BD arm. This result is consistent with the statistically significant analysis of the primary trial endpoint of PFS. Refer to Table 3 and Figure 1 for results.

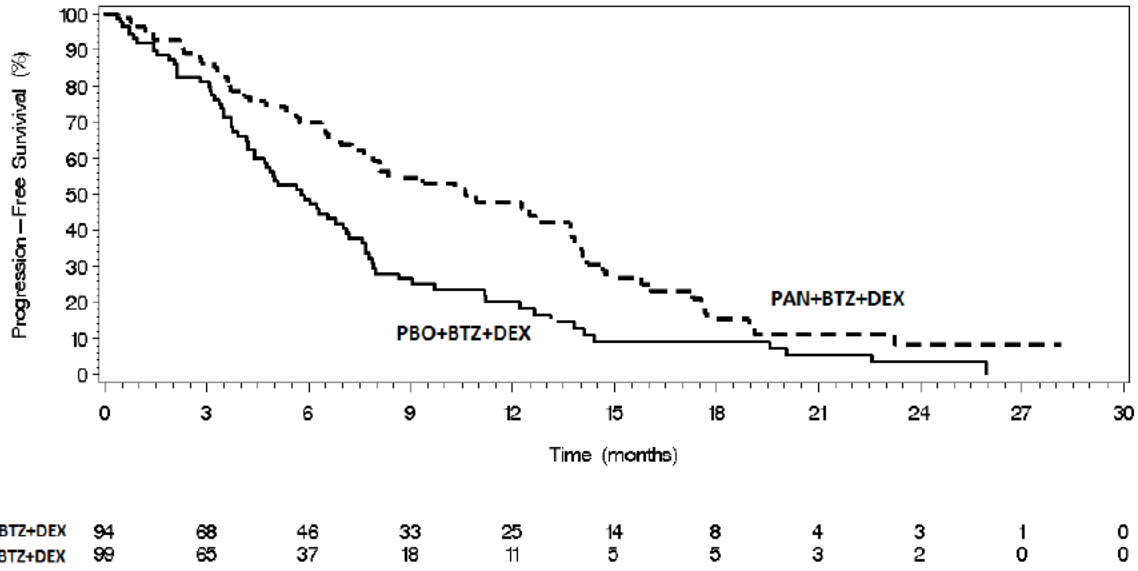
Noted is a reduction in the percentage of censoring that occurred within this subgroup population compared to the overall trial population. There is still an imbalance between arms with a greater amount of censoring occurring on the panobinostat + BD arm.

Table 3 Investigator-assessed Progression-free Survival (PFS) analysis of Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
PFS events, n	57 (60.6%)	72 (72.7%)
Censored[1], n	37 (39.4%)	27 (27.3%)
Median time to event, months (95% CI)	10.6 (7.6, 13.8)	5.8 (4.4, 7.1)
Hazard ratio[2] (95% CI)	0.52 (0.36, 0.76)	
p-value[3]	0.0005	

BD = bortezomib + dexamethasone, CI = confidence interval
[1] Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation
[2] Estimated using Cox model stratified by randomization factors
[3] Calculated based on log-rank test, stratified by the randomization factors

Figure 1 Kaplan Meier plot of investigator-assessed Progression-free Survival (PFS) from Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent



PAN+BTZ+DEX = panobinostat, bortezomib, and dexamethasone arm
PBO+BTZ+DEX = placebo, bortezomib, and dexamethasone arm

Overall responses were observed more frequently in the panobinostat + BD arm compared to the placebo + BD arm. Response rates and durations of response using modified EBMT criteria, are provided in Table 4.

Table 4 Response rate and duration of response in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
Overall response rate[1]	55 (58.5%)	41 (41.4%)
95% CI	(48.6, 68.5)%	(31.7, 51.1)%
Complete response	8 (8.5%)	2 (2.0%)
Near complete response	13 (13.8%)	7 (7.1%)
Partial response	34 (36.2%)	32 (32.3%)
Median DOR, months	12.0	8.3
95% CI	9.7, 13.9	6.1, 12.3

BD = bortezomib + dexamethasone

As lenalidomide is the more commonly prescribed immunomodulatory agent in the U.S., primarily due to improved safety and tolerability compared to thalidomide, an additional analysis for PFS was performed on the 79 patients who had been previously treated

with both bortezomib and with lenalidomide. With these small numbers, no difference between arms can be determined.

Table 5 Progression-free Survival (PFS) analysis of Trial 2308 subgroup: Prior bortezomib and lenalidomide

	Panobinostat + BD n=34	Placebo + BD n=45
PFS events, n	23 (67.6%)	33 (73.3%)
Censored[1], n	11 (32.4%)	12 (26.7%)
Median time to event, months (95% CI)	6.6 (3.3, 10.6)	4.2 (3.5, 6.2)
Hazard ratio (95% CI)	0.58 (0.32, 1.03)	
p-value[3]	0.0586	

BD = bortezomib + dexamethasone, CI = confidence interval
[1] Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation
[2] Estimated using Cox model stratified by randomization factors
[3] Calculated based on log-rank test, stratified by the randomization factors

4 Review of Safety

Safety Summary

From the 758 patients on Trial 2308, deaths within 30 days of treatment occurred more frequently in the panobinostat + BD arm compared to the placebo + BD arm, 8% vs. 5.1%. Deaths within 30 days due to causes other than disease progression occurred in 7% of patients in the panobinostat arm and 3.5% in the placebo arm. Non-fatal serious adverse events occurred in 60% of patients in the panobinostat + BD arm and 42% in the placebo + BD arm. SAEs with a ≥ 5% incidence in the panobinostat + BD arm were: pneumonia, diarrhea, thrombocytopenia, and sepsis.

In the trial subpopulation of patients who had received prior treatment with both bortezomib and an immunomodulatory agent, 191 patients received at least one dose of panobinostat or placebo and were included in the safety population.

4.1 Methods

Additional safety analyses were performed on the data from Trial 2308 and are presented in Section 4.2.

An exploratory analysis for additional risks was performed on the subgroup of patients enrolled on Trial 2308 who had received prior treatment with both bortezomib and an immunomodulatory agent (Section 4.3).

4.2 Major Safety Results

4.2.1 Deaths within 30 days of Treatment

On-study deaths (deaths within 30 days of treatment) occurred more frequently in the panobinostat arm compared to the placebo arm, 8% vs. 5.1%. Deaths due to disease progression occurred in 1% of patients in the panobinostat arm, compared to 1.6% in the placebo arm. Death due to causes other than disease progression occurred in 7.0% in the panobinostat arm and 3.5% in the placebo arm. All deaths occurring in the safety population are included in Table 6.

Table 6 Deaths of patients in Trial 2308

	Panobinostat + BD n=386		Placebo + BD n=372	
	n	%	n	%
On-Study Deaths	31	8.0	19	5.1
Non Progression	27	7.0	13	3.5
Infection	11	2.8	7	1.9
Hemorrhage	5	1.3	1	0.3
Cardiac Arrest or Failure	4	1.1	3	0.8
Renal	2	0.5	0	0
Sudden Death	1	0.3	0	0
Gastrointestinal	1	0.3	0	0
Neurologic	1	0.3	0	0
Drug Overdose	1	0.3	0	0
Respiratory	1	0.3	2	0.5
Progression	4	1.0	6	1.6

BD = bortezomib + dexamethasone

4.2.2 Serious Adverse Events

Non-fatal serious adverse events occurred in 60% of patients in the panobinostat arm and 42% in the placebo arm. SAEs that occurred in ≥2% of patients in the panobinostat arm are summarized in Table 7. The most common SAEs were pneumonia, diarrhea, and thrombocytopenia.

Table 7 Serious adverse events of patients in Trial 2308

	Panobinostat + BD n=386		Placebo + BD n=372	
	n	%	n	%
Blood and lymphatic system disorders				
Thrombocytopenia	28	7.3	8	2.2
Anemia	15	3.9	3	0.8
Gastrointestinal disorders				
Diarrhea	43	11.1	9	2.4
Vomiting	12	3.1	3	0.8
General disorders and administration site conditions				
Asthenia	17	4.4	5	1.3
Pyrexia	16	4.1	11	3.0
Fatigue	11	2.8	2	0.5
Infections and infestations				
Pneumonia[1]	70	18.1	53	14.2
Sepsis[2]	23	6.0	11	3.0
Urinary tract infection	8	2.1	4	1.1
Metabolism and nutrition disorders				
Dehydration	11	2.8	5	1.3
Hypokalemia	8	2.1	4	1.1
Vascular disorders				
Orthostatic hypotension	9	2.3	1	0.3

BD = bortezomib + dexamethasone

[1] Pneumonia includes the terms: pneumonia, lower respiratory tract infection, lobar pneumonia, lung infection, pneumonia fungal, pneumonia influenzal, atypical pneumonia, bronchopneumonia, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia haemophilus, pneumonia pneumococcal, pneumonia respiratory syncytial viral

[2] Sepsis Includes the terms: sepsis, septic shock, device related sepsis, neutropenic sepsis, streptococcal sepsis, haemophilus sepsis, staphylococcal sepsis, pneumococcal sepsis, candida sepsis

4.2.3 Adverse Events

Adverse events occurred in both arms; however, there was a higher rate of grade 3/4 AEs in the panobinostat arm. Adverse events occurred in 99.7% of patients in both the panobinostat and placebo arms. Grade 3/4 events occurred in 96% of patients in the panobinostat arm compared with 82% in the placebo arm.

Common grade 3/4 adverse events that occurred in ≥10% of patients with a ≥ 5% incidence in the panobinostat arm compared to the placebo arm are shown in Table 8. Among these, the most common were diarrhea and fatigue.

Laboratory based adverse events are not included in Table 8. Refer to the complete Clinical Review by Adam George for treatment-emergent laboratory abnormalities based on the laboratory dataset. The most common hematologic abnormalities

occurring more often on the panobinostat arm were decreased platelets and neutrophils. The most common decreases in chemistry parameters were hypocalcemia, hypophosphatemia, and hypokalemia.

Table 8 Adverse events[1] of patients in Trial 2308

	Panobinostat + BD n=386				Placebo + BD n=372			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Gastrointestinal disorders								
Diarrhea	264	68.4	98	25.4	153	41.1	29	7.8
Nausea	139	36.0	21	5.4	77	20.7	2	0.5
Vomiting	99	25.6	28	7.3	48	12.9	5	1.3
General disorders and administration site conditions								
Fatigue[2]	158	40.9	65	16.8	109	29.3	33	8.9
Edema peripheral	111	28.8	8	2.1	70	18.8	1	0.3
Pyrexia	100	25.9	5	1.3	55	14.8	7	1.9
Metabolism and nutrition disorders								
Decreased appetite	110	28.5	12	3.1	44	11.8	4	1.1
Cardiac Disorders								
Arrhythmia[3]	47	12.2	11	2.8	23	6.2	8	2.2
Investigations								
Weight decreased	44	11.4	7	1.8	17	4.6	2	0.5

BD = bortezomib + dexamethasone
[1] Not including adverse events based on laboratory values.
[2] Fatigue includes the terms: Fatigue, Malaise, Asthenia, Lethargy
[3] Arrhythmia includes the terms: Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Bradycardia, Cardiac arrest, Cardio-respiratory arrest, Sinus bradycardia, Sinus tachycardia, Supraventricular extra-systoles, Tachycardia, Ventricular arrhythmia, Ventricular tachycardia

4.2.4 ECG changes

Treatment-emergent ECG changes occurred in 64% of patients in the Panobinostat arm compared with 42% in the placebo arm. The incidence of QT-prolongation was similar between treatment arms, 12% in the panobinostat arm, and 8% in the placebo arm. New T-wave changes were reported in 40% of patients in the Panobinostat arm compared with 18% in the placebo arm. ST-segment depressions were reported in 22% of patients in the panobinostat arm, compared with 4% in the placebo arm.

4.3 Subpopulation: Prior bortezomib and an immunomodulatory agent

In the subpopulation of 191 patients who had received prior treatment with both bortezomib and an immunomodulatory agent, the median age of patients was 60 years of age. This is 3 years younger than the median age of the overall trial population. The overall incidence of adverse events appears lower in this subpopulation, which may be

due to the younger age of patients in the subpopulation (9 years younger than the median age at myeloma diagnosis in the U.S.).

4.3.1 Deaths within 30 days of treatment

On-study deaths (deaths within 30 days of treatment) occurred in 6.3% in the panobinostat arm compared to 5.2% in the placebo arm. Death due to causes other than disease progression occurred in 6.3% in the panobinostat arm and 4.2% in the placebo arm. All deaths occurring in the safety population are included in Table 1.

Table 9 Deaths of patients in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=95		Placebo + BD n=96	
	n	%	n	%
On-Study Deaths	6	6.3	5	5.2
Non Progression	6	6.3	4	4.2
Infection	2	2.1	2	2.1
Hemorrhage	1	1.0	1	1.0
Cardiac Arrest or Failure	1	1.0	1	1.0
Renal	1	1.0	0	0
Sudden Death	1	1.0	0	0
Progression	0	0	1	1.0

4.3.2 Serious Adverse Events

Nonfatal serious adverse events that occurred in ≥2% of patients in the panobinostat arm are summarized in Table 10.

Table 10 Serious adverse events of patients in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=95		Placebo + BD n=96	
	n	%	n	%
Blood and lymphatic system disorders				
Thrombocytopenia	6	6.3	2	2.1
Anemia	3	3.2	1	1.0
Neutropenia	2	2.1	1	1.0
Gastrointestinal disorders				
Diarrhea	9	9.5	4	4.2
Nausea	3	3.2	0	0
Vomiting	3	3.2	0	0
Constipation	2	2.1	1	1.0
Gastritis	2	2.1	0	0
General disorders and administration site conditions				
Asthenia/fatigue	7	7.4	2	2.1
Infections and infestations				
Pneumonia[1]	20	21.1	17	17.7
Sepsis[2]	4	4.2	5	5.2
Gastroenteritis	4	4.2	2	2.1
Herpes Zoster	2	2.1	1	1.0
Cellulitis	2	2.1	1	1.0
Metabolism and nutrition disorders				
Hypokalemia	2	2.1	1	1.0
Musculoskeletal and connective tissue disorders				
Myalgia	2	2.1	0	0
Nervous system disorder				
Loss of consciousness/syncope	2	2.1	1	1.0
Renal and urinary disorders				
Renal Failure[3]	6	6.3	4	4.2
Vascular disorders				
Hypotension	2	2.1	2	2.1
Hypovolemic Shock	2	2.1	0	0

[1] Pneumonia includes the terms: pneumonia, lower respiratory tract infection, lung infection, pneumonia fungal, pneumonia influenzal, lung infiltration, bronchopneumonia, pneumonia pneumococcal, pneumonia respiratory syncytial viral
[2] Sepsis includes the terms: sepsis, septic shock, neutropenic sepsis, streptococcal sepsis, staphylococcal sepsis
[3] Renal failure includes the terms: renal failure and renal failure acute

4.3.3 Adverse Events

Adverse events that occurred in ≥10% of patients with a ≥ 5% incidence in the panobinostat arm compared to the placebo arm are shown in Table 11. Among these, the most common were diarrhea and fatigue. Laboratory based adverse events were

underreported in the trial; they were more accurately identified in the laboratory datasets and are not included in this table.

Table 11 Adverse events[1] of patients in Trial 2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=95				Placebo + BD n=96			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Gastrointestinal disorders								
Diarrhea	70	73.7	29	30.5	43	44.8	12	12.5
Nausea	36	37.9	8	8.4	20	20.8	1	1.0
Constipation	26	27.4	2	2.1	31	32.3	2	2.1
Vomiting	25	26.3	6	6.3	9	9.4	2	2.1
Abdominal pain	21	22.1	2	2.1	11	11.5	2	2.1
Dyspepsia	14	14.7	1	1.1	8	8.3	1	1.0
General disorders and administration site conditions								
Fatigue[2]	66	69.5	27	28.4	46	47.9	12	12.5
Edema peripheral	19	20	2	2.1	17	17.7	0	0
Metabolism and nutrition disorders								
Decreased appetite	24	25.3	1	1.1	10	10.4	0	0
Musculoskeletal and connective tissue disorders								
Pain in Extremity	13	13.7	0	0	6	6.3	0	0
Nervous system disorders								
Peripheral Neuropathy	31	32.6	5	5.3	25	26.0	5	5.2
Cardiac Disorders								
Arrhythmia[3]	11	11.6	0	0	6	6.3	3	3.1
Respiratory, thoracic, and mediastinal disorders								
Cough	25	26.3	0	0	18	18.8	0	0
Infections and Infestations								
Upper Respiratory Tract Infection	30	31.6	4	4.2	17	17.7	0	0
Investigations								
Weight decreased	12	12.6	1	1.1	4	4.2	0	0

[1] Not including adverse events based on laboratory values.
[2] Fatigue includes the terms: Fatigue, Malaise, Asthenia
[3] Arrhythmia includes the terms: Arrhythmia, Atrial fibrillation, Atrial flutter, Bradycardia, Cardio-respiratory arrest, Sinus bradycardia, Sinus tachycardia, Supraventricular extra-systoles, Tachycardia

5 Appendices

5.1 Abbreviations

AE	adverse event
BD	bortezomib and dexamethasone
BTZ	bortezomib
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
DOR	duration of response
ECG	electrocardiogram
ORR	overall response rate
OS	overall survival
PAN	Panobinostat
PBO	placebo
PFS	progression free survival
SAE	serious adverse event
SD	standard deviation

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/s/

BARRY W MILLER
01/22/2015

CHIA-WEN KO
01/22/2015

NICOLE J GORMLEY
01/22/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205353
Priority or Standard	Priority
Submit Date(s)	March 22, 2014
Received Date(s)	March 24, 2014
PDUFA Goal Date	November 24, 2014
Division / Office	DHP/OHOP
Reviewer Name(s)	Adam George, PharmD.
Review Completion Date	08/27/14
Established Name	Panobinostat
(Proposed) Trade Name	Farydak®
Therapeutic Class	Histone Deacetylase Inhibitor
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	10 mg, 15 mg and 20 mg hard gelatin capsules
Dosing Regimen	20 mg orally once daily on days 1, 3, 5, 8, 10 and 12 of a 21 day cycle for a maximum of 16 cycles
Indication(s)	In combination with bortezomib and dexamethasone for the treatment of patients with

	multiple myeloma who have received at least 1 prior therapy
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical safety reviewer does not recommend granting the Applicant approval of NDA 205353 for the use of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. In the opinion of this reviewer, the increased rate of grade ≥3 toxicities and serious adverse events along with the imbalance of deaths due to treatment emergent events associated with the combination of panobinostat in combination with dexamethasone is not outweighed by a 3.9 month improvement in investigator assessed median progression free survival. This reviewer recommends that this application be presented to an Oncology Drugs Advisory Committee in order to seek the opinion of hematology oncology experts on the benefit:risk profile of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with relapsed multiple myeloma.

1.2 Risk Benefit Assessment

Risks
Based upon review of the safety data from 758 patients with relapsed multiple myeloma evaluable for safety in the randomized, double-blind, placebo controlled trial (D2308), the regimen of panobinostat 20 mg administered orally once daily 3 times a week (days 1, 3, 5, 8, 10, 12), on a 2 weeks on 1 week off schedule for up to 16 cycles in combination with bortezomib and dexamethasone is associated with added toxicity and is not well tolerated compared to treatment with bortezomib and dexamethasone. In trial D2308 there were 386 patients who were exposed to investigational therapy with panobinostat 20 mg in combination with bortezomib and dexamethasone. A total of 372 patients were exposed to the control arm of bortezomib in combination with dexamethasone (a standard U.S. regimen for the treatment of relapsed multiple myeloma).

Grade 1-4 adverse events occurred in 99.7% of patients in both treatment arms. The most common adverse events that occurred in ≥20% of patients in the panobinostat arm and at a ≥10% greater frequency than the control arm were diarrhea, thrombocytopenia, fatigue, nausea, neutropenia, peripheral edema, decreased appetite, hypokalemia, pyrexia and vomiting. The frequency of patients that experienced grade ≥3 adverse events was higher in the panobinostat arm 95% (n=367) compared to the incidence in the control arm 83% (n=307). The most common (≥10%) grade ≥3 toxicities that occurred more frequently in the panobinostat arm compared to the control arm were

thrombocytopenia (31% vs. 11%), diarrhea (26% vs. 9%), pneumonia (10% vs. 8%) and neutropenia (10% vs. 2%). Serious adverse events were also more common in the panobinostat arm with 230 patients (60%) experiencing at least 1 SAE compared to 155 patients (42%) in the control arm. The most common SAEs that occurred in ≥5% of patients in the panobinostat arm compared to the control arm were pneumonia (15% vs. 11%), diarrhea (11% vs. 2%) and thrombocytopenia (7% vs. 2%). Fifty-five percent of patients treated with panobinostat 55% (n=211) experienced an adverse event that led to hospitalization or prolongation of hospitalization compared to 37% (n=138) of patients treated with the control arm.

The addition of panobinostat to bortezomib and dexamethasone led to reduced tolerability. Overall, 36% of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20% of patients (n=76) in the control arm. The most common reason for treatment discontinuation in the panobinostat arm was diarrhea which accounted for 4% of patients in the panobinostat arm compared to 2% of patients in the control arm. Adverse events of any toxicity grade leading to treatment interruption or dose modification occurred 89% of patients in the panobinostat arm compared to 76% patients in the control arm. The two most common reasons for dose modification or treatment interruption in the panobinostat arm compared to the control arm were thrombocytopenia (31% vs. to 11%) and diarrhea (26% vs. 9%).

During the trial, 26 patients (7%) in the panobinostat arm died due to treatment-emergent toxicities compared to 12 patients (3%) in the control arm. The categories of hemorrhage and infection were the main contributors to the observed imbalance of deaths between the treatment arms. Five patients in the panobinostat arm died due to hemorrhage compared to 1 patient in the control arm. Ten patients died due to infection in the panobinostat arm compared to 6 in the control arm.

The toxicities of primary concern with this Applicant were asthenic conditions, severe gastrointestinal toxicity (nausea, vomiting and diarrhea) leading to serious events of dehydration, severe thrombocytopenia leading to serious hemorrhagic events, neutropenia resulting in severe infections such as pneumonia and sepsis. Of particular concern is the increased number of deaths due to hemorrhage. All 5 of the patients who died due to hemorrhage had grade ≥3 thrombocytopenia at the time of the event. Patients in the control arm of trial D2308 also experienced grade ≥3 events of thrombocytopenia but in contrast only 1 patient died. This finding implies that the dose modification and supportive care strategies used to mitigate the risk of hemorrhage due to thrombocytopenia with panobinostat were not adequate. This is particularly concerning given the fact that in clinical practice patients may not be monitored as frequently and may therefore be subjected to an increased risk of bleeding due to severe thrombocytopenia.

Risk conclusion
Trial D2308 demonstrated the proposed regimen of panobinostat in combination with bortezomib and dexamethasone is associated with severe toxicities such as asthenic conditions, severe gastrointestinal toxicity (nausea, vomiting and diarrhea) leading to serious events of dehydration, severe thrombocytopenia leading to serious hemorrhagic events, neutropenia resulting in severe infections such as pneumonia and sepsis. All of these toxicities occurred at a rate that is higher than the control arm of bortezomib and dexamethasone which is a standard regimen with known clinical benefit for the treatment of relapsed multiple myeloma. In addition, these toxicities contributed to an increased number of patients on panobinostat discontinuing therapy or requiring a dose reduction or treatment interruption. These toxicities also led to a two fold increase in treatment emergent deaths. In patients with multiple myeloma disease progression is not immediately life threating and does not typically require immediate initiation of therapy. For this reason it is difficult to justify that a 3.9 month improvement in median PFS outweighs the risk of the severe toxicity and increased number of deaths associated with panobinostat.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None proposed at the time of finalization of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer is recommending the Applicant receive PMRs for the following:

- Based upon the dose-related toxicity findings from trial B2207, the increased rate of adverse events requiring dose modification or interruption in trial D2308 and the Applicants dose intensity analysis, the Applicant should conduct a dose-ranging trial to evaluate the safety and efficacy of lower doses or an alternate dosing regimen of panobinostat in combination with bortezomib and dexamethasone.

- To submit the data from the final analysis of overall survival for trial D2308.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Panobinostat
Proprietary Name: Farydak
Pharmacologic class: histone deacetylase inhibitor (HDAC)

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Applicant's proposed indication: in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.

Applicant's proposed dosage and administration: 20 mg once daily orally, 3 times a week (days 1, 3, 5, 8, 10, 12), on a 2 weeks on 1 week off dosing regimen for eight cycles (each cycle consist of 3 weeks (21 days). Patients with clinical benefit should continue treatment for eight additional cycles [each cycle is 3 weeks long (21 days)].

2.2 Tables of Currently Available Treatments for Proposed Indications

There are 3 products that are indicated for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. In addition, cyclophosphamide, melphalan and carmustine have broad indications for the treatment of patients with multiple myeloma. In 2008 bortezomib was granted a broad indication for the treatment of patients with multiple myeloma. This approval was based upon new data submitted in an efficacy supplement from a randomized trial that compared bortezomib, melphalan and prednisone to melphalan and prednisone in patients with previously untreated multiple myeloma. The justification for the broad indication was also supported by the 2005 approval. Carfilzomib is approved for the treatment of patients with relapsed multiple myeloma, but after two prior therapies.

Table 1 Drugs approved for the treatment of relapsed multiple myeloma

Drug	Year Approved	Indication
Cyclophosphamide	1959	Multiple Myeloma
Melphalan	1964	Palliative treatment of Multiple Myeloma
Carmustine	1977	Multiple Myeloma in combination with prednisone
Bortezomib	2005	Multiple Myeloma patients who have received at

		least 1 prior therapy
Lenalidomide	2005	Treatment of patients with Multiple Myeloma, in combination with dexamethasone, in patients who have received at least 1 prior therapy
Liposomal doxorubicin	2007, Priority review	Multiple Myeloma in combination with bortezomib in patients who have not previously received bortezomib and have received at least 1prior therapy

2.3 Availability of Proposed Active Ingredient in the United States

Panobinostat is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Panobinostat is a histone deacetylase (HDAC) inhibitor. The pharmacologic class of HDAC inhibitors is associated with the following risks:

- Severe myelosuppression manifested as thrombocytopenia, leukopenia and anemia
- Serious and fatal infections including pneumonia and sepsis
- Electrocardiographic changes such as QT prolongation and T-wave and ST-segment changes.
- Severe nausea vomiting and diarrhea
- Severe dehydration
- Myocardial ischemia

Currently there are two histone deacetylase (HDAC) inhibitors which are approved for use in the United States, Zolinza® (vorinostat) and Istodax® (romidepsin). Both romidepsin and vorinostat are approved for use in patients with hematologic malignancies. The toxicities described above are known safety issues with the currently marketed HDAC inhibitors and are included in the labeling for either or both of these agents.

The Applicant is proposing an indication for “in combination with bortezomib” which is based upon the results of a randomized trial that evaluated panobinostat in combination with bortezomib and dexamethasone. For this reason it is also relevant to discuss the toxicities of bortezomib. Bortezomib is associated with the following toxicities:

- Severe neuropathy; sensory and motor
- Hypotension
- Acute development or exacerbation of congestive heart failure and new onset decreased left ventricular ejection fraction

- Severe and fatal pulmonary toxicity such as Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration
- Posterior Reversible Encephalopathy Syndrome
- Gastrointestinal toxicity: grade 3-4 nausea, vomiting, diarrhea and constipation
- Severe thrombocytopenia and neutropenia
- Hepatotoxicity such as acute liver failure

The major toxicities associated with dexamethasone are hypothalamic-pituitary adrenal (HPA) axis suppression, fluid retention, hypertension, increased risk for infection, hypokalemia, hyperglycemia, osteoporosis, and anxiety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 03/14/03, Novartis submitted to FDA/CDER their initial IND for *intravenous formulation of* LBH589 for a first-in-human trial (CLBH589A2101) to IND 67091. The initial 30-day review was determined to be safe-to-proceed and the 'study may proceed' letter was issued on 06/17/03.

On 05/17/04, Novartis submitted to FDA/CDER, IND # 69862, for the *oral formulation* of LBH589. This IND included a multicenter Phase IA dose-escalation study of two schedules of administration of oral LBH589 in patients with advanced solid tumors and hematologic malignancies. The clinical reviewer determined that the trial was safe to proceed from a clinical standpoint, but CMC deficiencies were issued by the CMC team. The study may proceed letter was issued upon resolution of these deficiencies on 11/09/04.

On 11/03/06, Novartis submitted four Special Protocol Assessment Requests to the FDA (SPA-1 for CTCL, SPA-2 for CML, SPA-3 for CML, and SPA-4 for multiple myeloma). SPA-4 proposed a single arm trial entitled "*Phase II study of LBH589 in adult patients with multiple myeloma who have received at least two prior lines of therapy and whose disease is refractory to the most recent line of therapy*".in patients with relapsed/refractory multiple myeloma. A non-agreement letter was issued on 12/18/06 with the main issues for non-agreement being that (b) (4) The Sponsor requested a meeting to discuss the SPA non-agreement letter and this meeting was held on 02/07/07. In the meeting, the Agency recommended that the Sponsor conduct a randomized trial, rather than proceeding with the single-arm trial for accelerated approval. The Agency did not agree to the proposed (b) (4) primary endpoint.

On 11/22/10, FDA notified the Sponsor that their proposed tradename (b) (4) was unacceptable.

On 01/25/12, FDA notified the Sponsor that their proposed tradename “Farydak” **was acceptable.**

The Agency and the Applicant had a type C meeting on February 29, 2012 to discuss the statistical and clinical issues related to the Phase 3 study CLBH589D2308. A summary of the discussions related to the safety of panobinostat are summarized below:

- The Agency recommended against the Sponsor’s proposed interim analysis for efficacy. During the meeting the Sponsor proposed using the first interim analysis for futility and moving the second interim analysis to the time of approximately 368 events (80% information). This was acceptable to the Agency.
- The Agency agreed to the Applicant’s proposal that the summary of clinical safety would include analyses of pooled safety data from 2 patient populations. The populations were; 1) patients with relapsed/refractory multiple myeloma that received panobinostat in combination with bortezomib and dexamethasone and 2) patients that received single agent panobinostat at a dose of 20 mg three time per week being treated for various disease states, including multiple myeloma
- The Agency agreed to the format of the datasets to be submitted for the NDA. The format was the Novartis standard data structure and not CDISC. We stated that CDISC datasets were preferred.

The Agency and the Applicant had a Type B meeting on February 5, 2014 to discuss the content and format of the NDA for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. A summary of the discussions related to the safety of panobinostat are summarized below:

- We agreed to the proposed content and format of the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) and to waive the requirement for providing an Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS)
- We recommended that diarrhea be included in the Applicant’s proposed analyses of notable adverse events in the SCS
- We agreed with the proposed categories for patient narratives
- We agreed to the proposed content of the safety update

2.6 Other Relevant Background Information

(b) (4)

(b) (4)

Summary of findings from trial E2214
For the 129 patients treated in study E2214, only 1 complete response (CR) was identified by independent review committee (IRC) assessment vs. 5 CR (< 4%) by investigator. The 22% (by IRC) to 27% (by investigator) ORR put forward by the applicant was primarily driven by patients who achieved a partial response (PR) (21% by IRC and 23% by investigator) which is not a meaningful clinical outcome in the proposed patient population and disease setting. The duration of the only one IRC assessed CR was less than two weeks.

Of the 129 patients exposed to panobinostat in trial E2214 the most frequent AEs of any grade were thrombocytopenia, diarrhea, nausea, fatigue, vomiting, anemia and pyrexia. The most frequent Grade 3/4 AEs were thrombocytopenia (79.1%), neutropenia (22.5%) and anemia (20.9%). Twelve (9%) patients experienced bleeding events on treatment (8 patients with grade 3/4), 11 patients recovered and 1 patient died due to sepsis/dengue fever. Among these 12 patients, all had thrombocytopenia of any grade. The most common bleeding events included epistaxis (11.6%) and petechiae (9.3%). Hypothyroidism regardless of causality was reported in 20 patients (15.5%), all of which were in grade 1 or 2 in severity with 17 of the 20 patients (85%) had prior radiation therapy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contained all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application was reasonable to begin review of the application. During review of the datasets the review team was unable to find a dataset for trial D2308 that included patient ID number and treatment arm assignment and were unable to confirm patient assignment to the investigational arm or control arm. The Applicant was sent an information request to provide this dataset. The Applicant provided this dataset in SD#3 of the NDA.

3.2 Compliance with Good Clinical Practices

For trials D2308, B2207 and DUS71 the protocols, protocol amendments and informed consents, were reviewed by independent ethic committee (IEC) or institutional review board (IRB) for each investigational site. All trials were conducted according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained

from each patient prior to the performance of any study-specific procedures. Patients were provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study.

OSI was consulted to inspect 2 investigational sites for trial D2308. Site# 561 from the United States was selected along with site# 262 from Brazil. The main purpose of these inspections is to evaluate the site's compliance with GCPs. At the time of this review the OSI consult review was not completed. Please refer to the CTDL review of this application.

3.3 Financial Disclosures

For trial D2308, B2207 and DUS71 ninety-nine percent of clinical investigators provided financial disclosure statement. The Applicant provided rationale for the missing financial disclosures. In addition, the Applicant concluded that this did not have an impact on the conduct of the trials. I have reviewed the Applicant's rationale and conclusions and agree. There were 3 investigators that had significant financial agreements to disclose.

- Trial D2308: Dr. (b) (6) at center number (b) (6) disclosed >$25,000 in funding received from an investigator initiated trial
- Trial DUS71:
  - Dr. (b) (6) at center number (b) (6) disclosed >$25,000 in funding form Speaker's bureau
  - Dr (b) (6) at center number (b) (6) disclosed >$25,000 from a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria

Reviewer comment: Trial D2308 enrolled a total of 768 patients of which Dr. (b) (6) at center (b) (6) enrolled (b) (6). Due to the small number of patients enrolled at this site it is unlikely that any potential bias by Dr. (b) (6) would have significantly impacted the results of the trial.

Additionally, trial DUS71 enrolled a total of 55 patients. At site (b) (6) Dr. (b) (6) and Dr. (b) (6) enrolled a total of (b) (6) patients. Enrollment at this site only accounts for (b) (6) % of the overall trial population. For this reason is unlikely that any potential bias by these investigators would have significantly impacted the results of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

At the time of finalization of the clinical safety review the reviews of other disciplines were pending. Please refer to the CDTL review for discussion of the chemistry manufacturing and controls, preclinical pharmacology/toxicology and clinical pharmacology reviews.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Clinical trials submitted to support NDA 205353

Study ID	Study Dates/CSR status	Support	Design	US Sites	Regimen	Number of patients enrolled
CLBH589D2308	December 21, 2009 to data cut-off September 10, 2013/Interim	Efficacy and safety	Multicenter, randomized (1:1), double-blind, active comparator control	Yes	Panobinostat + bortezomib + dexamethasone vs. placebo + bortezomib + dexamethasone	769 with relapsed multiple myeloma
CLBH589DUS71	June 22, 2010 to Data cut-off December 4, 2012/Interim	Supportive Efficacy and safety	Multicenter, open-label, single arm	Yes	Panobinostat + bortezomib + dexamethasone	55 with relapsed multiple myeloma
CLBH589B2207	October 18, 2007 to data cut-off August 10, 2011/Interim	Supportive efficacy and Safety	Multicenter, open-label dose escalation followed by dose expansion	Yes	Panobinostat + bortezomib + dexamethasone	47 dose escalation, 15 dose expansion
CLBH589B2201	January 2, 2007 to November 30, 2009/Final	Supportive Safety	Single-arm, open-label, multicenter	Yes	Single agent panobinostat oral formulation	Refractory cutaneous T-cell lymphoma
CLBH589B2202	February 19, 2007 to September 30, 2008/Abbreviated	Supportive Safety	Single-arm, three-stage, open-label, multicenter	Yes	Single agent panobinostat oral formulation	29 Relapsed chronic myeloid leukemia received at least 2

						prior tyrosine kinase inhibitors
CLBH589B2203	April 16, 2007 to January 3, 2011/Final	Supportive safety	Single-arm, three-stage, open-label, multicenter	Yes	Single agent panobinostat oral formulation	38 Relapsed /refractory multiple myeloma
CLBH589B2206	April 22, 2008 to May 31, 2012/Final	Supportive safety	Multicenter, open-label dose escalation	Yes	Panobinostat + lenalidomide + dexamethasone	46 relapsed multiple myeloma
CLBH589B2211	February 23, 2007 to August 26, 2008/Abbreviated	Supportive safety	Single-arm, three-stage, open-label, multicenter	Yes	Single agent panobinostat oral formulation	29 Chronic myeloid leukemia in accelerated or blast phase who received at least 2 prior tyrosine kinase inhibitors
CLBH589E2214	September 16, 2008 to June 11, 2010/Abbreviated	Supportive safety	Single-arm, three-stage, open-label, multicenter	Yes	Single agent panobinostat oral formulation	27 Chronic myeloid leukemia in accelerated or blast phase who received at least 2 prior tyrosine kinase inhibitors

5.2 Review Strategy

The review of efficacy data for NDA 205353 was conducted by Barry Miller and the review of safety was conducted by Adam George. Please refer to Mr. Miller's review for

discussion of the efficacy review strategy. The safety clinical review was primarily based on the safety data from trial D2308. The safety data for trial B2207 and DUS71 were also reviewed and provide supportive information to the safety evaluation of panobinostat for the proposed indication.

The electronic submission, with the clinical study reports, and other relevant documents from the submission were reviewed and analyzed. The key review materials and activities are outlined below:

- Electronic submission of NDA 205353
- Relevant published literature on patients with relapsed multiple myeloma
- Prior drug approvals in relapsed multiple myeloma
- Applicant responses to clinical reviewer information requests
- Clinical study reports for trials D2308, B2207 and DUS71
- Applicant safety analyses for trials D2308 were reproduced or audited
- Pooled safety analysis of the most common adverse events from trials D2308, B2207 and DUS71
- Regulatory background of INDs 69862 67091 for panobinostat were reviewed
- Applicant's proposed labeling was reviewed and revised

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 CLBH589D2308 (D2308)

5.3.1.1 Trial Title

A multicenter, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

5.3.1.2 Trial Design

Trial D2308 was a multicenter, randomized, double-blind, placebo controlled trial that evaluated panobinostat in combination with bortezomib and dexamethasone compared to placebo in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma. Patients were required to have received at least 1 prior therapy (but no more than 3 prior therapies) for their multiple myeloma and have a need for treatment per the International Myeloma Working Group (IMWG) definition. A total of 762 patients were planned to be randomized 1:1 to receive panobinostat+ bortezomib +dexamethasone or placebo + bortezomib+ dexamethasone. Patients were stratified based upon the following factors:

- Number of prior lines of therapy: 1 vs. 2 or 3

- Prior use of bortezomib: yes or no

The primary objective of the study was to compare progression-free survival (PFS) in patients treated with panobinostat in combination with bortezomib/dexamethasone vs. patients treated with placebo in combination with bortezomib/dexamethasone. The key secondary objective was to compare overall survival (OS) between the treatment arms.

Patients, investigator staff, persons performing the assessments, and data analysts were blind to treatment assignment from the time of randomization until final database lock. Unblinding was permitted in case of patient emergencies.

Trial population
(Source: protocol D2308 amendment version 5)
Inclusion criteria

1. Patient has a previous diagnosis of MM, based on IMWG 2003 definitions; all three of the following criteria had been met:
    a. Monoclonal immunoglobulin (M-component) on electrophoresis, and on immunofixation on serum or on total 24 hour urine (or demonstration of M protein in cytoplasm of plasma cell for non secretory myeloma)
    b. Bone marrow (clonal) plasma cells $\geq$10% or biopsy proven plasmacytoma
    c. Related organ or tissue impairment (CRAB symptoms: anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections)
2. Patient with 1 to 3 prior lines of therapy who requires retreatment of myeloma for one of the 2 conditions below:
    a. Relapsed, defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy or up to 60 days of last dose of this therapy. Patients who received prior treatment with bortezomib may be eligible
    b. Relapsed and refractory to a therapy provided that meets both conditions:
        i. Patient has relapsed to at least one prior line
        ii. And patient was refractory to another line (except bortezomib), by either not reaching a MR, or progressed while under this therapy, or within 60 days of its last dose
3. Patient has measureable disease at study screening defined by at least one of the following measurements as per IMWG 2003 criteria:
    a. Serum M-protein $\geq$1 g/dL
    b. Urine M-protein $\geq$200 mg/24 hour
4. Patient treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, is eligible. Two weeks must have lapsed since last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry to the protocol deferred until the radiotherapy is completed and 2 weeks have passed since the last date of therapy

5. Patient's age is ≥18 years at time of signing the informed consent
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2
7. Patient has the following laboratory values within 3 weeks before starting study drug:
    a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    b. Platelet count ≥100 x 10^9/L
    c. Serum potassium, magnesium, phosphorus, within normal limits (WNL) for institution
    d. Total calcium (corrected for serum albumin) or ionized calcium greater or equal to lower normal limits (≥ LLN) for institution, and not higher than CTCAE grade 1 in case of elevated value
    e. AST/SGOT and ALT/SGPT ≤2.5 x ULN
    f. Serum total bilirubin ≤1.5 x ULN (or ≤3 x ULN if patient has Gilbert syndrome)
    g. Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥60 ml/min
8. Patient has provided written informed consent prior to any screening procedures
9. Patient is able to swallow capsules
10. Patient must be able to adhere to the study visit schedule and other protocol requirements
11. Women of childbearing potential must have a negative serum pregnancy test at baseline

Exclusion criteria

1. Patients who have progressed under all prior lines of anti-MM therapy (primary refractory)
2. Patients who have been refractory to prior bortezomib (i.e., did not achieve at least a MR, or have progressed under it or within 60 days of last dose)
3. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression
4. Patient has shown intolerance to bortezomib or to dexamethasone or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information
5. Patient has grade ≥2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination within 14 days before randomization
6. Patient received prior treatment with deacetylase inhibitors including panobinostat
7. Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment
8. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period)

9. Patient has secondary primary malignancy <3 years of first dose of study treatment (except for treated basal or squamous cell carcinoma, or in situ cancer of the cervix)
10. Patient who received:
    a. A prior anti-myeloma chemotherapy or medication including IMiDs and dexamethasone ≤3 weeks prior to start of study
    b. Experimental therapy or biologic immunotherapy including monoclonal antibodies ≤4 weeks prior to start of study
    c. Prior radiation therapy ≤4 weeks or limited field radiotherapy ≤2 weeks prior to start of study
11. Patient has not recovered from all therapy related toxicities associated with above listed treatments to less than grade 2 CTCAE
12. Patient has undergone major surgery ≤2 weeks prior to starting study drug or who have not recovered from side effects of such therapy to less than grade 2 CTCAE
13. Patients with evidence of mucosal or internal bleeding
14. Patient has unresolved diarrhea ≥ CTCAE grade 2
15. Patient has impaired cardiac function, including any one of the following:
    a. LVEF <LLN of institutional normal, as determined by ECHO or MUGA
    b. Obligate use of a permanent cardiac pacemaker
    c. Congenital long QT syndrome
    d. History or presence of ventricular tachyarrhythmia
    e. Resting bradycardia defined as <50 beats per minute
    f. QTcF >450 msec on screening ECG
    g. Complete left bundle branch block, bifascicular block
    h. Any clinically significant ST segment and/or T-wave abnormalities
    i. Presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria
    j. Myocardial infarction or unstable angina pectoris ≤6 months prior to starting study drug
    k. Symptomatic congestive heart failure (NYHA class III-IV)
    l. Other clinically significant heart disease and vascular disease (e.g., uncontrolled hypertension)
16. Patient taking medications with relative risk of prolonging the QT interval or inducing Torsade de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug
17. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of panobinostat (e.g., ulcerative disease, uncontrolled nausea, vomiting, malabsorption syndrome, obstruction, or stomach and/or small bowel resection)
18. Patient has any other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any

cause, uncontrolled thyroid dysfunction) that could cause unacceptable safety risks or compromise compliance with the protocol
19. Patient has a known history of HIV seropositivity or history of active/treated hepatitis B or C (a test for screening is not required)
20. Women who are pregnant or breast feeding or women of childbearing potential not willing to use a double method of contraception during the study and 3 months after the study evaluation completion treatment, of which one must be a barrier method.
21. Patient is a male not willing to use a barrier method of contraception (a condom) during the study and for 3 months after the study evaluation completion treatment

Treatments
The trial was conducted in 2 treatment phases. In treatment phase 1 (cycles 1-8) patients received panobinostat at a dose of 20mg orally (or matching placebo) on days 1, 3, 5, 8, 10 and 12 of a 21 day cycle. Bortezomib was administered intravenously (IV) at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11. Dexamethasone was administered at a dose of 20 mg orally on days 1, 2, 4, 5, 8, 9, 11 and 12.

Patients who met the modified EBMT criteria for no change (NC) [i.e., did not meet the criteria for complete response (CR), near-complete response (nCR), partial response (PR), minimal response (MR), or progressive disease (PD)/relapse] or achieved a response of MR or better and did not have any toxicity greater than CTCAE grade $\geq$2 could enter treatment phase 2. Treatment phase 2 started with cycle 9. In treatment phase 2 (cycles 9-12) patients received panobinostat at a dose of 20 mg orally (or matching placebo) on days 1, 3, 5, 8, 10, 12, 22, 24, 26, 29, 31 and 33 of a 42 day cycle. Bortezomib as administered intravenously (IV) at a dose of 1.3 mg/m^2 on days 1, 8, 22 and 29 and dexamethasone was given at a dose of 20 mg orally on days 1, 2, 8, 9, 22, 23, 29 and 30.

Reviewer comment: The dose of bortezomib utilized for trial D2308 is slightly different than the dose schedule recommended in the prescribing information for Velcade. The recommended dose schedule of bortezomib for extended therapy of more than 8 cycles is 1.3 mg/m^2 administered once weekly for 4 weeks (Days 1, 8, 15 and 22) followed by a 13 day rest period (Days 23 to 35). The dosing regimen of bortezomib used for trial D2308 differs from the dosing regimen of bortezomib recommend in the prescribing information in that for trial D2308 the recommended day 15 dose was omitted and a day 29 dose was added. From a safety standpoint it is unlikely that the tolerability profile of the schedule used in trial D2308 will have any clinically meaningful difference from the schedule recommended in the prescribing information for Velcade.

Panobinostat/placebo
(Source: section 6.6.2 of D2308 protocol amendment 5)
Patients were instructed to take oral panobinostat/matching placebo three times a week at the same time on each dosing day. Doses were to be separated by a minimum of

30 hours. Each dose of panobinostat/placebo was to be taken with a large glass (approximately 240 mL) of non-carbonated water. Patients were instructed to swallow the capsules whole and not chew them. If vomiting occurred during the course of treatment, then no re-dosing of the patient was allowed before the next scheduled dose. Patients were instructed to avoid grapefruits, grapefruit juice, Seville (sour) oranges and Seville orange juice throughout the study period.

Bortezomib
(Source: section 6.6.2 of D2308 protocol amendment 5)
Before each dose of bortezomib the following criteria were to be met:

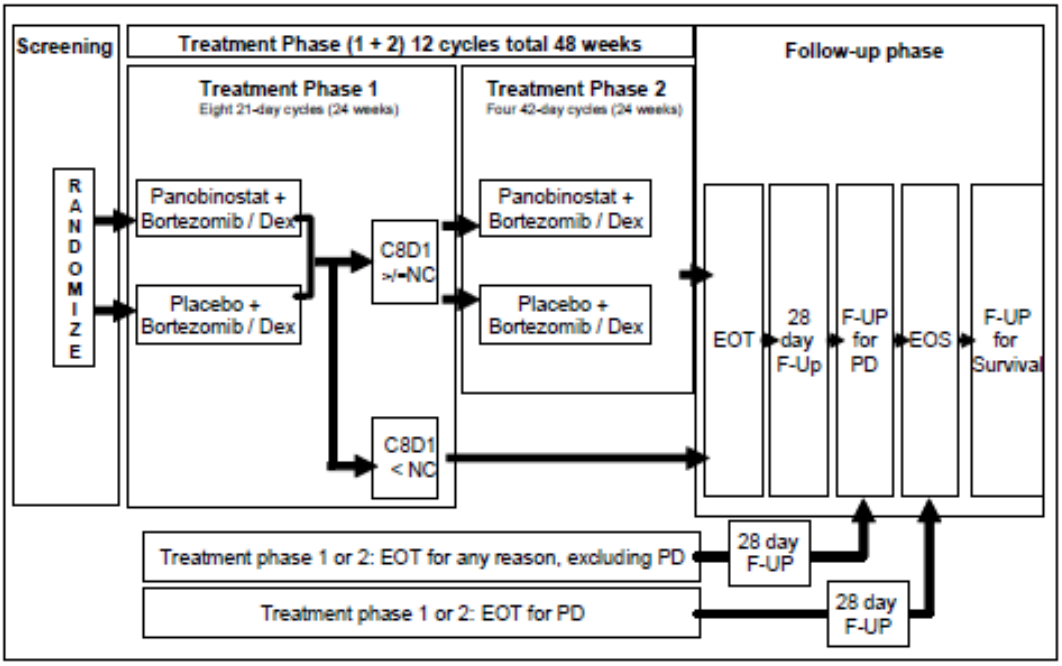
- platelet count was ≥ 25 x 10^9/L (platelet transfusion support was permitted)
- ANC was ≥ 750/µL (growth factor support was permitted as defined in the protocol)

The amount of drug to be administered was determined based on body surface area. Body surface area was calculated based on body weight using a standard nomogram. The dose was calculated on Day 1 of each cycle; the dose administered was to remain the same throughout each cycle but was recalculated at the start of the next cycle. If a patient experienced a notable change in weight (e.g. loss or gain of ≥ 8 lbs. or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose was recalculated at that time.

Dexamethasone
(Source: Source: section 6.6.3 of D2308 protocol amendment 5)
Patients were administered commercially available dexamethasone at a dose of 20 mg per day according to the schedule described above.

Figure 1 D2308 trial design

(Source: Figure 4-1 of D2308 protocol amendment 5)



Legend: C8D1: Cycle 8 Day 1 visit; NC: No change (as per EBMT criteria); EOT: End of treatment; F-UP: follow-up; PD: Progressive disease or relapse from CR; EOS: End of Study.

Dose modifications and interruptions

(Source: 9.4.6 of D2308 clinical study report)

Patients whose study treatment was interrupted due to an adverse event or abnormal laboratory value were to be followed at least once a week for 4 weeks, and subsequently at a minimum of every 4 weeks, until resolution or stabilization of the event, whichever came first.

If a patient required a dose delay of >21 days from the intended day of the next scheduled dose, the patient was to be discontinued from study treatment.

Panobinostat/placebo

The dose of panobinostat/placebo could be reduced to the levels described in Table 3. Dose levels lower than 10 mg three times per week in combination with a minimum 0.7 mg/m^2 dose of bortezomib, with or without dexamethasone, were not permitted. Patients requiring dose modifications lower than these minimum doses were to be discontinued from therapy.

Table 3 Panobinostat/placebo dose reductions

Current dosing level	Dose reduction
20 mg/day	Modify to 15 mg/day
15 mg/day	Modify to 10 mg/day
10 mg/day	No further reduction, discontinue permanently

Patients receiving a reduced dose level of panobinostat/placebo due to toxicity could be considered for dose re-escalation to their previously prescribed dose (i.e., 10 mg escalate to 15 mg) if either the study treatment-related AE had reverted in severity to grade ≤ 1 or baseline level, and at least nine scheduled doses at the reduced level had been administered and tolerated.

The protocol for trial D2308 provided the following guidelines for dose modifications due to toxicity:

Table 4 Panobinostat dose modification/interruption guidelines trial D2308

(Source: Table 6-3 of protocol D2308 amendment 5)

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)		Dose Modification Guidelines At any time during a cycle of therapy (including intended day of dosing)
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia (PLT)	Grade 3 (PLT < 50 x 10^9/L) uncomplicated	No change in dosing
	Grade 4 (PLT < 25 x 10^9/L) or Grade 3 (PLT < 50 x 10^9/L) with bleeding	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then, restart at reduced dose level as per Table 6-2
Neutropenia (ANC)	Grade 3 uncomplicated ANC < 1.0 - 0.75 x 10^9/L	No change in dosing
	ANC < 0.75 - 0.5 x 10^9/L	Single occurrence within cycle, no change in dosing. Two or more occurrences within cycle, hold until return to ≥ Grade 2 (ANC ≥ 1.0 x 10^9/L), and restart at same dose
	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue dosing until resolved to ≤ Grade 2 or baseline, then, restart at reduced dose level as per Table 6-2
	Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue dosing until fever resolved and ANC ≤ Grade 2, then restart at reduced dose level as per Table 6-2
Anemia	Grade 2 (Hgb < 10.0 g/dL)	No change in dosing - Consider supportive measures
	Grade 3 (Hgb < 8.0 - 6.5 g/dL) or Grade 4 (Hgb < 6.5 g/dL)	Temporarily discontinue dosing and use supportive measures until resolved to ≤ Grade 2, or baseline, then, restart at reduced dose level as per Table 6-2

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		Please refer to Section 6.6.5.1.6 and Section 7.5.7
GASTROINTESTINAL		
Diarrhea**	Grade 2 (4-6 stools/day over baseline, etc) persisting despite the use of optimal antidiarrheal medications	Temporarily discontinue dosing until resolved to ≤ Grade 1, or baseline, then restart at unchanged dose level
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue dosing until resolved to ≤ Grade 1, or baseline, then restart reduced by one dose level
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc) despite the use of optimal antidiarrheal medications	Discontinue dosing
Vomiting**/Nausea***	Grade 1 & 2 not requiring treatment **or** controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue dosing until resolved to ≤ grade 1, or baseline, then restart reduced by one dose level
Fatigue		
Fatigue	Grade 3	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then: - If resolved within 7 days after suspending dosing, then restart at an unchanged dose level - If resolved in more than 7 days after suspending dosing, then restart dosing reduced by one dose level
	Grade 4	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then restart dosing reduced by one dose level
HEPATIC		
Total Bilirubin	Grade 3 or 4	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then restart dosing reduced by one dose level
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.		

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)		Dose Modification Guidelines At any time during a cycle of therapy (including intended day of dosing)
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Temporarily discontinue dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor is present), or baseline, then: - If resolved within 7 days restart at unchanged dose level - If resolved in more than 7 days, then reduce dosing by one dose level
	> 10 x ULN	Temporarily discontinue dosing until resolved to ≤ grade 1, or baseline, then restart dosing reduced by one dose level
All dose modifications should be based on the worst preceding toxicity. * Common Terminology Criteria for Adverse Events (CTCAE Version 3.0) ** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing *** See also concomitant medication Section 6.6.7		

The protocol also provided guidelines for dose modifications of panobinostat/placebo due to QTcF abnormalities. If a patient could not be dosed due to prolonged QTcF for more than 7 days since last dose, they were to be discontinued from investigational therapy.

Table 5 Panobinostat/placebo dose modification criteria for QTcF abnormalities

(Source: Table 6-5 of D2308 protocol amendment 5)

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
Cycle 1 dose modification criteria:		
Pre-dose on cycle 1, days 1 and 5: 3 ECGs separated by 5-10 minutes, obtained prior to PAN/placebo dosing		**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Sponsor and transmit to eRT immediately for prompt review.
	Day 1: Average QTcF > 450 msec	If abnormality noted on Day 1 of Cycle 1: Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer study drug treatment.
	Day 5: Average QTcF: ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline average	If abnormality noted on Day 5 of Cycle 1: Delay dose at least 3 days and repeat 3 pre-dose ECGs. If the repeat 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria again, discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: Omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.
Post-dose on cycle 1, days 1 and 5: 3 ECGs separated by 5-10 minutes, obtained 3 hours +/- 0.5 hours after PAN/placebo dosing:	Average QTcF ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. **Monitor ECG hourly** or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose are <480. Notify Sponsor and transmit to eRT immediately for prompt review. Next scheduled dosing day: repeat 3 pre-dose ECGs. If these 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec), discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec) and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3) on the next scheduled dosing day.
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
Cycles 2-8 dose modification criteria:		
Pre-dose on day 1 of each cycle 3 ECGs separated by 5-10 minutes, obtained prior to PAN/placebo dosing	Day 1: Average QTcF > 450 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Sponsor and transmit to eRT immediately for prompt review. If abnormality noted on Day 1 of Cycles 2-8: Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer study drug treatment.
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: Omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.
Post-dose on day 1 of each cycle: 3 ECGs separated by 5-10 minutes, obtained 3 hours +/- 0.5 hours after PAN dosing:	Average QTcF ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. **Monitor ECG hourly** or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose are <480. Notify Sponsor and transmit to eRT immediately for prompt review. Next scheduled dosing day: repeat 3 pre-dose ECGs. If these 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec), discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec) and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
		same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3) on the next scheduled dosing day.
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

Bortezomib

The dose of bortezomib could be reduced by 25% (1.3 mg/m^2 dose reduced to 1.0 mg/m^2 dose; 1.0 mg/m^2 dose reduced to 0.7 mg/m^2 dose). The minimum allowed dose was 0.7 mg/m^2. Guidelines were provided for dose modifications of bortezomib due to toxicity (Table 6). Specific dose modification guidelines for neuropathy related to bortezomib were also provided (Table 7).

Table 6 Bortezomib dose modification guidelines for toxicity

(Source: Table 6-8 protocol D2308 amendment 5)

CTCAE Category	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Uncomplicated Gr 3 Neutropenia (ANC < 1.0 x 10^9/L) or uncomplicated Gr 3 Thrombocytopenia (PLT < 50 x 10^9/L)	No change in dosing
≥ Febrile neutropenia (Grade 3 ANC < 1.0 x 10^9/L , associated with fever, i.e. temperature ≥ 38.5° C) or Neutropenia Gr 4 (ANC < 0.5 x 10^9/L) and/or Thrombocytopenia Gr 3 (PLT < 50 x 10^9/L) with bleeding, or Gr 4 (PLT < 25 x 10^9/L)	Hold therapy until neutropenia and/or thrombocytopenia both resolve to ≤ Gr 2 ; if only one dose was omitted prior to correction to these levels, BTZ should be restarted at same dose, if two or more doses were omitted - consecutively, or within the same cycle - then BTZ should be restarted at a reduced dose by one dose level.
Peripheral Neuropathy	See Table 6-9
Herpes Zoster reactivation any grade	Hold therapy until lesions are dry.
Other BTZ related non-hematologic toxicity ≥ Gr 3	Determine attribution of toxicity and hold therapy. If toxicity resolves to ≤ Gr 2, resume therapy with one level dose reduction.

Table 7 Bortezomib dose modification guidelines for neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Gr 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Gr 1 with pain or Gr 2 (interfering with function but not with activities of daily living)	Reduce by one dose level
Gr 2 with pain or Gr 3 (interfering with activities of daily living)	Hold BTZ therapy until toxicity resolves to < Gr 2 When toxicity resolves, reinitiate with a reduction by one dose levels and change treatment schedule to once per week. (day 1 and 8) during cycles 1-8 During TP2 cycles discontinue BTZ
Gr 4 (Permanent sensory loss that interferes with function)	Discontinue BTZ
Grading based on NCI Common Terminology Criteria CTCAE v3.0 NCI Common Toxicity Criteria website - http://ctep.info.nih.gov/reporting/ctc.html ADL = activities of daily living	

Patients requiring discontinuation of bortezomib due to peripheral neuropathy could continue on panobinostat/placebo ± dexamethasone. Bortezomib could be restarted at any time during treatment phases 1 and 2 if clinically indicated and in accordance with the local prescribing instructions. Patients requiring permanent discontinuation of bortezomib due to any other reason or permanent discontinuation of panobinostat/placebo were to discontinue study treatment and be followed for progressive disease/relapse and survival.

Dexamethasone
The dose of dexamethasone could be reduced to 10 mg. Patients unable to tolerate the minimum dose of dexamethasone 10 mg could continue on the rest of their randomly assigned regimen without receiving dexamethasone. Dose modification guidelines for toxicity related to dexamethasone are described in Table 8.

Table 8 Dexamethasone dose modification guidelines for toxicity

(Source: Table 6-10 protocol D2308 amendment 5)

Dexamethasone dose modifications		
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Gr 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease Dex dose by 1 dose level
	> Gr 3 (requiring hospitalization or surgery)	Hold Dex until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue Dex and do not resume
	Acute pancreatitis	Discontinue Dex and do not resume
Cardiovascular	Edema > Gr 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease Dex dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue Dex and do not resume if symptoms persist despite second reduction
Neurology	Confusion or Mood alteration > Gr 2 (interfering with function +/- interfering with activities of daily living)	Hold Dex until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue Dex do not resume.
Musculoskeletal	Muscle weakness > Gr 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease Dex dose by one dose level. If weakness persists despite above measures decrease dose by one dose level. Discontinue Dex and do not resume if symptoms persist
Metabolic	Hyperglycemia > Gr 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory

Management of diarrhea

(Source: section 6.6.5.1.4 of D2308 protocol amendment 5)

Patients were instructed to contact their physician at the onset of diarrhea. Each patient was instructed to have loperamide readily available and begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements that were more frequent than normally expected. Prophylaxis with loperamide was not recommended.

Prohibited therapies

Prohibited treatments included chemo-, biologic or immunologic therapy and/or other investigational agents, as well as deacetylase inhibitors, including valproic acid. Prophylactic anti-emetics such as granisetron could be administered at the discretion of the Investigator. However, anti-emetics associated with QT prolongation (e.g. dolasetron, ondansetron, tropisetron) were prohibited.

Co-medications which are known to prolong the QT interval and/or induce Torsades de Pointes (strong CYP3A4/5 inhibitors or CYP2D6 substrates) were prohibited unless approved by the Sponsor.

Concomitant medications

Growth factor support

Granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) was not to be used prophylactically in the first cycle. G-CSF was to be initiated for an individual patient in accordance with American Society of Clinical Oncology's guidelines (Smith, et al 2006), if the patient experienced febrile neutropenia and/or grade 4 neutropenia for >7 days. Growth factors could then be administered prophylactically in all subsequent cycles for that patient.

Patients who were receiving available recombinant erythropoiesis stimulating agents (ESA) such as epoetin and darbepoetin prior to starting study treatment could continue therapy throughout the study. ESA therapy could also be introduced during the study.

5.3.1.3 Clinical trial landmarks and protocol amendments

Date	Landmark
January 29, 2010	First patient enrolled
June, 30, 2010	Amendment 1, 34 patients randomized: Local, country-specific amendment for Japan whose main purpose was to include hospitalization of Japanese patients during the first cycle of treatment in order to comply with the local bortezomib label. Secondly, this amendment included PK sampling on Cycle 1 Day 1 and Cycle 1 Day 8 in Japanese patients. Thirdly, this amendment added the commercially available dosage form of bortezomib available in Japan as part of the global protocol. As of the release date of this amendment, 34 patients had been randomized worldwide.
December 22, 2011	Amendment 2, 668 patients randomized: Global amendment to adjust the sample size to compensate for a higher than expected drop-out rate in the absence of any safety concerns. A review of blinded data concluded that the drop-out rate was higher than originally assumed. The main reason for the drop-out rate was that patients who discontinued treatment withdrew their consent to be followed for response assessment as per protocol. As a consequence, the expected drop-out rate as written in the statistical section of the original protocol needed to be updated.
March 7, 2012	Amendment 3, 742 patients randomized: This amendment was a global amendment to enhance robustness of the second interim analysis (IA2), in order to provide a more precise estimate of the treatment effect and to increase the probability of detecting a treatment effect. This amendment increased the PFS event fraction for IA2 from 67% to 80% (306 to 368 events). If the study were to be stopped at IA2, the higher fraction of planned PFS events would reduce the risk of an overestimation of the treatment effect. The treatment effect assumptions (HR 0.74) were unchanged. The power to detect a treatment effect and to stop the study at IA2 for efficacy

	was increased from 53% to 71%. The cumulative type I error was unchanged (less than 5 %, two-sided). Based on the recommendation of the Study Steering Committee, an additional secondary objective was added: to compare nCR plus CR between treatment arms per mEBMT criteria. The definition of PFS was clarified as an event of progression, relapse or death; events defining PFS and the statistical methodology to analyze this endpoint remained unchanged.
October 2, 2012	Amendment 4, 87 remaining on treatment: The main aim of this global amendment was to clarify that the collection of serum calcium variables (ionized serum calcium and/or total serum calcium and serum albumin for the derivation of albumin-adjusted serum calcium) should continue after the end of treatment until the end of follow-up for disease evaluations.
March 1, 2013	Last patient completed treatment
May 6, 2013	Amendment 5, 768 patients randomized, For efficacy assessments, the study protocol required measurement of M-protein spikes by PEP in serum and urine as per mEBMT criteria. Sites participating in the study used their local laboratories to perform the M-protein assessments. However, it was discovered that some patients were being monitored using either PEP without specific measurement of the M-protein spike (e.g. globulin gamma fraction was used as the indicator for an IgG M-component) or by alternative methods, other than PEP (e.g. nephelometric quantification of immunoglobulin levels). Although these methods are used in routine clinical practice, they are not protocol-defined for measuring M-protein per mEBMT criteria. Accordingly, the objective of this protocol amendment was: • to document PEP results without specific measurement of the M-protein spike, and • to document use of measurement methods other than PEP (e.g. nephelometry) Patients continued to be followed with the same method throughout the study to ensure intra-patient consistency. The analysis of the primary endpoint of PFS remained based on the Investigator's response assessment following the ITT principle. The newly

	collected data was used in sensitivity analyses of PFS and other efficacy-related endpoints, including an analysis using an independent response assessment in patients for whom M-protein was not measured by PEP or PEP was used without measurement of M-protein spike. The independent response assessments were to be performed by an IRC.
September 10, 2013	Data cut-off for clinical study report

Reviewer comment: These protocol amendments did not impact the safety evaluation of the treatment arms. I defer to the clinical efficacy reviewer for evaluation of the impact of these amendments on the efficacy findings from trial D2308.

5.3.1.4 Safety evaluation

Figure 2 Trial D2308 Schedule of Study Assessments

	Screening	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 (day 1 to 21)					Cycle 2 to cycle 8 (day 1 to 21)				Cycle 9 - 12 (day 1 to 42)				End of Treatment	28 day Follow-up	Follow-up	Study Evaluation Completion	Survival
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	-21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
Demography/ informed consent	X																		
Inclusion/exclusion criteria	X																		
Medical history/ current medical conditions	X																		
Diagnosis & history of multiple myeloma	X																		
Prior antineoplastic therapy	X																		
Vital signs	X	X		X			X				X				X				
Height	X																		
Weight/Body Surface Area	X	X					X				X				X				
Physical examination	X	X					X				X				X				
ECOG performance status	X	X					X				X				X				
12-lead ECG	X	X		X			X												

	Screening	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 (day 1 to 21)					Cycle 2 to cycle 8 (day 1 to 21)				Cycle 9 - 12 (day 1 to 42)				End of Treatment	28 day Follow-up	Follow-up	Study Evaluation Completion	Survival
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	-21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
LVEF (MUGA or ECHO)	X	X																	
Hematology	X	X	X		X	X	X	X	X	X	X	X	X	X	X				
Coagulation	X																		
Biochemistry	X	X				X	X			X	X[a]		X		X		X		
Urinalysis	X																		
Calculated Creatinine Clearance	X						X				X				X				
Pregnancy test	X														X				
PRO/QoL questionnaires (QLQ-C30, MY20, FACT GOG/NTx)	X	X					X				X							X	
Patient/Investigator Global Change							X											X	
Patient/Investigator Global Severity	X						X												
Thyroid function	X						X								X				
Disease status:																			
Serum M-protein (S-PEP)	X	X					X				X		X		X		X		

	Screening	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 (day 1 to 21)					Cycle 2 to cycle 8 (day 1 to 21)				Cycle 9 - 12 (day 1 to 42)				End of Treatment	28 day Follow-up	Follow-up	Study Evaluation Completion	Survival
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	-21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
Urine M-protein (U-PEP)	X	X					X				X		X		X		X		
Serum free light chain							X				X								
Serum immunofixation	X						X				X		X		X		X		
Urine immunofixation	X						X				X		X		X		X		
Skeletal survey (Bone X-ray)	X																		
Evaluation of soft-tissue plasmacytomas	X						X				X		X		X		X		
Bone marrow for plasma cell count and for flow cytometry	X																		
Panobinostat/Placebo blood PK samples		X			X														
Bortezomib blood PK samples					X														
Bortezomib bolus intravenous injection		X	X		X	X	X	X	X	X	X	X	X	X					
Panobinostat / Placebo		Days 1-3 -5 + 8-10-12 (3 times weekly, 2 weeks on & 1 week off, 21 day cycle)									Days 1-3-5, 8-10-12 & 22-24-26, 29-31-								

	Screening	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 (day 1 to 21)					Cycle 2 to cycle 8 (day 1 to 21)				Cycle 9 - 12 (day 1 to 42)				End of Treatment	28 day Follow-up	Follow-up	Study Evaluation Completion	Survival
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	-21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
											33 (42 days cycle)								
Dexamethasone		Days 1-2-4-5 + 8-9-11-12									Days 1-2-8-9 + 22-23-29-30								
Adverse Events	X	Continuous																	
Prior/Concomitant medications	X	Continuous																	
Anti-neoplastic medications since discontinuation of study treatment															X	X	X	X	X
Survival																		X	

(Source: section 9.5.4 of D2308 clinical study report)
Safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. Assessments also included the regular monitoring of hematology, coagulation and blood chemistry panels and urinalyses performed at study centers, as well as regular assessments of vital signs, physical condition including performance status, and body weight. A central ECG laboratory ([redacted] (b) (4) was used for independent review of ECG evaluations.

(Source: section 7.5 of D2308 clinical study report
Physical examinations including a systematic, abbreviated neurological assessment were conducted at screening, day 1 cycle 1, day 1 of each cycle prior to the administration of study treatment and at the end of treatment visit. Vital signs including oral temperature, respiratory rate, sitting blood pressure, and sitting pulse were conducted at screening, day 1 cycle 1, day 5 cycle 1, day 1 of each cycle prior to the administration of study treatment and at the end of treatment visit. Performance status was evaluated at screening, day 1 cycle 1, day 1 of each cycle prior to the administration of study treatment and at the end of treatment visit. Weight/BSA was measured at baseline, at the start of every cycle, and at the EOT visit. ECG assessments were conducted according the schedule outlined in (Table 9)

Table 9 Schedule of ECG assessments trial D2308

(Source: Table 7-3 study D2308 protocol amendment 5)

Cycle	Day of cycle	ECG monitoring [a]
	Screening [b]	1 single ECG
Cycle 1	1, 5 [c]	Pre-dose: 3 sequential ECGs separated by at least 5-10 minutes Post-dose at 3 hours ± 0.5 hour: 3 sequential ECGs separated by at least 5-10 minutes
Cycle 2-8	1	Pre-dose: 3 sequential ECGs recorded at least 5-10 minutes apart

[a] Refer to Table 6-5 for the recommended dose modifications due to QTc interval prolongation

[b] The screening ECGs will be analyzed centrally to assess eligibility of the patient. (Note: the mean QTc interval at baseline must be ≤ 450msec for the patient to be eligible for participation in the trial)

[c] Cycle 1 Day 5: Pre-dose ECGs can be done on Cycle1 Day 4 visit when patient is at the site for BTZ injection (but not post-dose ECGs of Day 5 as relative to PAN dosing)

Note: If no significant QTcF prolongation is noted during the first 8 cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion, if medically indicated.

A baseline multiple gated acquisition (MUGA) scan or echocardiogram (ECHO) was to be performed at screening (or at day 1 cycle 1 if screening assessment was conducted >7 days prior to first dose of investigational therapy). If the result from this MUGA/ECHO shows a clinically relevant change (e.g. a reduction of >5% or as defined by the institution), a formal cardiac evaluation was to be sought and a repeat MUGA/echo be conducted at the beginning of every-other treatment cycle (or at the discretion of the cardiologist/investigator). More frequent assessments could be performed if medically indicated as determined by the Investigator, and these evaluations were to be recorded on the Unscheduled Visit CRF.

(Source: section 9.6.3 of D2308 clinical study report)
Hematology, coagulation, biochemistry, urinalysis and thyroid function tests were performed by local laboratories. Analyses of serum and urine M-protein, and serum and urine immunofixation assays were also performed locally by the site labs or by locally selected laboratories that served as "central laboratory" for a few sites.

Hematology included the following parameters: complete blood count (CBC) consisting of red blood cell (RBC), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count. Hematology assessments were conducted at screening at day 1 cycle 1, prior to each administration of Bortezomib or ≤72 hours prior to dosing and at the end of treatment visit.

Coagulation profile included prothrombin time (PT) or International Normalized Ratio (INR), activated partial thromboplastin time (aPTT) and fibrinogen. A coagulation profile was required be performed at screening. More frequent assessments could be performed if medically indicated as determined by the investigator, and these

evaluations were to be recorded on the unscheduled visit CRF. Coagulation parameters were to be monitored more frequently for patient receiving warfarin or other anti-coagulant therapy.

Urinalysis included dipstick and microscopic exams. Dipstick examination included protein, glucose, blood, and specific gravity. Microscopic examination is only required if dipstick analysis is abnormal (with exception of proteinuria) and includes: WBC/HPF, RBC/HPF, and any additional findings. A urinalysis was required to be performed at screening. Repeat assessments were performed if medically indicated.

Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine) were measured at screening, prior to treatment on Day 1 of following treatment cycles: 2, 3 and 4 and at the end of treatment visit. More frequent assessments could be performed if medically indicated. Findings from these evaluations were to be recorded on the Unscheduled Visit CRF.

(Source: section 7.5.5 of D2308 clinical study report)
At any time during the trial abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), were to be recorded in the CRF. When abnormal laboratory values or test results constituted a clinically significant adverse event, they were to be recorded on the CRF Adverse Events page.

6 Review of Efficacy

Efficacy Summary

Please refer to Mr. Miller's review for discussion of the efficacy review of NDA 205353.

7 Review of Safety

Safety Summary

The safety review of the Applicant's proposed dosing regimen of panobinostat 20 mg administered orally once daily 3 times a week (days 1, 3, 5, 8, 10, 12), on a 2 weeks on 1 week off dosing regimen for up to 16 cycle in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy utilized the results of the randomized multicenter, randomized, double-blind, placebo controlled trial D2308. The safety review of panobinostat in combination with bortezomib and dexamethasone also included the results of a dose escalation trial (B2207) and a single arm trial (DUS71).

Trial B2207 was a dose escalation trial that explored the tolerability of doses of panobinostat from 10 mg to 30 mg in combination with bortezomib at doses of 1 mg/m^2 or 1.3 mg/m^2 administered weekly for 3 weeks. In this trial a total of 17 patients were exposed to panobinostat 20 mg administered 3 times weekly every week of a 21 day cycle which was determined to be the maximum tolerated dose (MTD) in combination with bortezomib 1.3 mg/m^2. Fifteen patients were evaluable for dose limiting toxicities (DLT) and of these patients 3 experienced a DLT (Table 13). In comparison none of the 11 patients treated at lower dose cohorts experienced a DLT. Out of 17 patients exposed to panobinostat in combination with bortezomib at the MTD, 77% of patients had at least 1 adverse event that required dose adjustment or interruption. In comparison, out of the 14 patients in cohort 1 and 2 that were evaluable for toxicity 8 patients (57%) experienced at least 1 adverse event that led to dose adjustment or interruption. Eight patients (47%) treated at the MTD experienced thrombocytopenia that led to dose adjustment or interruption. In comparison, out of the 14 patients in cohort 1 and 2 that were evaluable for toxicity 5 (36%) experienced thrombocytopenia that led to dose adjustment or interruption. All of the patients (100%) dosed at the MTD experienced a grade 3-4 adverse event. More important is the finding that 77% (n=13) of patients treated at the MTD experienced a serious adverse compared to 43% (n=6) patients in cohorts 1 and 2.

Reviewer Comment: This early dose escalation trial provides preliminary evidence that the dose and schedule selected for the MTD of panobinostat in combination with bortezomib and dexamethasone is associated with severe toxicity is difficult for patients to tolerate.

During the dose expansion phase of trial B2207 a dose the schedule of panobinostat 20 mg administered 3 times per week for 2 weeks on and 1 week off of a 21 day cycle in combination with bortezomib and dexamethasone was explored. The rationale for exploring this schedule was to allow for platelet recovery and minimize dose interruptions. In the dose expansion phase 15 patients were evaluable for toxicity. A total of 11 patients (73%) had at least 1 adverse event that led to dose adjustment or interruption. Thrombocytopenia led to dose adjustment or interruption in 4 (27%) of patients. Grade 3-4 adverse events occurred in 87% of patients and SAEs occurred in 40% with 33% experiencing adverse events that led to hospitalization. Despite the reduced dosing schedule from weekly for 3 weeks to weekly for 2 weeks of a 21 days cycle, 75% were not able to tolerate the intended dose schedule. In addition, severe toxicity occurred in 87% of the patients.

Reviewer Comment: The results of the dose expansion phase are consistent with the findings from the dose escalation phase. The Applicant's proposed dosing schedule of panobinostat 20 mg in combination with bortezomib and dexamethasone is associated with severe toxicity and is difficult for patients to tolerate.

Despite the early signals of severe toxicity and issues with tolerability the Applicant further investigated the 20 mg dose of panobinostat in combination with bortezomib and dexamethasone in an adequately designed randomized, double-blind, placebo controlled trial. The control arm of bortezomib 1.3 mg/m^2 in combination with dexamethasone is a standard of care regimen commonly used for the treatment of patients with relapsed multiple myeloma.

In trial D2308 a total of 758 patients with relapsed multiple myeloma were exposed to investigational therapy and evaluable for safety. There were 368 patients who received at least one dose of panobinostat in combination with bortezomib and dexamethasone, and 372 patients that received at least one dose of placebo in combination with bortezomib and dexamethasone. Overall the demographics of the trial populations were well-balanced between the treatment arms. The mean age of 62 years for both treatment arms is consistent with the mean age of the trial populations for other products approved for second line multiple myeloma (e.g., bortezomib and lenalidomide). The median duration of exposure to panobinostat + bortezomib + dexamethasone was more than a month shorter than the median exposure for patients who received placebo + bortezomib +dexamethasone (153 days panobinostat vs. 184 days placebo) suggesting that the investigational arm was less tolerable than the control arm.

The percentage of patients in each treatment arm that experienced an adverse event of any grade was 99.7% for the panobinostat arm and the control arm. The most common adverse events that occurred in $\geq$20% of patients in the panobinostat arm and at a $\geq$10% greater frequency than the control arm were diarrhea, thrombocytopenia, fatigue, nausea, neutropenia, peripheral edema, decreased appetite, hypokalemia, pyrexia and vomiting (Table 30). The incidence of patients that experienced grade $\geq$3 adverse events was higher in the panobinostat arm 95% (n=367) compared to the incidence in the control arm 83% (n=307). Grade $\geq$3 thrombocytopenia was the most common severe adverse event (experienced by 57% of patients in the panobinostat arm compared to 25% of patients in the control arm). The most common grade $\geq$3 adverse events that occurred in $\geq$10% of patients in the panobinostat arm were thrombocytopenia, diarrhea, neutropenia, hypokalemia, anemia, fatigue, pneumonia, lymphopenia, asthenia and hyponatremia. It is important to point out that grade 3-4 diarrhea, neutropenia and hypokalemia occurred and a 3 fold higher rate than in the control arm (Table 22). Serious adverse events were also more common in the panobinostat arm with 230 patients (60%) experiencing at least 1 SAE compared to 155 patients (42%) in the control arm. The most common SAEs that occurred in $\geq$5% of patients in the panobinostat arm were pneumonia, diarrhea and thrombocytopenia (Table 19). Fifty-five percent of patients treated with panobinostat (n=211) experienced an adverse event that led to hospitalization or prolongation of hospitalization compared to 37% (n=138) of patients treated in the control arm.

The percentage of patients that discontinued therapy due to an adverse event was higher in the panobinostat arm compared to the control arm. 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. The most common reason for treatment discontinuation in the panobinostat arm was diarrhea which accounted for 4% of patients in the panobinostat arm which is 2 fold higher than the rate in the control arm (Table 18). Adverse events of any toxicity grade leading to treatment interruption or dose modification occurred in 342 (89%) of patients in the panobinostat arm compared to 281 (76%) patients in the control arm. The most common reason for dose modification or treatment interruption in the panobinostat was thrombocytopenia which occurred in 31% of patients (Table 21) treated with panobinostat compared to 11% of patients in the control arm. These data corroborate the data from the early phase trials that the proposed dose regimen of panobinostat in combination with bortezomib and dexamethasone is associated with severe toxicity the frequency of which is greater than a standard of care regimen for multiple myeloma (bortezomib + dexamethasone). This increase in severe toxicity is also accompanied by and increased frequency of patients requiring treatment interruption/dose modification or treatment discontinuation.

During the review of the safety data a number of primary safety concerns were identified:

- Grade $\geq$3 asthenic conditions including fatigue, malaise and weakness were reported in in 93 (24%) of patients in the panobinostat arm compared to 47 (13%) of patients in the control arm. Due to asthenic conditions 90 patients (23%) in the panobinostat arm compared to 42 patients (11%) in the control arm had a treatment modification or interruption. Asthenic conditions also lead to treatment discontinuation in 23 patients (6%) in the panobinostat arm compared to 11 patients (3%) in the control arm. Exploratory reviewer analysis of submitted QOL data from trial D2308 suggests that panobinostat had a greater negative impact on the QOL of patients in the panobinostat arm compared to patients in the control arm. Formal statistical analyses with alpha allocation were not conducted on the QOL data. Therefore, these findings should be interpreted with caution.
- Severe gastrointestinal toxicity manifested as nausea, vomiting and diarrhea that led to serious events of dehydration
- Severe thrombocytopenia and neutropenia. Events of severe thrombocytopenia led to an increase in grade 3-4 hemorrhagic events in the panobinostat arm, 4% vs 2% for the control arm. In addition, 5 patients receiving panobinostat died due to hemorrhage compared to 1 patient receiving the control arm.
- Grade 3-4 infections/infestations occurred in 119 patients (31%) in the panobinostat arm compared to 90 (24%) patients in the control arm. Pneumonia, sepsis and septic shock occurred at a rate $\geq$2% more frequent in the panobinostat arm. In addition, deaths due to infection occurred in 10 patients (3%) in the panobinostat arm compared to 6 patients (2%) in the control arm. These findings are consistent with the known toxicity profile of HDAC inhibitors.

The severity of toxicity with this panobinostat regimen is also evidenced by an imbalance in treatment emergent deaths. There were 26 patients (7%) in the panobinostat arm who died due to treatment emergent toxicities compared to 12 patients (3%) in the control arm. This reviewer did not agree with the reported event preferred term for a number of the deaths. For this reason, deaths were also grouped into reviewer categories based upon the reviewer's interpreted cause of death. The reviewer categories of hemorrhage and infection were the main contributors to the observed imbalance of deaths between the treatment arms. Hemorrhage and infection are both toxicities associated with panobinostat therapy which lends support that this observed imbalance in deaths is likely due to panobinostat toxicity and not simply a chance finding.

Of additional concern is that there were 2 patient sub-populations identified that experienced a high frequency of adverse events compared to the broader D2308 trial population. Patient's age ≥65 years experienced higher rates of diarrhea, thrombocytopenia, anemia and fatigue. Most notably patients age ≥65 years experienced a 10% increase in grade ≥3 diarrhea, 17% increase in grade ≥3 thrombocytopenia, 5% increase in grade ≥3 anemia and 10% increase in grade ≥3 fatigue (Table 35). Adverse reactions leading to treatment discontinuation occurred in 44% (n=71) of patients age ≥65 years compared to 30% (n=68) of patients age <65 years who received panobinostat. Adverse reactions leading to treatment interruption and/or dose modification occurred in 91% of patients age ≥65 years compared to 87% age <65 years who received panobinostat. There were 14 patients (9%) age ≥65 years compared to12 patients (5%) age <65 years who died due to a reason other than disease progression in the panobinostat arm.

Patients of Asian race also experienced a higher frequency of adverse events compared to the non-Asian D2308 trial population. Overall Asian patients experienced a higher frequency of grade 1-4 and grade ≥3 adverse reactions compared to Caucasian patients. Most notably, Asian patients experienced a 13% increase in grade ≥3 diarrhea, 11% increase in grade ≥3 thrombocytopenia and 20% increase in grade ≥3 hypokalemia (Table 36).

7.1 Methods

The safety review of panobinostat in combination with bortezomib and dexamethasone was performed by reviewing the following items submitted by the Applicant:

- Summary of clinical safety
- Study protocols for trials D2308, B2207 and DUS71
- Clinical study reports for trials D2308, B2207 and DUS71
- Raw and analysis datasets for trials D2308, B2207 and DUS71
- Case report forms for trials D2308, B2207 and DUS71
- Narratives for deaths, SAEs, withdrawals due to AEs and clinically notable AEs
- Integrated summary of safety datasets

- Applicant response to information requests
- Proposed labeling for Farydak

Reviewer comment: Overall the Applicant's safety analyses were able to be replicated almost to the exact number and frequency and were therefore exceptionally reliable. For this reason the Applicant's results for some of the more complex analyses were utilized in order to meet the timelines of this priority review Application. The only discrepancy was with the treatment assignment for 5 patients in the Applicant's proposed safety analysis population. This is further discussed in section 7.2.1.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study reports and raw and analysis data sets were provided for trial CLBH589B2207, LBH589DUS71 and the randomized controlled trial CLBH589D2308. The randomized controlled trial D2308 will serve as the main trial to evaluate the safety of panobinostat in combination with bortezomib and dexamethasone due to the large number of patients evaluable for safety (n=758) and the inclusion of a control arm (placebo + bortezomib + dexamethasone) which will allow for a direct comparison of safety between the two arms. The safety findings from trials B2207 and DUS71 will be discussed briefly as they provide supportive information for evaluating the toxicity profile of panobinostat in a single-arm setting.

7.1.2 Categorization of Adverse Events

D2308
(Source: section 7.5 of D2308 amendment 5 protocol)
Adverse events were assessed according to the common toxicity criteria for adverse events (CTCAE) version 3.0. If CTCAE grading did not exist for an event, the severity of mild, moderate, severe or life-threatening, or grades 1-4 could be used. CTCAE grade 5 was not used for this trial. Information regarding death was collected in the end of treatment or study evaluation completion CRF page. Adverse event monitoring was continued for at least 4 weeks following the patient receiving their last dose of study treatment. According the protocol abnormal laboratory values or test results were considered adverse events only if they induced clinical signs or symptoms, were considered clinically significant or required therapy (e.g., any hematological abnormality that requires transfusion or cytokine treatment). These events were captured on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

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

An analysis of all grade 1-4 adverse events was conducted and included all patients who received panobinostat at a dose of 20mg orally on days 1, 3, 5, 8, 10 and 12 of a 21 day cycle in combination with bortezomib and dexamethasone in clinical trials of

relapsed multiple myeloma submitted to the NDA (Table 10). This analysis includes the 386 patients exposed to panobinostat in trial D2308, 15 patients in the expansion cohort of trial B2207 and 55 patients enrolled in trial DUS71. In trial B2207 only the 15 patients in the expansion cohort received panobinostat at the same dose and schedule as that used for trial D2308.

Table 10 Adverse events in ≥10% of patients with multiple myeloma who received panobinostat at the recommended dosing schedule

Preferred term, n (%)	**All trials at recommend dosing schedule Grade 1-4 Pan + Bor + Dex (n=456)**	**Trial D2308 Grade 1-4 Pan + Bor + Dex (n=386)**	**Trial D2308 Grade 1-4 Pbo + Bor + Dex (n=372)**
Diarrhea	316 (69)	264 (68)	153 (41)
Thrombocytopenia	296 (65)	249 (65)	151 (41)
Fatigue	206 (45)	158 (41)	109 (29)
Anemia	191 (42)	160 (42)	124 (33)
Nausea	182 (40)	139 (36)	22 (21)
Decreased appetite	142 (31)	110 (29)	44 (12)
Neuropathy peripheral	141 (31)	119 (31)	132 (36)
Peripheral edema	138 (30)	119 (31)	132 (36)
Neutropenia	133 (29)	114 (30)	40 (11)
Constipation	131 (29)	104 (27)	121 (33)
Hypokalemia	125 (27)	106 (28)	52 (14)
Vomiting	122 (27)	99 (26)	48 (13)
Pyrexia	117 (26)	99 (26)	54 (15)
Asthenia	103 (23)	85 (22)	54 (15)
Dizziness	101 (22)	73 (19)	60 (16)
Cough	98 (22)	83 (22)	68 (18)
Upper respiratory tract infection	92 (20)	68 (18)	55 (15)
Insomnia	90 (20)	73 (19)	61 (16)
Dyspnea	81 (18)	57 (15)	43 (12)
Pneumonia	75 (16)	65 (17)	48 (13)
Leukopenia	71 (16)	63 (16)	30 (8)
Hypotension	68 (15)	54 (14)	34 (9)
Headache	65 (14)	53 (14)	39 (11)
Lymphopenia	68 (15)	52 (13)	35 (9)
Back pain	64 (14)	50 (13)	45 (12)
Hyponatremia	58 (13)	49 (13)	19 (5)
Decreased weight	57 (13)	44 (11)	17 (5)
Dysgeusia	54 (12)	36 (9)	26 (7)
Hypophosphatemia	52 (11)	44 (11)	31 (8)
Pain in extremity	48 (11)	40 (10)	54 (15)
Blood creatinine increased	47 (10)	38 (10)	22 (6)

Reviewer comment: Overall the incidence of adverse events was similar between patients enrolled in trial D2308 and all patients with relapsed multiple myeloma that received panobinostat in combination with bortezomib and dexamethasone at the recommended dosing schedule used in trial D2308.

7.2 Adequacy of Safety Assessments

In general, the safety assessments conducted in trial D2308 were adequate to evaluate the toxicity profile of panobinostat in combination with bortezomib and dexamethasone. The one exception is that routine clinical laboratory testing was not adequate to evaluate if panobinostat had an effect on platelet function. Refer to section 7.2.4 of this review for further discussion.

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

The datasets for trial D2308 included 769 unique patient ID numbers. The Applicant was sent an information request (IR) to clarify why 769 patients were included in the dataset but the clinical study report states that only 768 patients were randomized. The Applicant responded as followed:

"There were a total of 768 patients randomized in the study but 769 patient IDs were assigned to randomized treatment code. One patient was randomized twice with patient ID (SID1A = 0261_00001) and patient ID (SID1A = 0261_00003), both times randomized to PBO+BTZ+Dex.

This patient was randomized under the SID1A of 0261_00001 on 20-Jun-2011 and never received any treatment. The same patient was again randomized on 20-Jul-2011 under the SID1A of 0261_00003 and received study treatment from 22-Jul-2011 till (sic) 25-Sep-2011. The patient was initially screened and did not meet all inclusion-exclusion criteria but was not documented as screen failure since the screening period exceeded three weeks, which is the allowed screening period in the protocol. Therefore, the patient was subsequently randomized again with a different ID.

This patient was considered in both Full Analysis Set and Safety set with the second randomization ID (0261_00003), and assigned to PBO+BTZ+Dex for both analysis sets. The patient with ID 0261_00001 was considered to be a protocol violation with severity code=8 (i.e. exclusion from all analysis) and was not included in any efficacy or safety analysis.

This describes the difference in FAS consisting of 768 patients though 769 patients IDs were assigned randomization treatment code.

For transparency, all relevant raw and derived datasets (including ATTEEBMT and AAEV) include all 769 assigned patient IDs."

In the clinical study report for trial D2308 the Applicant reports that a total of 758 patients received at least one dose of investigational therapy with 381 patients having received panobinostat and 377 patients receiving placebo. During review of the IVR raw dataset it was discovered that 2 patients received medication packs that contained drug which was different from the patient's randomization assignment. The Applicant was sent an IR and they confirmed that 2 patients (0292_00002 and 0087_00001)received medication packs that contained drug which was different from the patient's randomization assignment. The Applicant responded to the IR as followed:

Patient CLBH589D2308_0292_00002 received placebo matching panobinostat (LBH589) 20 mg on Cycle 1 day 1 (first dose) instead of assigned panobinostat. From Cycle 3 day 1 onwards this patient received panobinostat. This patient is assigned to panobinostat as randomized for full analysis set and placebo as treated in safety set (D2308 CSR table 11-1)

Reviewer comment: I disagree with the Applicants proposal to include this patient in the placebo group for safety analyses. The patient was randomized to the panobinostat arm and received treatment with panobinostat from Cycle 3 through cycle 9. For the majority of the duration of therapy the patient was exposed to panobinostat. For exposure and safety analyses this patient will be included in the panobinostat group.

Patient CLBH589D2308_0087_00001 received panobinostat (LBH589) 20 mg on Cycle 5 day 1 (not the first dose) instead of assigned placebo. Since "as treated" is analyzed according to the first non-zero dose of the study drug, this patient is assigned to placebo for both full analysis set and safety set.

Reviewer comment: I disagree with the Applicants proposal to include this patient in the placebo (control) group for the safety analyses. This patient received 2 cycles of therapy with panobinostat. For exposure and safety analyses this patient will be included in the panobinostat group.

Based upon this response to IR the applicant was sent an additional IR to re-conduct the major safety analyses assigning patients 0292_00002 and 0087_00001 to the panobinostat arm. In response to this IR (SD 19) the Applicant also identified 3 additional patients who were randomized to placebo and received at least one dose of panobinostat. These patients are 0170_00002, 0319_00005 and 0909_00001. In their response to IR the Applicant re-conducted the major safety analyses with all 5 of the patients randomized to placebo who received at least 1 dose of panobinostat and assigned them to the panobinostat arm. The Applicant titled this analysis "modified safety set 2". The Applicant's modified safety set 2 analyses will be utilized for the purposes of this safety review.

7.2.1 Demographics of Safety/Exposure population

For analyses of safety and exposure the modified safety set 2 from the Applicants response to IR (SD 19) was used. In the modified safety set 2 analysis population there were a total of 386 patients that received treatment with at least 1 dose of panobinostat and 372 patients received treatment with placebo.

Overall the demographics were well balanced between the treatment arms (Table 11). The mean age of 62 years for both treatment arms is consistent with the mean age of the trial populations other products approved for second line multiple myeloma (e.g., bortezomib and lenalidomide). Forty-two percent of patients in both treatment arms were age ≥65 years.

Table 11 Demographics for safety population trial D2308

Demographic parameter	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Age (years)		
• Mean (SD)	62 (9.4)	62 (9.3)
• Median	63	63
• Range	28, 84	32, 83
• Groups		
o <65 years	224 (58)	214 (58)
o ≥65 years	162 (42)	155 (42)
Sex, n (%)		
• Male	206 (53)	200 (54)
• Female	180 (47)	172 (46)
Race		
• Caucasian	246 (64)	245 (66)
• Black	5 (1)	17 (5)
• Asian	129 (33)	101 (27)
• Other	6 (2)	9 (2)

As a class, HDAC inhibitors are associated with cardiac toxicity such as myocardial ischemia and electrocardiographic changes including T-wave and ST-segment changes as well as QT prolongation. For this reason it is relevant to present the number of patients that had an underlying medication history of cardiac disorders. Overall 65 patients (17%) in the panobinostat + bortezomib + dexamethasone arm had a medical history of a cardiac disorder (system organ class) compared to 51 patients (14%) in the placebo + bortezomib + dexamethasone arm. Since the rate of cardiovascular

disorders was balanced between the treatment arms this will not be a confounding factor in analyzing the occurrence of cardiac events that occurred in trial D2308.

7.2.2 Exposure

The median duration of exposure to panobinostat + bortezomib +dexamethasone was more than a month shorter than the median exposure for patients who received placebo + bortezomib +dexamethasone (153 days panobinostat vs. 184 days placebo) (Table 12). This finding provides the first clue that the dosing regimen of panobinostat + bortezomib + dexamethasone used in trial D2308 is less tolerable then the control arm (placebo + bortezomib + dexamethasone) which is currently a standard of care for the treatment of relapsed multiple myeloma. It is relevant to point out that the median duration of exposure for the patients in the modified safety set 2 was nearly identical to the safety analysis set presented in the clinical study report for trial D2308.

In the clinical study report for trial D2308, the Applicant provided an analysis of exposure by categories. Categories were based upon a cycle length of 3 weeks (Table 12). Based upon this analysis it becomes evident that starting early on in treatment, less patients were able to tolerate the combination of panobinostat + bortezomib + dexamethasone compared to the control arm of placebo + bortezomib + dexamethasone. This is supported by the fact that by week 6 (cycle 2) 16% of patients in the panobinostat arm received less than 2 cycles compared to 10% of patients in the placebo arm. By week 12 (cycle 4) 32% of patients in the panobinostat arm received less than 12 weeks of therapy compared to 24% of patients in the placebo arm. By week 24 (end of treatment phase 1) 54% percent of patients in the panobinostat arm received less than 8 cycles of therapy compared to 46% of patients in the control arm.

Table 12 Exposure to therapy trial D2308

	CSR analysis population		Modified safety set 2	
	Pan + BTZ + Dex (n=381)	**Pbo+BTZ+ Dex (n=377)**	**Pan+BTZ+ Dex (n=386)**	**Pbo+BTZ+Dex (n=372)**
Duration of exposure (days)				
Mean	184	195	184	195
Standard deviation	125.75	118.33	125.24	118.78
Median (min, max)	152 (3, 411)	187 (3, 443)	153 (3, 411)	184 (3, 443)
Exposure categories, n (%)				
<3 weeks	29 (8)	20 (5)	29 (8)	20 (5)
≥3 weeks and <6 weeks	28 (7)	19 (5)	29 (8)	18 (5)
≥6 weeks and <12 weeks	60 (16)	53 (14)	60 (16)	53 (14)
≥12 weeks and <24 weeks	86 (23)	83 (22)	86 (22)	83 (22)
≥24 weeks and <48 weeks	118 (31)	153 (41)	122 (32)	149 (40)
≥48 weeks and <56 weeks	55 (14)	46 (12)	55 (14)	46 (12)
≥56 weeks	5 (1)	3 (1)	5 (1)	3 (1)

Reviewer comment: Given the fact that patients in the panobinostat are were exposed to less therapy in the first treatment phase, the case to be made is that this is a direct result of toxicity as opposed to discontinuation due to disease progression.

7.2.2 Explorations for Dose Response

7.2.2.1 Trial B2207

In trial B2207 the Applicant explored doses of panobinostat from 10 mg to 30 mg in combination with bortezomib at doses of 1 mg/m^2 or 1.3 mg/m^2. Patients in the trial could also receive dexamethasone 20 mg after completing cycle 1. In the dose escalation phase of the trial, patients received panobinostat 3 times per week every week of a 21 day cycle. In the dose escalation phase the MTD was determined to be panobinostat 20 mg in combination with bortezomib 1.3 mg/m^2. Table 13 shows the number of patients evaluable for dose limiting toxicity (DLT) in each cohort and the number of DLTs observed in each cohort. Despite the fact that 3 DLTs were observed in cohort 6, the MTD was determined to be panobinostat 20 mg in combination with bortezomib 1.3 mg/m^2. The Applicant provided reason for this is that since a total of 15 patients were treated at this dose (cohort 3 + cohort 6) and only 3 DLTs were observed the DLT rate was less than the prespecified rate of 33%.

Table 13 Dose limiting toxicities in trial B2207

	Dose	Patients evaluable for DLTs	DLTs
Cohort 1	Panobinostat 10 mg Bortezomib 1 mg/m^2	6	0
Cohort 2	Panobinostat 20 mg Bortezomib 1 mg/m^2	5	0
Cohort 3	Panobinostat 20 mg Bortezomib 1.3 mg/m^2	6	0
Cohort 4	Panobinostat 30 mg Bortezomib 1.3 mg/m^2	6	4 (Grade 3 fatigue, weakness) (Grade 4 thrombocytopenia) x 2 (Grade 2 asthenia and decreased appetite)
Cohort 5	Panobinostat 25 mg Bortezomib 1.3 mg/m^2	6	2 (Grade 2 tumor lysis syndrome) (Grade 4 thrombocytopenia)
Cohort 6	Panobinostat 20 mg Bortezomib 1.3 mg/m^2	9	3 (Grade 3 orthostatic hypotension) (Grade 3 vomiting) (Grade 4 thrombocytopenia)

Reviewer comment: The DLTs observed in cohort 6 are consistent with the severe toxicities that were observed with greater frequency in the panobinostat arm compared to the placebo arm in trial D2308. When evaluating the toxicity findings from the randomized trial in conjunction with trial B2207, it is evident that the DLTs observed during dose escalation were early signals of the severe toxicity of the regimen proposed for this NDA.

Out of 17 patients exposed to panobinostat in combination with bortezomib at the MTD 77% of patients had at least 1 adverse event that required dose adjustment or interruption. In comparison, out of the 14 patients in cohort 1 and 2 that were evaluable for toxicity 8 (57%) experienced at least 1 adverse event that led to dose adjustment or interruption. Eight patients (47%) treated at the MTD experienced thrombocytopenia that led to dose adjustment or interruption. In comparison, out of the 14 patients in cohort 1 and 2 that were evaluable for toxicity 5 (36%) experienced thrombocytopenia that led to dose adjustment or interruption. More important is the finding that 77% (n=13) of patients treated at the MTD experienced a serious adverse compared to 43% (n=6) patients in cohorts 1 and 2. In addition, 100% of patients dosed at the MTD experienced a grade 3-4 adverse event.

Table 14 Summary of adverse events in dose escalation trial B2207

(Source: Table 12-8 of trial B2207 clinical study report)

Category	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Adverse event (AE) [1]	7 (100)	7 (100)	17 (100)	7 (100)	9 (100)	47 (100)
Suspected to be treatment related	6 (85.7)	5 (71.4)	17 (100)	7 (100)	9 (100)	44 (93.6)
Grade 3 or 4 AE	6 (85.7)	6 (85.7)	17 (100)	7 (100)	9 (100)	45 (95.7)
Suspected to be treatment related	5 (71.4)	5 (71.4)	16 (94.1)	7 (100)	8 (88.9)	41 (87.2)
All deaths						
On-treatment deaths [2]	1 (14.3)	1 (14.3)	0	0	0	2 (4.3)
Serious adverse events	4 (57.1)	2 (28.6)	13 (76.5)	3 (42.9)	7 (77.8)	29 (61.7)
AEs leading to treatment discontinuation	1 (14.3)	2 (28.6)	8 (47.1)	4 (57.1)	3 (33.3)	18 (38.3)
Other significant AEs						
AEs requiring dose adjustment or interruption	4 (57.1)	4 (57.1)	13 (76.5)	6 (85.7)	8 (88.9)	35 (74.5)
AEs requiring hospitalization	4 (57.1)	1 (14.3)	10 (58.8)	3 (42.9)	7 (77.8)	25 (53.2)
Clinically notable AEs (CNAE) [3]	6 (85.7)	6 (85.7)	17 (100)	7 (100)	9 (100)	45 (95.7)
Grade 3/4 CNAEs [3]	6 (85.7)	6 (85.7)	16 (94.1)	7 (100)	8 (88.9)	43 (91.5)

[1] Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
[2] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[3] Clinically notable adverse events are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.
Source: Table 14.3.1-1.2, Table 14.3.1-1.3, Table 14.3.1-1.4, Table 14.3.1-1.5, Table 14.3.1-1.6, Table 14.3.1-1.7, Table 14.3.1-1.8, Table 14.3.1-1.9.

Reviewer comment: The toxicity findings from the dose escalation phase with the 20 mg panobinostat and 1.3 mg/m^2 regimen are quite concerning. The rate of grade 3-4 adverse events, SAEs and adverse events leading to hospitalization are exceedingly high; 100%, 77% and 59% respectively. In addition, there is a clear dose:toxicity relationship given the fact that lower dose cohorts experienced substantially less toxicity. As will be discussed in this review, the high rate of toxicity observed in this trial is consistent with the findings from the randomized trial D2308.

Following a review of the safety data from the dose escalation phase, the decision was made to explore a schedule of panobinostat administered 3 times per week for 2 weeks on and 1 week off of a 21 day cycle. The rationale for exploring this schedule was to allow for platelet recovery and minimize dose interruptions. In the dose expansion phase 15 patients were evaluable for toxicity. A total of 11 patients (73%) had at least 1 adverse event that led to dose adjustment or interruption. Thrombocytopenia led to dose adjustment or interruption in 4 (27%) of patients. Grade 3-4 adverse events occurred in 87% of patients and SAEs occurred in 40% with 33% experiencing adverse events that led to hospitalization.

Table 15 Summary of adverse events in dose expansion trial B2207

Category	PAN 20 mg (2 weeks on/ one week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15 n (%)
Adverse event (AE) [1]	**15 (100)**
AE suspected to be treatment related	15 (100)
Grade 3 or 4 AE	13 (86.7)
Suspected to be treatment related	11 (73.3)
All deaths	
On-treatment deaths [2]	2 (13.3)
Serious adverse events	**6 (40.0)**
AEs leading to study treatment discontinuation	**5 (33.3)**
Other significant AEs	
AEs requiring dose adjustment or interruption	11 (73.3)
AEs requiring hospitalization	5 (33.3)
Clinically notable AEs [3]	**15 (100)**
Grade 3/4 clinically notable adverse events [3]	13 (86.7)

[1] Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
[2] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[3] Clinically notable adverse events are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.
Source: Table 14.3.1-1.2, Table 14.3.1-1.3, Table 14.3.1-1.4, Table 14.3.1-1.5, Table 14.3.1-1.6, Table 14.3.1-1.7, Table 14.3.1-1.8, Table 14.3.1-1.9.

Reviewer comment: The 2 week on 1 week off dosing schedule evaluated in the dose- expansion phase lowered the incidence of events of thrombocytopenia that led to dose reduction or interruption. The overall incidence of adverse events leading to dose reduction or interruption was similar, 75% weekly for 3 weeks schedule vs. 73% for 2 week on 1 week off schedule. In addition, the rate of grade 3-4 adverse events was still extraordinarily high at 87%. In the opinion of this reviewer, the altered treatment schedule did not improve the overall tolerability of the regimen. This finding indicates that the issue with tolerability is dose dependent and not schedule dependent.

7.2.2.2 Trial DUS71

Trial DUS71 was a phase 2, two stage, single arm design, that investigated panobinostat 20 mg administered 3 times a week for 2 weeks on 1 week off of a 21 day cycle in combination in with bortezomib and dexamethasone in patients with relapsed multiple myeloma that received at least 2 prior therapies. In this study 55 patients were evaluable for safety.

This trial was conducted in patients with later stage disease (at least 2 prior therapies) than trials B2207 and the randomized trial D2308. Patients with later stage disease tend to be a sicker population than those who have received at least 1 prior therapy and therefore are more susceptible to toxicity. Despite this, trial DUS71 utilized the same dosing regimen of panobinostat + bortezomib and dexamethasone as trial D2038 as is

worth mentioning. Also, it is the opinion of this reviewer that the safety findings from this trial are consistent with those from trial D2308 and B2207 (Table 16).

Similar to the findings from trial B2207, ninety percent of patients in trial DUS71 experienced a grade 3-4 adverse event and 71% of patients experience a SAE. The most common grade 3-4 toxicities were thrombocytopenia (64%), diarrhea (20%), fatigue (20%), anemia (15%), neutropenia (15%), and pneumonia (15%). Again, calling into question the tolerability and risk of this regimen 87% of patients experienced an adverse events leading to treatment interruption or dose modification. The most common of these events were thrombocytopenia (42%), fatigue (24%), diarrhea (20%), and vomiting (11%).

Table 16 Summary of adverse events trial DUS71

(Source: Table 12-3 of trial DUS71 clinical study report)

AE category	PAN + BTZ + Dex (N=55) n (%)
Adverse events (AEs)	54 (98.2)
AEs of grade 3-4	49 (89.1)
AEs of grade 3-4 suspected to be related to study treatment	45 (81.8)
SAEs	39 (70.9)
On-treatment death[a]	4 (7.3)
AEs causing study treatment discontinuation	10 (18.2)
Adverse events causing study treatment discontinuation suspected to be related to study treatment	7 (12.7)
Clinically notable AEs[b]	52 (94.5)
Clinically notable AEs suspected to be related to study treatment	46 (83.6)
Other significant AEs	
AEs leading to dose adjustment or temporary dose interruption	48 (87.3)
AEs requiring additional therapy[c]	52 (94.5)

AE=adverse event; BTZ=bortezomib; Dex=dexamethasone; PAN=panobinostat; SAE=serious adverse event
Categories are not mutually exclusive.
AEs occurring more than 28 days after the discontinuation of study treatment were not summarized.
[a]Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[b]Clinically notable AEs are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.
[c]Includes AEs with action taken: 3=concomitant medication taken and 4=non-drug therapy given.
Source: Table 14.3.1-1.1

Reviewer comment: In the opinion of this reviewer this early trials served as preliminary evidence that the regimen of 20 mg of panobinostat 3 times weekly for 2 weeks of a 21 week cycle is intolerable and exposed patients to significant toxicity.

7.2.3 Special Animal and/or In Vitro Testing

Refer to summary of the Preclinical Pharmacology/Toxicology review in Section 4.3.

7.2.4 Routine Clinical Testing

Routine clinical testing assessments for in trial D2308 included physical exam, ECOG performance status, electrocardiogram (ECG), cardiac imaging [echocardiogram (ECHO) or multiple gated acquisition (MUGA)] and laboratory tests (serum chemistry panel, CBC with differential). Due to the preclinical findings of hypothyroidism thyroid function was monitored. Monitoring of thyroid function included thyroid stimulating hormone (TSH) and free T4 (thyroxine) at screening, prior to dosing cycle 2 day 1, cycle 3 day 1, cycle 4 day 1, and at the end of treatment.

Routine clinical testing was not adequate to evaluate if panobinostat had an effect on platelet function. This is particularly important given the findings of serious events of hemorrhage that were observed in the randomized trial. PT/PTT were only evaluated at the discretion of the investigator. Activated clotting time was not evaluated.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to summary of the Clinical Pharmacology review in Section 4.4.

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

Refer to section 7.3.5

7.3 Major Safety Results

7.3.1 Deaths

D2308

Deaths due to reasons other than disease progression are described in Table 18. Brief synopses of the narratives for patients who died in the panobinostat arm are provided below. The narratives for the deaths in the panobinostat arm were reviewed. This reviewer did not agree with the reported event preferred term for a number of the deaths. For this reason deaths were also grouped into reviewer categories based upon the reviewer's interpreted cause of death.

The narratives for the deaths in the placebo arm were also reviewed. For the events in the placebo arm, I agree with the reported event preferred term for 11 of the 12 events. After review of the narrative for patient 0510_00001 it is likely that the cause of anoxic brain injury was due to cardiac arrest secondary to sepsis from *hemophilus influenzae* infection. For this reason the cause of death will be considered infectious.

A total of 48 patients died during treatment or within 28 days after received their last dose of investigational therapy. Of these 48 patients 10 died due to disease progression, 4 patients in the panobinostat arm and 6 patients in the placebo arm. Therefore, 26 patients (7%) in the panobinostat arm died due to treatment emergent toxicities compared to 12 patients (3%) in the placebo arm. The categories of hemorrhage and infection were the main contributors to the observed imbalance of deaths between the treatment arms. This finding is particularly relevant given the fact these are toxicities associated with panobinostat therapy. This lends support that imbalance in deaths is likely due to panobinostat toxicity and not simply a chance finding in a randomized trial.

Table 17 Table of deaths within 28 days of last dose in trial D2308

Reviewer categories	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Total	30 (8)	18 (5)
Due to progressive disease	4 (1)	6 (2)
Reasons other than progressive disease	26 (7)	12 (3)
Reviewer category		
Hemorrhage	5 (1)	1 (<1)
Cardiac disorders		
• Ischemic cardiac disease	3 (1)	0
• Cardiac arrest	1 (<1)	2 (1)
• Cardiac failure	0	1 (<1)
Infection	10 (3)	6 (2)
Gastrointestinal	1 (<1)	0
Sudden death	1 (<1)	0
Renal	2 (1)	0
Respiratory (non-infectious)	1 (<1)	2 (1)
Neurologic	1 (<1)	0
Drug overdose	1 (<1)	0

Reviewer comment: Deaths due to hemorrhage and infection were the main contributors to the imbalance in deaths observed in the panobinostat arm compared to the placebo arm.

Table 18 Deaths due to reasons other than disease progression D2308

Panobinostat + bortezomib + dexamethasone			
Patient ID	***Cause of Death (preferred term)***	***Reviewer category***	***Investigator Causality***
0010-00003	Hemodynamic, hemorrhagic, septic shock	Hemorrhage	Suspected
0055-00001	Drug overdose	Drug overdose	Not suspected
0060-00001	Infectious pneumopathy, sepsis	Infection	Not suspected
0095-00006	Myocardial infarction	Cardiac	Not suspected
0111-00016	Intestinal ischemia	Gastrointestinal	Not suspected
0155-00008	Sudden death	Sudden death	Not suspected
0214-00001	Pneumonia	Infection	Suspected
0262-00003	Pulmonary hemorrhage	Hemorrhage	Suspected
0263-00004	Acute renal failure	Renal	Not suspected
0312-00005	Cerebral hemorrhage	Hemorrhage	Not suspected
0319-00011	Septic shock	Infection	Not suspected
0325-00006	Gastrointestinal hemorrhage	Hemorrhage	Not suspected
0325-00014	Pulmonary tuberculosis	Infection	Suspected
0337-00007	Septic shock	Infection	Not suspected
0337-00013	Pneumonia	Infection	Not suspected
0386-00002	Bronchopneumonia	Infection	Not suspected
0386-00009	Septic shock	Infection	Not suspected
0395-00004	Cardiac arrest	Cardiac	Not suspected
0406-00006	Myocardial infarction	Cardiac	Suspected
0415-00011	Acute renal failure	Renal	Not suspected
0415-00012	Respiratory failure	Infection	Not suspected
0425-00002	Pulmonary edema	Pulmonary	Not suspected
0430-00001	Acute cardiac failure, myocardial ischemia	Cardiac	Not suspected
0503-00003	Cerebrovascular accident	Neurologic	Not suspected
0812-00001	Acute respiratory failure	Hemorrhage	Suspected
0904-00001	Respiratory failure	Infection	Not suspected

Placebo + bortezomib + dexamethasone			
Patient ID	***Cause of Death (preferred term)***	***Reviewer category***	***Investigator Causality***
0055-00002	Pulmonary embolism	Respiratory	Not suspected
0172-00007	Acute respiratory failure due to aspiration	Respiratory	Not suspected
0267-00001	Cardiopulmonary failure	Cardiac	Not suspected
0275-00001	Necrotizing fasciitis	Infection	Not suspected
0317-00003	Pneumonia	Infection	Not suspected
0325-00005	Sepsis (neutropenic)	Infection	Not suspected
0335-00012	Cardiac arrest	Cardiac	Suspected
0336-00004	Pneumonia	Infection	Not suspected
0385-00003	Cerebral hemorrhage	Hemorrhage	Suspected
0396-00003	Pneumonia	Infection	Suspected
0415-00019	Cardiorespiratory arrest (cardiac failure)	Cardiac	Not suspected
0510-00001	Anorexic brain injury (H. influenzae)	Infection	Not suspected

Hemorrhagic events

Patient# 0010-00003
This was a 78 year old female that received her first dose of panobinostat on (b) (6) Baseline hemoglobin was 13.6 g/dL, platelet count was 248 x 10^9/L and absolute neutrophil count (ANC) was 2.6 x 10^9/L. On cycle 1 day 9 the patient developed grade 2 thrombocytopenia with a platelet count of 65 x 10^9/L which worsened to grade 3 in severity by cycle 1 day 12 (platelet count 31 x10^9/L). On C1D14 the patient was hospitalized with hematemesis, hypotension and melena and was diagnosed with septic shock (grade 4) and hemorrhagic shock (grade 4). On the same day the event of thrombocytopenia worsened to grade 4 (platelet count 17 × 10^9/L). The patient was treated with amoxicillin/clavulanate potassium, dobutamine hydrochloride, pantoprazole sodium, somatostatin, piperacillin/tazobactam, atropine, midazolam, fentanyl and transfusions of platelets, plasma and packed red blood cells. On C1D14 thrombocytopenia resolved. The patient's urine and blood cultures were positive for Escherichia coli, confirming the urosepsis. On C1D15 platelet count was 85 × 10^9/L. On the same day, the patient died of hemodynamic shock due to the combined events of hemorrhagic and septic shock. The patient received the last dose of bortezomib on C1D11 and the last dose of dexamethasone and panobinostat on C1D12.

Reviewer comment: The patient had normal baseline platelet counts. At the time of the onset of the event the patient's platelet count was less than 20 x 10^9/L. The patient was not on any concomitant anticoagulants during the time period surrounding the event. It is likely the hemorrhagic event was due to severe thrombocytopenia

Patient# 0262-00003
Patient 00003 was a 62 year old male who received prior treatment with thalidomide and dexamethasone as first line of therapy and bortezomib, dexamethasone and melphalan followed by autologous stem cell transplant as second line of therapy for multiple myeloma. Relevant medical history included anemia and thrombocytopenia.

The patient received his first dose of investigational therapy on (b) (6). His baseline platelet count was 124 x 10^9/L. On C2D7 he developed grade 2 thrombocytopenia. Treatment with panobinostat was continued and the event worsened to grade 3 on C2D10. Treatment with panobinostat was interrupted on C2D7 (b) (6)) and therapy was restarted on C3D1 (b) (6). On (b) (6) the event resolved. On C4D8 (b) (6) the patient developed grade 2 thrombocytopenia which resolved on C4D10. During this time on C4D1 (b) (6) treatment with panobinostat and dexamethasone was temporarily interrupted and on C4D8 bortezomib was interrupted. On C4D11 ((b) (6)) bortezomib and dexamethasone were restarted. C5D1 the patient had another episode of grade 2 thrombocytopenia. Panobinostat was restarted on (b) (6) and the event of thrombocytopenia resolved on (b) (6). On (b) (6) the patient developed another event of grade 2 thrombocytopenia. Therapy was continued. On

[redacted] the patient developed grade 3 thrombocytopenia (29 x 10^9/L) andtherapy was continued. The next day the patient was diagnosed with grade 4 pulmonary hemorrhage and was hospitalized. No action was taken with study treatment and on [redacted] the patient died due to pulmonary hemorrhage. The patient had received the last dose of bortezomib on C6D11 ([redacted]) and the last dose of panobinostat and dexamethasone on C6D12 ([redacted]).

Reviewer comment: The patient was not on any concomitant anticoagulants during the time period surrounding the event. The patient's platelet count was not below 20,000 at the time of the event. Therapy continued through the grade 3 event of thrombocytopenia but was discontinued at the onset of pulmonary hemorrhage. Grade 3 thrombocytopenia was a likely contributing factor the event of pulmonary hemorrhage and the death.

Patient# 0312-00005
Patient 00005 was a 74 year old female who received first line treatment for MM with lenalidomide. Her only relevant current medical condition was anemia. She received her first dose of study therapy on [redacted]. At baseline her platelet count was 151 x 10^9/L. On C1D2 she developed grade 2 pancytopenia and the event was reported as resolved on [redacted]. On C1D6 ([redacted]) she was diagnosed with a grade 4 cerebral hemorrhage and was hospitalized. A CT scan of the brain confirmed a large intracerebral hemorrhage in the right frontal area and a small hemorrhage at left proximal frontal area. An MRI scan of the brain revealed multiple myeloma involvement in the leptomeningeal myelomatosis. Treatment with investigational therapy was permanently discontinued. She received her last dose of panobinostat on [redacted]. Between [redacted], the patient was noted with fluctuating grades of pancytopenia (grade 1 to grade 3) and thrombocytopenia. Platelet count on [redacted] was 40 x 10^9/L (grade 3) and no treatment was reported for this event. The patient died due to cerebral hemorrhage on [redacted] The investigator suspected a relationship between the event (pancytopenia-first episode) and panobinostat, but did not suspect a relationship between the events (cerebral hemorrhage, thrombocytopenia-two episodes, pancytopenia-second episode) and panobinostat.

Reviewer comment: The patient was not on any concomitant anticoagulants during the time period surrounding the event. While it is possible that CNS involvement of multiple myeloma confounds this case, the possibility of panobinostat playing a causal role cannot be ruled out due to the fact that the patient had ongoing pancytopenia/thrombocytopenia at the time of the event. The patient's platelet count was not below 20,000 at the time of the event. She received platelets on [redacted].

Patient# 0325-00006
Patient 00006 was a 61 year old female who received prior first line treatment with thalidomide and dexamethasone for MM. Her relevant current medical conditions include anemia and nephrotic syndrome. Baseline platelet count was 255 x 10^9/L. She received her first dose of study therapy on [redacted]. On C1D11 ([redacted]) she developed grade 4 thrombocytopenia (platelet count 17 x 10^9/L) and study treatment was interrupted. She received platelets and the event resolved on [redacted]. On the same day she was diagnosed with a pleural effusion and was hospitalized. On [redacted] she was diagnosed with a gastric hemorrhage, platelet count was not reported. On [redacted] treatment with panobinostat was restarted and bortezomib was started on the [redacted]. On [redacted] the patient developed grade 3 thrombocytopenia (platelets 42 x 10^9/L) and she was diagnosed with grade 4 gastrointestinal hemorrhage and grade 4 myocardial infarction. Study therapy was permanently discontinued. Her last dose of panobinostat and bortezomib was [redacted]. She subsequently died on [redacted] due to gastrointestinal hemorrhage.

Reviewer comment: According to the raw LRS2 dataset the patient's platelet count was 238,000 on [redacted] Her platelet count continued to decline rapidly through [redacted] but remained above 20,000. The patient was not on any concomitant anticoagulants during the time period surrounding the event. On [redacted] the patient received platelets for gastrointestinal bleeding.

Patient# 0812-00001
Patient 00001 was a 71 year old male who received prior treatment with vincristine, doxorubicin, dexamethasone, prednisolone and melphalan as first line therapy and prednisolone and melphalan as second line therapy for multiple myeloma. Past medical history includes intracranial aneurysm and pneumonia. The patient had anemia as the only relevant current medical condition.

At screening ([redacted] the patient was hospitalized but the reason was not specified. Hemoglobin was 88 g/L and platelet count was 199 x 10^9/L. He received his first dose of investigational therapy on [redacted]. On [redacted] (C1D10) the patient developed thrombocytopenia (platelet count 63 x 10 /L). On [redacted] platelet count worsened to 27 x 10^9/L (reported as grade 4 but per CTCAE V3 was actually grade 3). No action was taken with study drug during these events of thrombocytopenia. On C1D15 [redacted]), the patient's blood pressure was 116/63 mmHg, heart rate was 98 bpm, oxygen saturation level was 99%, and the body temperature was 36.5°C. Later during the same day, the patient's condition changed and the patient was noted with declining consciousness (grade 1). The patient also experienced labored breathing and cough with hemoptysis (grade 3). An electrocardiography (ECG) showed sinus tachycardia (HR was between 130 and 140 bpm). As blood pressure decreased to 82/52 mmHg and SpO2 was 64%, oxygen therapy was started. The patient repeatedly had a small amount of hemoptysis. A blood test revealed anemia (hemoglobin 7.8 g/dL) and advancing thrombocytopenia (platelet

count 14 × 10^9/L). When the patient's heart rate decreased to 20 to 40 bpm, cardiac massage was started. Despite resuscitation ECG became flat. The patient was confirmed dead. The cause of death was acute respiratory failure (grade 4). The investigator suspected a relationship between the events (thrombocytopenia, acute respiratory failure, hemoptysis) and panobinostat.

Reviewer comment: Based upon this narrative and the clinical course of the patient it is possible the cause of respiratory failure was pulmonary hemorrhage as evidenced by grade 3 hemoptysis and severe grade 4 thrombocytopenia (platelet count <20 x 10^9/L). The patient was not on any concomitant anticoagulants during the time period surrounding the event.

Infections

Patient# 0060-00001
This was a 78 year old male who received his first dose of treatment with panobinostat + bortezomib + dexamethasone on (b) (6). Prior therapy for MM included bortezomib and dexamethasone for first line treatment. On C3D14 (b) (6)), he was diagnosed with respiratory failure (grade 4) and was hospitalized and treated with oxygen therapy. During hospitalization, on C3D16 (b) (6)), the patient was diagnosed with infectious pneumopathy (lung disorder; grade 3), sepsis (ANC 16.8 × 10^9/L; grade 4) and experienced hypoxia (grade 4). The patient was treated with paracetamol, ceftriaxone sodium, ciprofloxacin and oxygen therapy. On C3D21 (b) (6)), the patient died due to the event lung disorder. The patient received the last dose of bortezomib on C3D11 (b) (6) and the last dose of panobinostat and dexamethasone on C3D12 (b) (6)).

Reviewer comment: The cause of death documented as "lung disorder" is vague. Based upon the narrative it is likely that the patient died due to infection (i.e., infectious pneumopathy and/or sepsis). For the purposes of this review the cause of death will be counted in the reviewer grouping infection.

Patient# 0904-00001
Patient 00001 was a 51 year old male who received prior treatment with dexamethasone, melphalan and thalidomide as for line therapy for MM. He had no relevant medical history or current medical conditions. At screening his ANC was 2 x 10^9/L. He received his first dose of investigational therapy on (b) (6). On (b) (6) (C3D8) he developed an upper respiratory tract infection and had grade 3 thrombocytopenia (platelet count 26 x 10^9/L). ANC on the (b) (6) was 2.6 x 10^9/L. Treatment with bortezomib was interrupted due to thrombocytopenia. He was treated with antibiotics and the event resolved on (b) (6) but thrombocytopenia persisted. Bortezomib was restarted on (b) (6). His ANC on the (b) (6) was 3.7 x 10^9/L. On (b) (6) (C3D13) he developed a fever (38°C) and was shivering. On

[redacted] he was diagnosed with pneumonia (grade 4), septic shock (grade 4) and respiratory failure (grade 4) and was hospitalized and required mechanical ventilation. An ANC was not reported. The patient died on [redacted] due to respiratory failure. The investigator did not suspect a relationship between the events (pneumonia, respiratory failure, septic shock) and panobinostat. His last dose of panobinostat was [redacted].

Reviewer comment: Based upon this narrative it is likely that the underlying cause of respiratory failure was pneumonia and septic shock. Due to the fact that the patient developed pneumonia and septic shock 1 day after receiving his last dose of panobinostat a causal relationship to panobinostat cannot be ruled out.

Patient# 0214-00001
Patient 00001 was a 77 year old female who received melphalan and prednisolone as first line of therapy, thalidomide and dexamethasone as second line of therapy, and bortezomib and dexamethasone as third line of therapy for treatment of MM. Relevant medical history includes hypertension, and hypercholesterolemia for which she was receiving a thiazide, doxazosin, moxonidine, atenolol and amlodipine.

The patient received her first dose of therapy on [redacted] One of the patient's pre-dose ECG was abnormal with intraventricular conduction delay (IVCD). The patient had a mean pre-dose QTcF of 436 ms (range 426 to 443 ms). The post-dose ECGs were normal with premature ventricular complex (PVC) and a mean QTcF of 447 ms (range 437 to 455 ms). On C3D6 [redacted]), the patient experienced grade 1 diarrhea, vomiting, weakness and malaise. The patient developed grade 4 pneumonia and was hospitalized. No action was taken with the study treatment and no treatment was reported. On C3D7 [redacted], the patient was noted with neutropenia (ANC 0.002× 10^9/L) and was diagnosed with myocardial infarction (grade 4) with a background of recent onset pancytopenia. No action was taken with the study treatment and no treatment was reported for the events. On C3D7 ([redacted]), the patient died due to lung infection. The patient received the last dose of bortezomib on C3D4 [redacted]) and the last dose of dexamethasone and panobinostat on C3D5 ([redacted]).

Patient# 0319-00011
Patient 00011 was a 60 year old male who received prior treatment with prednisolone and cyclophosphamide and two autologous stem cell transplants for treatment of multiple myeloma. The patient did not have any other relevant current medical conditions. At screening (Day −7, [redacted]), the patient was noted with asthenia (grade 3) and was hospitalized. No treatment was reported for this event. On Day −1 [redacted] the patient's laboratory values included hemoglobin (Hb) of 80 g/L, platelet count of 232 × 10^9/L, and absolute neutrophil count (ANC) of 7.2 × 10^9/L.

He received his first dose of investigational therapy on [redacted] During the first 11 days of cycle 1 he experienced multiple event events of grade 4 anemia. On C1D7 he was diagnosed with grade 2 pneumonia and study treatment was temporarily interrupted. He was treated with intravenous antibiotics. The narrative reports that the pneumonia extended the patient's hospital stay. On C1D14 ([redacted]) the patient experienced septic shock and treatment was permanently discontinued. He received his last dose of panobinostat on [redacted]. On [redacted] the patient died due to septic shock. No ANCs were provided for the time period during which the patient experienced septic shock.

Patient# 0325-00014
Patient 00014 was a 69 year old male who received prior therapy with an investigational monoclonal antibody (CNTO 328), bortezomib, melphalan and prednisolone for first line treatment of multiple myeloma. He had no relevant current medical conditions. He received his first dose of study treatment on [redacted]. At C8D8 ([redacted]) the patient was hospitalized for grade 2 thrombocytopenia and grade 4 pneumonia. His ANC was 2.5 x 10^9/L. He received treatment with antibiotics and no action was taken with investigational therapy. During his hospitalization thrombocytopenia worsened to grade 4. On C8D15 he was diagnosed with pulmonary tuberculosis (grade 4). His ANC was 5.8 x 10^9/L at the time of diagnosis. He was treated with antibiotics including isoniazid. On C8D19 ([redacted]) the patient was diagnosed with acute respiratory distress syndrome (grade 4) and respiratory failure (grade 4) and he was intubated. On [redacted] he was diagnosed with disseminated intravascular coagulation (grade 4). On [redacted] the patient was started on hemodialysis and on the same day he was diagnosed with ischemic hepatitis, gastrointestinal hemorrhage (grade 4), acute renal failure (grade 4) and septic shock (grade 4). On [redacted] the patient died due to pulmonary tuberculosis. He received his last dose of panobinostat on [redacted] (C8D12).

Patient# 0337-00007
Patient 00007 was a 51 year old female who received prior therapy with thalidomide, dexamethasone, melphalan, cyclophosphamide and bortezomib for MM. She also received an autologous stem cell transplant. She had no relevant current medical conditions and received her first dose of investigational therapy on [redacted]. At C6D13 ([redacted]) she was diagnosed with grade 3 pneumonia, acute renal failure (grade 4) and sepsis and was hospitalized. Her ANC was 4.4 x 10^9/L on August 11th and creatinine was 10.8 mg/dL at the time of hospitalization. The patient was treated with primaxin, vecuronium bromide, dobutamine, dopamine, fluconazole, oseltamivir, dexamethasone, and underwent hemodialysis. On [redacted] she was diagnosed with septic shock and investigational therapy was permanently discontinued. She received her last dose of panobinostat on [redacted]. The patient died on [redacted] due to septic shock.

Patient# 0337-00013
Patient 00013 was a 57 year old male who received prior therapy with thalidomide and dexamethasone for first line treatment and cyclophosphamide, doxorubicin and prednisolone as second line therapy. Relevant current medical conditions included anemia, peripheral neuropathy and hypoalbuminemia. His ANC was 2.8 x 10^9/L at screening on (b) (6). He received his first dose of investigational therapy on (b) (6). At C4D14 on (b) (6) he was diagnosed with grade 4 pneumonia and respiratory failure (grade 4) and was hospitalized. He was treated with antibiotics. On (b) (6) the patient died due to pneumonia. He received his last dose of panobinostat on (b) (6).

Patient# 0386-00002
Patient 00001 was a 49 year old male who received vincristine, doxorubicin and dexamethasone for first line treatment of multiple myeloma. Relevant current medical conditions include lower respiratory tract infection, pneumothorax and renal failure. He received his first dose of investigational therapy on (b) (6). At baseline his ANC was 1.5 x 10^9/L. At C1D13 on (b) (6) he was diagnosed with grade 3 bronchopneumonia. He was treated with ceftriaxone. On (b) (6) he died due to bronchopneumonia. His last dose of panobinostat was on (b) (6).

Patient# 0386-00009
Patient 00009 was a 65 year old male who received treatment with melphalan and a corticosteroid for first line treatment of MM. He received localized radiotherapy. Relevant current medical conditions included increased B2 microglobulin and anemia. He received his first dose of investigational therapy on (b) (6).

At C7D13 on (b) (6) the patient was diagnosed with disease progression and treatment with investigational therapy was permanently discontinued. He received his last dose of panobinostat on (b) (6). On (b) (6) the patient developed urinary tract infection and was hospitalized. During hospitalization he was diagnosed with sepsis on (b) (6). He subsequently died on (b) (6) due to septic shock.

Reviewer comment: Disease progression is a confounding factor in assessing the relationship of this event with panobinostat.

Patient# 0415-00012
Patient 00012 was a 60 year old female who received prior treatment with vincristine, doxorubicin, dexamethasone, melphalan and autologous stem cell transplant for first line therapy and bortezomib, cyclophosphamide and dexamethasone as second line therapy for MM. She received two localized radiotherapies. Relevant current medical conditions include diabetes mellitus, pulmonary hypertension, mitral valve calcification, tricuspid valve incompetence, hypertension and malignant pleural effusion. She received her first dose of investigational therapy on (b) (6) On (b) (6)

(C1D16) she developed acute dyspnea with cough and was hospitalized with grade 4 pneumonia and grade 4 respiratory failure. Her ANC was 1.8 x 10^9/L and platelet count was 12 x 10^9/L on the same day. Investigational therapy was permanently discontinued and she received her last dose of panobinostat on (b) (6). She was treated with antibiotics, oxygen therapy and received platelets. On (b) (6) the patient died due to respiratory failure and pneumonia. The investigator suspected a relationship between the events (pneumonia, thrombocytopenia) and panobinostat, but did not suspect a relationship between the event (respiratory failure) and panobinostat.

Cardiac events

Patient# 0095-00006
Patient 00006 was a 61 year old male with a relevant prior medial history of renal failure, diabetes mellitus, hypertension, deep vein thrombosis and hypertensive heart disease. Prior therapy for multiple myeloma included idarubicin, dexamethasone, epirubicin, ifosfamide, etoposide, melphalan, antithymocyte immunoglobulin, fludarabine and an autologous stem cell transplant followed by an allogeneic stem cell transplant as first line of therapy and dexamethasone and bortezomib as second line of therapy.

The patient received his first dose of investigational therapy on (b) (6). At baseline the patient's pre-dose ECG findings were abnormal with inverted T waves. The patient had a mean pre-dose QTcF of 411 ms (range 399 to 428 ms). The patient's post dose ECG findings were abnormal inverted T waves and depressed ST segment. The patient had a mean post-dose with a mean QTcF of 428 ms (range 415 to 435 ms). Treatment with investigational therapy was permanently discontinued on C12D8 due to an event of peritoneal necrosis. The patient's last dose of panobinostat was on (b) (6) C12D12. On (b) (6) the patient developed atrial tachycardia (grade 3) which resolved with treatment. On (b) (6) the patient died due to myocardial infarction.

Reviewer comment: This case is confounded by the patient's medical history of renal failure, diabetes, and hypertensive heart disease

Patient# 0395-00004
Patient 00004 was a 64 year old male who received prior therapy with vincristine, doxorubicin and dexamethasone for first line therapy and prednisolone, melphalan and autologous stem cell transplant for second line therapy for MM. Relevant current medical conditions include type 2 diabetes and plasmacytoma. He received his first doses of investigational therapy on (b) (6) On (b) (6) the patient developed grade 2 pneumonia and was hospitalized. Treatment with investigational therapy was temporarily interrupted. He was treated with antibiotics and was discharged on (b) (6) The event on pneumonia resolved on (b) (6) and therapy was reinitiated. On (b) (6) (C3D14) the patient died at home due to cardiac arrest. The patient received his last dose of panobinostat on (b) (6)

Reviewer comment: This case is confounded by the patient's medical history of diabetes.

Patient# 0406-00006
Patient 00006 was a 66 year old female who received thalidomide for first line treatment of MM. Relevant medical history includes hyperthyroidism, diabetes mellitus, renal failure, anemia, and left ventricular hypertrophy. At baseline she was receiving treatment with propranolol. She received her first dose of investigational therapy on (b) (6) Screening ECG should sinus bradycardia with QTcF of 385 ms. Her blood pressure was 120/70 mmHg at screening. On (b) (6) (C2D13) the patient experienced musculoskeletal pain, headache and back pain and was hospitalized. On the same day she was diagnosed with cardiac arrest, hypotension (grade 4), grade 1 hyperkalemia and grade 4 bradycardia. Cardiopulmonary resuscitation was administered and mechanical ventilation was initiated. She experienced a 2nd event of cardiac arrest and she subsequently died due to myocardial infarction. Investigational therapy was permanently discontinued and she received her last dose of therapy on (b) (6).

Reviewer comment: This case is confounded by the patient's medical history.

Patient# 0430-00001
Patient 00001 was a 72 year old male who received prior treatment with bortezomib and melphalan as first line therapy and bortezomib dexamethasone and thalidomide as second line therapy for MM. Relevant current medical conditions include coronary artery disease, essential hypertension and type 2 diabetes mellitus. At baseline he was being treated with valsartan.

He received his first dose of investigational therapy on (b) (6). Baseline ECGs revealed abnormal findings of first degree AV block, flat T waves and biphasic T waves. Mean QTcF was 426 ms (range 412 to 444 ms). On C2D1 (b) (6), three pre-dose ECGs revealed abnormal ectopic supraventricular rhythm. The mean QTcF was 422 ms (range 416 to 426 ms). On C6D1 (b) (6)), the pre-dose ECGs were abnormal with findings of first degree AV block, flat T waves and biphasic T waves. The mean QTcF was 418.3 ms (range 338 to 443 ms). On (b) (6) the patient was diagnosed with acute cardiac failure and myocardial ischemia and died. He received his last dose of panobinostat on (b) (6) The investigator did not suspect a relationship between the events (cardiac failure acute, myocardial ischemia) and panobinostat.

Reviewer comment: The case is confounded by the patient's age and past medical history. The patient's cardiac conduction abnormalities at baseline appeared to remain stable. However, based on the information provided in this report a causal relationship

between panobinostat and this event cannot be entirely ruled out due to the fact that therapy was on going at the time of the event.

Gastrointestinal

Patient# 0111-00016
Patient 00016 was an 81 year old male that received prior melphalan, lenalidomide and prednisolone as first line treatment of MM. The patient had no prior history of radiotherapy. He had no relevant medical history. He began treatment with investigational therapy on (b) (6). On C10D24 (b) (6)) he experienced an event of ileus that included symptoms of vomiting, diffuse abdominal pain and fecal retention. Treatment with dexamethasone and panobinostat were temporarily interrupted. On C10D26 the ileus deteriorated and the patient was diagnosed with inguinal hernia (grade 4) and was hospitalized and underwent surgery. He was diagnosed with intestinal ischemia (grade 4) and subsequently died due to this event on (b) (6) (C10D29). The patient received the last dose of bortezomib on C5D4 (b) (6), the last dose of dexamethasone on C10D23 (b) (6) and the last dose of panobinostat on C10D24 (b) (6).

Sudden death

Patient# 0155-00008
Patient 00008 was a 74 year old male who received prior treatment with melphalan and prednisone as first line of therapy, thalidomide, cyclophosphamide and dexamethasone as second line of therapy, and bortezomib and cyclophosphamide and dexamethasone as third line of therapy. No prior antineoplastic radiotherapy or stem cell transplant was reported. He received his first dose of investigational therapy on (b) (6). At baseline Pre-dose ECGs findings were abnormal with inverted T waves. The mean QTcF was 430 ms (range 392 to 451 ms). The post-dose ECG findings were abnormal with inverted T waves and atrial premature contractions (APC). The mean QTcF was 447.6 ms (range from 441 to 452 ms). On (b) (6) (C1D18) he was diagnosed with an upper respiratory tract infection and was hospitalized and treated with aminophylline and antibiotics (amoxicillin/clavulanate and ceftriaxone). The event resolved on (b) (6). On (b) (6) (C3D14) the patient died suddenly. An autopsy was not performed. The patient received the last dose of panobinostat on C3D10 (b) (6)), the last dose of dexamethasone on C3D11 (b) (6)) and the last dose of bortezomib on C3D11 (b) (6).

Reviewer comment: Aminophylline is associated with QTc prolongation however since the event of upper respiratory tract infection resolved on (b) (6) it is highly unlikely that aminophylline had a contributory role to an event that occurred almost 1 month later.

Renal

Patient# 0263-00004
Patient 00004 was a 68 year old male who received melphalan, prednisone, thalidomide and dexamethasone as first line treatment of multiple myeloma as well as localized radiotherapy. Current medical conditions included hypertension and plasmacytoma. He was receiving treatment with captopril and nifedipine. He received his first dose of study therapy on (b) (6) At baseline his creatinine was 99.8 µmol/L. On (b) (6) therapy was interrupted due to adverse events of myocardial ischemia and grade 3 thrombocytopenia. Therapy was restarted on C2D1. On C2D8 thrombocytopenia worsened to grade 3 and therapy was interrupted. On C2D17 the event of myocardial ischemia worsened to grade 3 and therapy was permanently discontinued. The last dose of panobinostat was on (b) (6) (C2D4). On (b) (6) the patient was diagnosed with disease progression. He was hospitalized due to acute renal failure and thrombocytopenia on (b) (6) and on (b) (6) he died due to acute renal failure.

Reviewer comment: It is likely that disease progression was the major contributing factor to the patient's death.

Patient# 0415-00011
Patient 00011 was a 58 year old female who received prior treatment with dexamethasone, bortezomib, thalidomide, melphalan and autologous stem cell transplant as first line therapy for MM. She also received localized radiotherapy. She had no relevant current medical conditions. On (b) (6) she received her first dose of investigational therapy. At C4D1 on (b) (6) she was diagnosed with disease progression however the patient continued to receive investigational therapy until (b) (6) (C7D12). During that time therapy was temporarily interrupted due to adverse events of hypotension, diarrhea, vomiting and urinary tract infection for which the patient was hospitalized. Four days after she received her last dose of panobinostat on (b) (6) the patient developed a second urinary tract infection and was hospitalized. On (b) (6) the patient developed acute renal failure. The patient's family refused further treatment and she was discharged. On (b) (6) the patient died due to acute renal failure.

Reviewer comment: It is likely that disease progression and urinary tract infection were the main contributors to the patient's death.

Pulmonary non-infectious

Patient# 0425-00002
Patient 00002 was a 59 year old male who received prior treatment with prednisolone, melphalan, lomustine, cyclophosphamide and vincristine for first line therapy for multiple myeloma. Relevant current medical conditions included hypertension and chronic

pyelonephritis. He received his first dose of investigational therapy on (b) (6). At screening ECGs were normal.

On (b) (6) (C4D12) the patient was diagnosed with bronchitis which resulted in hospitalization. During hospitalization he experienced grade 3 atrial fibrillation. Bortezomib was temporarily interrupted. Patient was treated for these events and they resolved on (b) (6). On (b) (6) the patient was re-hospitalized for asthenia, dizziness and general physical health deterioration. The next day patient lost consciousness. On (b) (6) he was diagnosed with grade 4 pulmonary edema and edema of the brain (grade 4). Panobinostat and dexamethasone were permanently discontinued. Bortezomib therapy continued to be discontinued from prior event. The patient was treated for these events but subsequently died due to pulmonary edema on (b) (6). Their last dose of panobinostat was on (b) (6) The investigator did not suspect a relationship between the events (bronchitis, atrial fibrillation, asthenia, dizziness, general physical health deterioration, loss of consciousness, brain edema, pulmonary edema) and panobinostat.

Neurologic

Patient# 0503-00003
Patient 00003 was a 78 year old female who received prior treatment with lenalidomide and dexamethasone as first line treatment for MM. Past medical history is significant for deep vein thrombosis. Relevant current medical conditions included hypertension, hyperlipidemia and anemia. She was receiving treatment with metoprolol, valsartan, atorvastatin, furosemide and diltiazem. At screening her BUN was modestly elevated at 7.4 mmol/L (normal 2.1 to 7.1 mmol/L) and creatinine was 88.4 µmol/L (normal 44.2 to 132.6 µmol/L).

The patient received her first dose of investigational therapy on (b) (6). ECG was normal at QTcF was 410.6 ms. On (b) (6) (C1D4) patient experience grade 4 fatigue and panobinostat and dexamethasone were temporarily interrupted. On (b) (6) she experienced grade 3 hypotension and was hospitalized. The event resolved on (b) (6) and the dose bortezomib and dexamethasone were reduced and therapy was restarted. On (b) (6) (C2D1) fatigue resolved and panobinostat was restarted at a reduced dose.

On (b) (6) (C2D13) she was hospitalized due to grade 3 diarrhea, grade 3 dehydration and grade 4 sepsis. Treatment with panobinostat, bortezomib and dexamethasone were interrupted at this time. During hospitalization on (b) (6) she was diagnosed with pneumonia and pseudomonal bacteremia. Her ANC at the time of diagnosis was 5.7 x 10^9/L. On (b) (6) she developed atrial fibrillation and on the (b) (6) she developed acute renal failure. The next day (b) (6)) she experienced a cerebral vascular accident confirmed by MRI (lacunar infarction). Ten days after receiving her last dose of panobinostat the patient died on (b) (6) due

to cerebrovascular accident. The investigator did not consider the case of death as related to panobinostat.

Reviewer comment: The events of diarrhea, dehydration, infections and acute renal failure were likely major contributing factors to the patient's death. Diarrhea, dehydration and infection are toxicities associated with panobinostat. For this reason it is difficult to rule out panobinostat as a contributing factor in this event.

Drug overdose

Patient# 0055-00001
Patient 00001 was a 65 year old female with a history of depression and a current medical condition of hypothyroidism who received prior treatment with bortezomib, dexamethasone and melphalan followed by an autologous stem cell transplant as first line of therapy for MM. The patient received the first dose of the study treatment on (b) (6) . On C2D15 (b) (6), the patient had an overdose of morphine (overdose; grade 3) due to which the patient experienced confusion and had a fall and developed traumatic hematoma (grade 1). On the same day, the patient was hospitalized due to overdose while the event (fall) resolved. The study treatment was temporarily interrupted from (b) (6) due to the event (overdose). No treatment was reported. On (b) (6) this event resolved and the patient was discharged. On C3D1 (b) (6)), the event (traumatic hematoma) resolved and the study treatment was restarted. On C7D15 (b) (6)), the patient intentionally took an unknown dose of all ongoing drugs including the study treatment (panobinostat and dexamethasone) (intentional overdose; grade 4) and died the same day. The patient received the last dose of bortezomib on C3D11 (b) (6)) and the last dose of panobinostat and dexamethasone on C7D12 (b) (6)). The investigator did not suspect a relationship between the events (overdose, intentional overdose, neuropathy peripheral) and panobinostat.

Reviewer comment: This case is significantly confounded the patient's history of depression. In addition, the case is also confound by the patient's concomitant use of Cymbalta (duloxetine) which has a boxed warning for suicidal thoughts and behaviors as well as Xanax (alprazolam) which has a precaution for risk of suicide.

Progressive disease

Patients 0011-00003, 0111-00007, 0111-0014, 0335-00004 died due to disease progression.

B2207

Hemorrhagic events
Patient# 0002-00011

Patient 00011 was a 71 year old female who received prior therapy with ifosfamide, epirubicin, etoposide, melphalan, bortezomib, lenalidomide, dexamethasone and everolimus for MM. She received prior localized radiotherapy (site not specified). She had no relevant past medical conditions. Relevant current medical conditions included secondary immunodeficiency, increased blood creatine phosphokinase. The patient received her first dose of panobinostat 20 mg in combination with bortezomib 1.3 mg/m^2 and dexamethasone 20 mg on (b) (6) On (b) (6) (Day 126) the patient was hospitalized due to dizziness, stupor and aphasia. She was diagnosed with a transient ischemic attack. Study medication was permanently discontinued and she received her last dose of study medication on (b) (6). On (b) (6) the patient was discharged and all events were reported as resolved. No laboratory results or medical treatments for this event were provided in the narrative. On (b) (6) the patient experienced stupor and aphasia and was hospitalized for the second time. It is reported that she had a cerebral infarction on (b) (6). CT scan on the day of the infarction revealed major CNS bleeding. She was diagnosed with a ischemic stroke and cerebral hemorrhage. The patient fell into a coma and subsequently died on (b) (6). The investigator did not suspect a relationship between the events (dizziness, stupor, aphasia, transient ischemic attack, ischemic stroke, cerebral hemorrhage) and the study treatment.

Reviewer comment: No platelet counts for the time period surrounding the event were available.

DUS71

Four patients died on treatment or within 28 days of study treatment. Of the four on-treatment deaths, three were attributed to the underlying malignancy (plasma cell myeloma). The other death (patient DUS71-1009/00009) was due to multiple organ failure in a 72 year old female patient who died at day 96, 19 days after having discontinued therapy with study drug on day 77.

Patient 1009-00009
The patient was a 72 year old female with relapsed multiple myeloma. Prior therapy included localised radiotherapy, bortezomib, dexamethasone, doxorubicin, lenalidomide and perifosine. Her first dose of study treatment was on (b) (6)

During the course of treatment she had multiple events of grade >3 thrombocytopenia but no events of grade ≥3 neutropenia. On C4D11 (b) (6) the patient developed shortness of breath and was hospitalized due to grade 4 pneumonia. Pneumonia was confirmed by x-ray. The patient received the last dose of the study treatment on (b) (6) (C4D12). She received treatment with azithromycin. The patient's respiratory state continued to deteriorate and over several days, the patient went into multiple system organ failure with renal failure and significant volume overload. On (b) (6), 19 days after the last dose of the study treatment, the patient became hypotensive, consistent with her sepsis syndrome and progressive multiple

system organ failure, and died due to multi-organ failure. The investigator did not suspect a relationship between pneumonia and study treatment.

Reviewer comment: The underlying cause of this event was likely the grade 4 event of pneumonia which caused the patients hospitalization on (b) (6). Given the fact that panobinostat is associated with serious infections it is difficult to rule out the relationship of panobinostat to this event. Pneumonia, which occurred during treatment with panobinostat + bortezomib + dexamethasone was the event that initiated the patients downward cascade sepsis and progressive organ failure.

B2207

In trial B2207 a total of 2 patients died during the dose escalation phase due to disease progression. During dose expansion 2 patients died. One patient 0002-00011 died due to an ischemic stroke and patient 0501-00010 died due to injuries sustained from a road traffic accident.

Patient# 0002-00011
The patient was a 71 year old female with multiple myeloma in second relapse. Prior therapy included ifosfamide, epirubicin, etoposide, melphalan, bortezomib, lenalidomide, dexamethasone and everolimus. The patient had no relevant medical history. On Day 126 ((b) (6)), the patient had dizziness grade 2, stupor grade 3, and aphasia grade 1 and was hospitalized. The patient was diagnosed with transient ischemic attack grade 3. The study treatment was permanently discontinued following the transient ischemic attack. The patient received the last dose of bortezomib and dexamethasone on Day 124 ((b) (6)), and the last dose of panobinostat on Day 126 ((b) (6)). On (b) (6), three days after the last dose of the study treatment, the events (dizziness, stupor, aphasia, transient ischemic attack) resolved and the patient was discharged from the hospital.

On (b) (6), five days after the last dose of panobinostat, the patient experienced stupor and aphasia and was hospitalized. On the same day the patient had cerebral infarct and a CT scan done on the next day showed major CNS bleeding. The patient was diagnosed with ischemic stroke and cerebral hemorrhage (both CTC grade 4) and fell into coma grade 4. The patient received lysis treatment and heparin. On (b) (6), six days after the last dose of panobinostat the patient died due to the ischemic stroke. An autopsy was not performed. The events (ischemic stroke, cerebral hemorrhage, coma) were ongoing at the time of patient's death. The investigator did not suspect a relationship between the events dizziness, stupor, aphasia, transient ischemic attack, ischemic stroke, cerebral hemorrhage) and the study treatment.

Reviewer comment: Based upon review of the patient's platelet counts from the period of time surrounding the event of cerebral hemorrhage the patient did not have grade 3-4 thrombocytopenia.

7.3.2 Nonfatal Serious Adverse Events

D2308

In the panobinostat arm 230 patients (60%) experienced at least 1 SAE compared to 155 patients (42%) in the placebo arm. The most common SAEs that occurred in ≥5% of patients in the panobinostat arm were pneumonia, diarrhea and thrombocytopenia (Table 19). The raw AE dataset included a field for events that led to hospitalization and/or prolongation of hospitalization. In patients treated with panobinostat 55% (n=211) experienced an adverse event that led to hospitalization or prolongation of hospitalization compared to 37% (n=138) of patients treated with placebo.

Table 19 SAEs in ≥2% of patients in the panobinostat arm in trial D2308

Preferred term	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Pneumonia*	56 (15)	40 (11)
Diarrhea*	43 (11)	8 (2)
Thrombocytopenia*	28 (7)	8 (2)
Asthenia*	17 (4)	5 (1)
Anemia*	15 (4)	3 (1)
Pyrexia	15 (4)	10 (3)
Vomiting*	12 (3)	3 (1)
Dehydration*	11 (3)	4 (1)
Fatigue*	11 (3)	2 (1)
Orthostatic hypotension	9 (2)	1 (<1)
Sepsis	9 (2)	7 (2)
Septic shock	9 (2)	2 (<1)
Hypokalemia	8 (2)	4 (1)
Urinary tract infection	8 (2)	4 (1)
Gastroenteritis	7 (2)	2 (<1)
Nausea*	7 (2)	0
Acute renal failure	7 (2)	9 (2)
Respiratory failure*	6 (2)	0

*Events that occurred at a rate ≥2% more frequently in the panobinostat arm.

7.3.3 Dropouts and/or Discontinuations

The percentage of patients that discontinued therapy due to an adverse event was higher in the panobinostat arm compared to the placebo arm. Overall 36% (n=139) of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20% of patients (n=76) in the placebo arm. The most common reason for

treatment discontinuation in the panobinostat arm was diarrhea which accounted for 4% of patients (Table 20).

Table 20 AEs leading to treatment discontinuation in ≥2% of patients in trial D2308

Preferred term	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Diarrhea*	17 (4)	6 (2)
Peripheral neuropathy*	14 (4)	7 (2)
Asthenia*	11 (3)	0
Fatigue	11 (3)	11 (3)
Thrombocytopenia	6 (2)	2 (1)

*Events that occurred at a rate ≥2% more frequently in the panobinostat arm.

Adverse events of any toxicity grade leading to treatment interruption or dose modification occurred in 342 (89%) of patients in the panobinostat arm compared to 281 (76%) patients in the placebo arm. The most common reason for dose modification or treatment interruption in the panobinostat was thrombocytopenia which occurred in 31% of patients (Table 21).

Table 21 AEs requiring treatment interruption or dose modification in ≥5% of patients trial D2308

Preferred term	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Thrombocytopenia*	119 (31)	40 (11)
Diarrhea*	99 (26)	33 (9)
Fatigue *	62 (16)	27 (7)
Peripheral neuropathy	48 (12)	54 (15)
Pneumonia*	40 (10)	29 (8)
Neutropenia*	39 (10)	9 (2)
Anemia*	32 (8)	16 (4)
Asthenia*	32 (8)	11 (3)
Neuralgia	32 (8)	33 (9)
Pyrexia*	30 (8)	11 (3)
Upper respiratory tract infection*	25 (6)	16 (4)
Vomiting*	23 (6)	6 (2)
Peripheral sensory neuropathy	21 (5)	20 (5)
Hypokalemia*	19 (5)	5 (1)
Platelet count decreased*	18 (5)	5 (1)

*Events that occurred at a rate ≥2% more frequently in the panobinostat arm.

7.3.4 Significant Adverse Events

The incidence of patients that experienced grade ≥3 adverse events was higher in the panobinostat arm 95% (n=367) compared to the incidence in the placebo arm 83% (n=307). Grade ≥3 thrombocytopenia was the most common severe adverse event experienced by 57% of patients in the panobinostat arm. The most common grade ≥3 adverse events that occurred in ≥10% of patients in the panobinostat arm were thrombocytopenia, diarrhea, neutropenia, hypokalemia, anemia, fatigue, pneumonia, lymphopenia, asthenia and hyponatremia.

Table 22 Grade ≥3 AEs occurring in ≥5% of patients in the panobinostat arm D2308

Preferred term	Panobinostat + bortezomib + dexamethasone (n=386)	Placebo + bortezomib + dexamethasone (n=372)
Thrombocytopenia*	219 (57)	92 (25)
Diarrhea*	98 (25)	29 (8)
Neutropenia*	92 (24)	30 (8)
Hypokalemia*	74 (19)	24 (6)
Anemia	65 (17)	58 (16)
Fatigue*	65 (17)	33 (9)
Pneumonia	48 (12)	39 (10)
Lymphopenia*	47 (12)	28 (8)
Asthenia*	37 (10)	14 (4)
Hyponatremia*	37 (10)	13 (3)
Leukopenia*	35 (9)	12 (3)
Platelet count decreased*	35 (9)	13 (3)
Hypophosphatemia*	34 (9)	23 (6)
Vomiting*	28 (7)	5 (1)
Peripheral neuropathy	26 (7)	21 (6)
Nausea*	21 (5)	2 (<1)

*Events that occurred at a rate ≥2% more frequently in the panobinostat arm.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Asthenic conditions (Fatigue, Malaise, Weakness, Asthenia)

Bortezomib is associated with a relatively high rate of asthenic conditions. The prescribing information for bortezomib informs prescribers that based upon an integrated analysis of data from patients with relapsed multiple myeloma and mantle cell lymphoma asthenic conditions were reported in 54% of patients with grade ≥3 events occurring in 3-7% of patients.

Based upon the results of trial D2308, panobinostat added toxicity to this regimen with regard to asthenic conditions. In trial D2308 asthenic conditions including fatigue, malaise and weakness were reported in 224 patients (58%) who received panobinostat + bortezomib + dexamethasone compared to 156 patients (42%) who received placebo + bortezomib + dexamethasone. Grade ≥3 adverse events occurred in 93 (24%) of patients in the panobinostat arm compared to 47 (13%) of patients in the placebo arm. In addition, 90 patients (23%) in the panobinostat arm compared to 42 patients (11%) in the placebo arm had an asthenic condition that led to treatment modification or

interruption. Asthenic conditions also lead to treatment discontinuation in 23 patients (6%) in the panobinostat arm compared to 11 patients (3%) in the placebo arm.

This finding is important because asthenic conditions can have a negative impact on how a patient feels and functions in their daily life. In part, this is reflected by the fact that there was a two fold increase in the frequency of patients who discontinued treatment with panobinostat + bortezomib + dexamethasone over patients in the placebo + bortezomib + dexamethasone arm.

In trial D2308, quality of life (QOL) and symptom data was collected using 3 different rating scales; EORTC-QLQ-C30, EORTC-QLQ-MY20 and FACT/GOG-NTX. These instruments are usually incorporated into trials because the EU requests this information. The US FDA has identified limitations of these instruments and rarely are they found adequate to support labeling claims. These endpoints were not alpha-controlled and no claims were proposed by the Applicant based upon them.

An exploratory analysis was conducted by this reviewer to evaluate the findings from these instruments. The evaluation found that there was excessive missing data, rendering the data unreliable.

For example, for each one of the three rating scales by week 12 (cycle 4) roughly 50% of patients in each treatment arm fully completed the assessments. By week 24 (cycle 8) only 60-70% of patients were missing completed assessments. Despite the limitations of these data it is reasonable, from an exploratory standpoint, to present the findings from the individual questions of these rating scales that relate to asthenic conditions in order to further understand the impact of these events on patients.

Due to the increasing amount of missing data for the QOL assessments at later timepoints, the week 12 results will be presented for the following reasons: 1) week 12 is cycle 4 which is a reasonable enough duration of time to evaluate toxicity and 2) because this time point had the least amount of missing data of timepoints $\geq$12 weeks. The EORTC-QLQ-C30 change from baseline to week 12 scores for fatigue were higher for patients treated with panobinostat + bortezomib + dexamethasone compared to patients treated with placebo + bortezomib + dexamethasone (Table 23) indicating worsening fatigue for patients who received panobinostat.

For the FACT/GOG-NTX the physical well-being subscale includes 7 questions and of these questions there is 1 question each about lack of energy, nausea and patient bother from side effects of treatment. These questions are relevant to the toxicities associated with panobinostat. One additional limitation to the findings from the FACT/GOG-NTX is that the Applicant did not present findings from the individual questions in the physical well-being subscale. The results presented were for the total physical well-being subscale. For this reason the Table 23 will present the results from the physical well-being subscale as a whole. The results of this subscale show that the

change from baseline to week 12 scores were lower for patients treated with panobinostat + bortezomib + dexamethasone compared to patients treated with placebo + bortezomib + dexamethasone indicating a worsening of physical well-being for patients treated with panobinostat. This finding suggests that lack of energy, nausea and patients being bothered by sides effects of treatment had a greater negative impact on patients treated with panobinostat.

Table 23 Quality of life assessment for fatigue, trial D2308

	Panobinostat + bortezomib + dexamethasone (n=387)		**Placebo + bortezomib + dexamethasone (n=381)**	
Preferred term	Baseline Mean Score	Week 12 Mean Score	Baseline Mean Score	Week 12 Mean Score
EORTC-QLQ-C30, mean score[1]				
• Fatigue	3	48	35	39
FACT/GOG-NTX, mean score[2]				
• Physical well-being subscale	21	18	21	20

[1] Higher symptom scores indicate worsening
[2] Higher scores indicate improvement

7.3.5.2 Gastrointestinal toxicity

Severe gastrointestinal toxicity manifested as nausea, vomiting and diarrhea occurred more frequently in patients receiving panobinostat + bortezomib + dexamethasone (Table 24) compared to patients who received placebo +bortezomib + dexamethasone. This finding is significant because bortezomib is associated with gastrointestinal toxicity for which the prescribing information contains a warning.

Table 24 Gastrointestinal toxicity trial D2308

	Panobinostat + bortezomib + dexamethasone (n=386)		**Placebo + bortezomib + dexamethasone (n=372)**	
Preferred term	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea	264 (68)	98 (25)	153 (41)	29 (8)
Nausea	139 (36)	21 (5)	77 (21)	2 (<1)
Vomiting	99 (26)	28 (7)	48 (13)	5 (1)

Of the gastrointestinal toxicities diarrhea had the largest impact on the tolerability of the panobinostat. Diarrhea lead to treatment interruption or dose modification in 26% of patients treated with panobinostat compared to 9% of patients in the placebo arm (Table 21). Diarrhea was also the most common adverse event leading to discontinuation of treatment for 4% of patient receiving panobinostat compared to 2% of patients receiving placebo (Table 20). In trial D2308 management of diarrhea included instructing patients to initiate loperamide at the first episode of poorly formed or loss stools. Premedication with loperamide was not recommended. During the trial 173 (45%) patients in the panobinostat arm compared to 96 (26%) required antipropulsives (e.g., Lomotil or Immodium). Events of non-infection colitis were rare but did occur in 3 patients (<1%) in the panobinostat arm compared to 0 patients in the placebo arm. None of the 3 events were grade $\geq$3 in severity. Events of ileus (including sub-ileus and paralytic ileus) occurred in 2% (n=9) of patients in the panobinostat arm (2%) and in 2% of patients (n=7) of patients in the placebo arm.

Reviewer comment: The fact that 26% of patients receiving panobinostat had treatment interruption or modification due to diarrhea despite specific guidelines for the treatment of diarrhea further suggests that the 20 mg dose of panobinostat may not be optimal. It does appear that treatment with antipropulsives and/or dose modification/interruption can adequately manage this toxicity based upon the fact that despite the high frequency of this toxicity only 4% of patients discontinued therapy due to this event. For this reason it may be important to communicate in labeling the need for these measures to mitigate this risk.

Nausea and vomiting had a lesser impact on the tolerability of panobinostat each leading to treatment discontinuation in only 2 patients (1%). Vomiting requiring dose adjustment or interruption occurred in 23 (6%) of patients in the panobinostat arm compared to 6 (2%) of patients in the panobinostat arm. Nausea requiring dose adjustment or interruption occurred in 17 (5%) of patients in the panobinostat arm compared to 8 (2%) of patients in the placebo arm. The protocol for trial D2308 did not include specific guidelines for prophylaxis or treatment of nausea/vomiting. However, there were 162 patients (42%) in the panobinostat arm compared to 99 (27%) that received medications for treatment or prophylaxis of nausea and/or vomiting.

Reviewer comment: Since the protocol for trial D2308 did not include specific guidelines for prophylaxis or treatment of nausea/vomiting it is reasonable to assume that standard of care measures were utilized along with the protocol guidelines for treatment interruption/dose modification. It is evident that the community standard of care for treatment and prophylaxis for management for the nausea and vomiting associated with panobinostat are adequate. It would be reasonable to communicate in the prescribing information for panobinostat the nausea/vomiting guidelines for dose medication/treatment interruption.

Dehydration
Severe gastrointestinal toxicities of nausea, vomiting and diarrhea can often cause dehydration. In trial D2308 adverse events of dehydration were reported more frequently in patients receiving panobinostat compared to patients receiving placebo. However, the incidence of dehydration was significantly less than the incidence of nausea, vomiting or diarrheas. There were no grade 4 events of dehydration in either treatment arm. Serious adverse events of dehydration occurred in 11 (3%) of patients in the panobinostat arm compared to 5 (1%) in the placebo arm. Dehydration led to hospitalization in 10 patients (3%) in the panobinostat arm compared to 3 patients (1%) in the placebo arm.

Table 25 Incidence of dehydration in trial D2308

	Panobinostat + bortezomib + dexamethasone (n=386)		**Placebo + bortezomib + dexamethasone (n=372)**	
Preferred term	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Dehydration	28 (7)	10 (3)	10 (3)	5 (1)

Reviewer comment: In reviewing the SAEs of dehydration there were cases in which patients had events of vomiting and/or diarrhea and subsequently became dehydrated. For this reason it is important to communicate that the gastrointestinal toxicities associated with panobinostat can lead to serious events of dehydration.

In the proposed draft prescribing information for panobinostat the Applicant is proposing to include in the warning for gastrointestinal disorders a statement that "Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances" This statement can be strengthened to reflect the fact that serious events of dehydration have occurred. However, I agree with the Applicant's proposal to communicate the risk of dehydration due gastrointestinal toxicity.

5.3.5.3 Cytopenias

Thrombocytopenia
Grade 3/4 thrombocytopenia occurred in 57% of patients in the panobinostat arm compared to 25% of patients in the placebo arm. Severe thrombocytopenia is concerning as it can increase a patient's risk of bleeding which may require platelet transfusion. Severe hemorrhagic events due to grade 3/4 thrombocytopenia were uncommon but did occur in 11 patients (3%) the panobinostat arm. The most likely reason for relatively small number of severe hemorrhagic events is that grade 3/4

thrombocytopenia was managed with dose interruption/modification of panobinostat and administration of platelets. This assumption is corroborated by the fact that 30% of patients in the panobinostat arm required a platelet transfusion due to thrombocytopenia compared to 10% of patients in the placebo arm (Table 26). Additionally, 31% of patients in the panobinostat arm required dose modification/interruption due to thrombocytopenia compared to 11% of patients in the placebo arm (Table 21).

Table 26 Reasons for platelet transfusion trial D2308

Reason for platelet transfusion	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Any reason, n (%)	127 (33)	41 (11)
Thrombocytopenia	115 (30)	36 (10)
Hemorrhage	10 (3)	5 (1)
Febrile neutropenia	1 (<1)	0
Septic shock	1 (<1)	0

Neutropenia
Events of severe neutropenia grade ≥3 are clinically important because patients with an absolute neutrophil count (ANC) less than 1000 are at increased risk of infection. Adverse events of grade 3/4 neutropenia occurred in 24% of patients in the panobinostat arm compared to 8% of patients in the placebo arm. Additionally, neutropenia that required dose interruption or modification occurred in 10% of patients in the panobinostat arm compared to 2% of patients in the placebo arm. Consistent with the increased rate of severe neutropenia, colony stimulating factor (GCSF or GMCSF) use was higher in the panobinostat arm (13%) compared to 4% in the placebo arm. Pancytopenia was rare but did occur in 5 patients (1%) in the panobinostat arm compared to 2 patients (<1%) in the placebo arm.

Reviewer comment: Bortezomib is associated with severe thrombocytopenia and neutropenia for which the prescribing information contains a warning. The increase in frequency of severe (grade 3-4) events of thrombocytopenia and neutropenia with panobinostat are concerning given the fact that this increase is additional toxicity over what is observed with bortezomib therapy. In addition, the increase in toxicity is profound with a two-fold increase in grade 3-4 thrombocytopenia and grade 3-4 neutropenia. Also, concerning is the numbers of patients in the panobinostat arm that required dose modification/interruption for these toxicities.

7.3.5.4 Hemorrhage

In trial D2308 five patients died due to events of hemorrhage. All 5 patients had grade ≥3 thrombocytopenia at the time of the hemorrhagic event. To further evaluate this

toxicity signal a MAED analysis was conducted for the narrow SMQ hemorrhage. The rate of hemorrhagic events of all toxicity grades 1-4 was 8% greater in the panobinostat arm compared to the placebo arm. There was also a two fold increase in severe (grade 3-4) and serious events of hemorrhage in the panobinostat arm compared to the placebo arm (Table 27). In the panobinostat arm 10 patients (3%) received a platelet transfusion due to a hemorrhagic event compared to 5 patients (1%) in the placebo arm.

Table 27 MAED SMQ analysis hemorrhage trial D2308

Broad SMQ	**Panobinostat + bortezomib + dexamethasone (n=386)**	**Placebo + bortezomib + dexamethasone (n=372)**
Hemorrhage, n (%)		
• All grade	79 (20)	44 (12)
• Grade 3/4	16 (4)	9 (2)
• SAEs	17 (4)	8 (2)

The grade 3-4 hemorrhagic events in the panobinostat arm were further reviewed. Out of the 16 patients that had a grade 3/4 hemorrhagic event there were 11 patients that had grade 4 thrombocytopenia at the time of the event with all 11 patients having a platelet count less than 20 x 10^9/L. This is relevant because a platelet count <20 x 10^9/L significantly increases a patient's risk for bleeding. One patient (0039_00003) out of 11 was receiving concomitant warfarin which also increases the risk of bleeding. Of the remaining 5 patients, 4 had an adverse event of grade 3 thrombocytopenia at the time of the hemorrhagic event. Patient 0312_00005 had grade 3 thrombocytopenia but the event of cerebral hemorrhage was confounded by central nervous system involvement with disease which increases the risk of cerebral hemorrhage. The 1 patient (0335_00004) who did not have grade 3/4 thrombocytopenia at the time of the hemorrhagic event had factors that significantly confound the case. Prior to the grade 4 event of upper gastrointestinal hemorrhage the patient had adverse events grade 4 hepatic cirrhosis and grade 4 liver failure which began approximately 6 days prior to the onset of gastrointestinal hemorrhage. The patient died of progressive disease 5 days after the onset of gastrointestinal hemorrhage and autopsy confirmed that the patient had liver involvement with disease. The patient's last dose of panobinostat was on August 2nd approximately 18 days prior to the bleeding event. It is likely that progressive disease was the cause of the gastrointestinal hemorrhage and not panobinostat.

Severe thrombocytopenia is one of the major toxicities of panobinostat occurring in 57% of the patients who received panobinostat in trial D2308. Based upon the findings form the dose escalation trial B2207 this toxicity appears to be dose related. For this reason it is relevant to discuss the impact of dose modification/interruption on the cases of grade 3/4 hemorrhage. In trial D2308 the dose of panobinostat was to be interrupted

and reduced for any grade 3 event of thrombocytopenia with bleeding and any grade 4 event of thrombocytopenia. Thrombocytopenia (grade 1-4) that required dose interruption/modification occurred in 31% of patient in the panobinostat arm compared to 11% of patient in the placebo arm. Despite the fact that 57% of patients experienced grade 3-4 thrombocytopenia, only 4% of patients in the panobinostat arm had a severe (grade 3-4) hemorrhagic event. This finding is supportive of the fact that the dose modification guidelines for thrombocytopenia in trial D2308 were effective in mitigating severe bleeds. However, the risk of hemorrhage with panobinostat is still greater than that observed with bortezomib, a product associated with hemorrhage.

It is also important to point out cases of severe hemorrhagic events that occurred in scenarios where the dose modification guidelines for trial D2308 were not followed. Of the 16 patients in the panobinostat arm that experienced a grade 3/4 hemorrhagic event there were 5 patients that experienced adverse events of thrombocytopenia that met the requirements for dose-reduction but the dose of panobinostat was not reduced. It is important to note that none of these patients died due to a hemorrhagic event. Based upon this finding it is important to communicate to prescribers the importance of adhering the dose modification/interruption guidelines proposed in labeling.

Reviewer comment: It will also be important to describe these severe and fatal events of hemorrhage in the prescribing information for panobinostat in order to communicate the risk of severe hemorrhage to prescribers.

7.3.5.5 Infection

Serious and fatal infections including pneumonia and sepsis are associated with the pharmacologic class of HDAC inhibitors. As a SOC grade 1-4 infections/infestations occurred at a similar incidence between the 2 treatment arms. In the panobinostat arm 265 (69%) patients compared to 250 (67%) patients in the placebo arm experienced a grade 1-4 infection. In contrast severe (grade $\geq$3) infections occurred more frequently in patients treated with panobinostat compared to placebo. Grade 3-4 infections/infestations occurred in 119 (31%) in the panobinostat arm compared to 90 (24%) patients in the placebo arm. Pneumonia, sepsis and septic shock occurred at a rate $\geq$2% more frequent in the panobinostat. In addition, deaths due to infection occurred in 10 patients (3%) in the panobinostat arm compared to 6 patients (2%) in the placebo arm. These findings are consistent with the known toxicity profile of HDAC inhibitors.

Table 28 Grade ≥3 infections and infestations trial D2308

SOC Preferred term	**Panobinostat + bortezomib + dexamethasone (n=386)** Grade 3-4	**Placebo + bortezomib + dexamethasone (n=372)** Grade 3-4
Infections/infestations, n (%)		
Total	*119 (31)*	*90 (24)*
Pneumonia	48 (12)	39 (10)
Sepsis	11 (3)	6 (2)
Septic shock	10 (3)	3 (1)
Upper respiratory tract infection	9 (2)	6 (2)
Urinary tract infection	9 (2)	6 (2)
Gastroenteritis	6 (2)	2 (1)
Infection	6 (2)	3 (1)
Respiratory tract infection	5 (1)	5 (1)
Herpes zoster	4 (1)	7 (2)

Hepatitis B virus infection
There were 3 patients in the panobinostat arm compared to 1 patient in the placebo arm that developed hepatitis B virus infection. Testing for prior hepatitis B or C infection was not required at screening. Eligibility criteria for trial D2308 only queried for known history of infection. None of the 4 patients had a known prior history of hepatitis B infection and therefore there is no information to conclude that these are cases of re-activation of hepatitis B infection. It is important to point out that all 3 cases in the panobinostat arm occurred in patients at site 355 located in Taiwan. The one case in the placebo arm occurred in a patient at site 311 located in Korea.

Reviewer comment: Hepatitis B infection is more prevalent in Asian counties. Based upon review of table 14.1-1.2 of the clinical study report there were a total of 131 patients (34%) from the regions of South East Asia and Western Pacific enrolled in the panobinostat arm. In contrast 107 patients (29%) from these regions were enrolled in the placebo arm. It is likely that the difference between the treatment arms in the number of cases of hepatitis B infection is due the increased number of patients from Asian counties enrolled in the panobinostat arm.

7.3.5.6 Cardiac ischemic events

Cardiac ischemic events are an uncommon but serious adverse events associated with the pharmacologic class of HDAC inhibitors. Cardiac toxicity mainly described as congestive heart failure and decreased ventricular ejection fraction is associated with bortezomib and is a warning in the prescribing information. However, the prescribing information for bortezomib also describes an increased risk of ischemic adverse

reactions. In trial D2308 there was an increase in the number of cardiac ischemic deaths. Three patients in the panobinostat arm (1%) died due to cardiac ischemic events compared to 0 in the placebo arm. Two of the patients died due to myocardial infarction and 1 due to myocardial ischemia. To further evaluate this signal a MAED narrow SMQ analysis was conducted to evaluate the risk of ischemic heart disease with panobinostat. Consistent with the finding of an increased number of deaths there was also an increase in the number of grade 1-4 cardiac ischemic events. A total of 14 patients (4%) in the panobinostat arm compared to 5 (1%) in the placebo arm had a grade 1-4 event of ischemic heart disease. Of these events 8 (2%) in the placebo arm were grade 3/4 compared to 1 (<1%) in the placebo arm. A breakdown of these events by preferred term is provided in Table 29.

Table 29 MAED Narrow SMQ ischemic heart disease trial D2308

	Panobinostat + bortezomib + dexamethasone (n=386)		**Placebo + bortezomib + dexamethasone (n=372)**	
Narrow SMQ Preferred term	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Ischemic heart disease, n (%)				
Total	14 (4)	8 (2)	5 (1)	1 (<1)
Angina pectoris	6 (2)	1 (<1)	5 (1)	1 (<1)
Myocardial ischemia	3 (1)	3 (1)	0	0
Acute coronary syndrome	2 (1)	1 (<1)	0	0
Myocardial infarction	2 (1)	2 (1)	0	0
Acute myocardial infarction	1 (<1)	1 (<1)	0	0
Arteriosclerosis coronary artery	1 (<1)	0	0	0
Troponin T increased	1 (<1)	0	0	0

Reviewer comment: The increase in the number of ischemic cardiac events in the panobinostat +bortezomib arm is not overwhelmingly high compared to the placebo + bortezomib + dexamethasone arm. However, it should not be ignored that this is an increase in frequency over and above the control arm which is also associated with cardiac toxicity.

In addition, there was an increase in the frequency of these events in the panobinostat arm compared to the control arm. For this reason these findings could be communicated in labeling. An option would be to describe the rate these events compared to the control arm in the adverse events section of the prescribing information.

7.3.5.7 Hypothyroidism

Pre-clinical studies in animals showed that the TSH fell in animals treated with panobinostat. Human hypothyroidism is heralded by a rise in TSH. Based upon review of the raw adverse event dataset, 5 patients (1%) experience grade $\leq$2 adverse events of hypothyroidism in panobinostat arm compared to 3 patients (1%) in the control arm. A description of the cases for both treatment arms is below.

Panobinostat
0003_00007: patient had current condition of hypothyroidism at baseline but was not receiving treatment. Patient developed grade 2 hypothyroidism and was treated with levothyroxine.

0075_00003: no prior history of hypothyroidism, elevated FT4 at baseline. Patient developed grade 1 hypothyroidism but did not receive treatment for the event.

0121_00006: no prior history of hypothyroidism, elevated TSH at baseline. Patient developed grade 1 hypothyroidism but did not receive treatment for the event.

0318_00006: no prior history of hypothyroidism, elevated TSH at baseline, Patient developed grade 1 hypothyroidism and was treated with levothyroxine

0336_00005: no prior history of hypothyroidism, normal baseline thyroid function, Patient develop grade 2 hypothyroidism but did not receive treatment

Placebo
0064 00002; patient had current condition of hypothyroidism for which they were receiving treatment with levothyroxine. The patient subsequently developed grade 2 worsening of hypothyroidism.

0075 00014; no prior history of hypothyroidism, the patients thyroid function was normal at baseline. The patient developed grade 1 hypothyroidism but did not receive treatment for this event.

0325 00008; no prior history of hypothyroidism, low FT4 levels and normal TSH at baseline, 2 days after last dose patient was diagnosed with grade 2 hypothyroidism and treated with levothyroxine.

Reviewer comment: Based upon these cases and the fact that the rate of hypothyroidism was similar between treatment arms, it does not appear that panobinostat is associated with hypothyroidism.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

D2308
Out of 758 patients that were exposed to at least 1 dose of investigational therapy 756 (99.7%) experienced at least 1 adverse event during the trial. The percentage of patients in each treatment arm that experienced an adverse event of any grade was 99.7% for the panobinostat arm and the placebo arm. The most common adverse events that occurred in ≥20% of patients in the panobinostat arm and at a ≥10% greater frequency than the placebo arm were diarrhea, thrombocytopenia, fatigue, nausea, neutropenia, peripheral edema, decreased appetite, hypokalemia, pyrexia, vomiting (Table 30).

Table 30 Adverse reactions reported with ≥10% incidence, ≥2% difference between the treatment arms, and higher in panobinostat arm

Preferred term, n (%)[*]	Grade 1-4 Pan + Bor + Dex (n=386)	Grade 1-4 Pbo + Bor + Dex (n=372)
Diarrhea*	264 (68)	153 (41)
Thrombocytopenia*	249 (65)	151 (41)
Anemia	160 (41)	124 (33)
Fatigue*	158 (41)	109 (29)
Nausea*	139 (36)	77 (21)
Peripheral neuropathy	119 (31)	132 (35)
Neutropenia*	114 (30)	40(11)
Peripheral edema*	111 (29)	70 (19)
Decreased appetite*	110 (29)	44 (12)
Hypokalemia*	106 (27)	52 (14)
Constipation	104 (27)	121 (33)
Pyrexia*	99 (26)	54 (15)
Vomiting*	99 (26)	48 (13)
Asthenia	85 (22)	54 (15)
Cough	83 (22)	68 (18)
Dizziness	73 (19)	60 (16)
Insomnia	73 (19)	61 (16)
Upper respiratory tract infection	68 (18)	55 (15)
Pneumonia	65 (17)	48 (13)
Leukopenia	63 (16)	30 (8)
Dyspnea	57 (15)	43 (12)
Hypotension	54 (14)	34 (9)
Headache	53 (14)	39 (11)
Lymphopenia	52 (13)	35 (9)
Abdominal pain	51 (13)	40 (11)
Hyponatremia	49 (13)	19 (5)
Hypophosphatemia	44 (11)	31 (8)
Decreased weight	44 (11)	17 (5)
Platelet count decreased	43 (11)	17 (5)
Pain extremity	40 (10)	54 (15)
Blood creatinine increased	38 (10)	22 (6)

*Events that occurred at a rate ≥10% more frequently in the panobinostat arm.

7.4.2 Laboratory Findings

In general laboratory abnormalities occurred more frequently than corresponding reports of adverse events of hematologic toxicity or electrolyte abnormalities. The frequency of grade 3-4 reported adverse events was consistent with corresponding

laboratory abnormalities. This highlights the fact that grade 1-2 adverse events of hematologic toxicity and electrolyte abnormalities were underreported in this trial.

Thrombocytopenia, neutropenia and leukopenia occurred more frequently in patients receiving panobinostat in combination with bortezomib and dexamethasone compared to patients who received placebo in combination with bortezomib and dexamethasone. This finding is consistent with the adverse event reports of these toxicities (Table 31).

Table 31 Laboratory adverse events of hematologic toxicity trial D2308

	Panobinostat + bortezomib + dexamethasone (n=386)		**Placebo + bortezomib + dexamethasone (n=372)**	
Hematology parameter	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hemoglobin	341 (88)	73 (19)	331 (89)	77 (21)
Platelets	377 (98)	258 (67)	327 (88)	118 (32)
Absolute neutrophil count	299 (77)	133 (34)	142 (38)	42 (11)
White blood cell count	330 (85)	89 (24)	203 (55)	31 (8)
Absolute lymphocyte count	324 (84)	205 (53)	278 (75)	154 (41)

Table 32 Laboratory adverse events of chemistry parameters trial D2308

	Panobinostat + bortezomib + dexamethasone (n=386)		Placebo + bortezomib + dexamethasone (n=372)	
Chemistry parameter, n (%)	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hypocalcemia	272 (70)	21 (5)	220 (60)	8 (2)
Hypophosphatemia	246 (64)	79 (20)	173 (47)	46 (12)
Hyperalbuminemia	241 (64)	7 (2)	145 (39)	7 (2)
Hyperglycemia	259 (67)	22 (6)	238 (64)	29 (8)
Hypokalemia	207 (54)	72 (19)	137 (37)	26 (7)
Hyponatremia	213 (55)	55 (14)	156 (42)	30 (8)
Increased creatinine	192 (50)	4 (1)	99 (27)	7 (2)
Increased AST (SGOT)	139 (36)	6 (2)	125 (34)	5 (1)
Increased ALT (SGPT)	137 (35)	7 (2)	152 (41)	5 (1)
Increased alkaline phosphatase	122 (32)	7 (2)	79 (21)	1 (<1)
Hypermagnesemia	109 (28)	19 (5)	57 (15)	5 (1)
Hypomagnesemia	107 (28)	0	86 (23)	2 (1)
Hyperbilirubinemia	82 (21)	3 (1)	50 (13)	1 (<1)
Hypoglycemia	80 (21)	2 (1)	81 (22)	2 (1)
Hyperkalemia	77 (20)	15 (4)	64 (17)	7 (2)
Hypernatremia	48 (12)	0	54 (15)	1 (<1)
Hypercalcemia	29 (8)	1 (<1)	39 (10)	5 (1)

Reviewer comment: The laboratory adverse events observed are consistent with the fact that panobinostat is associated with dehydration, severe vomiting and diarrhea.

7.4.3 Vital Signs

There was no clinically meaningful difference between the treatment groups with regard to increases or decreases in systolic/diastolic blood pressure, heart rate, body temperature or respiratory rate.

Consistent with the finding of an increased incidence of adverse reactions of decreased body weight in patients treated with panobinostat + bortezomib + dexamethasone, there was a decrease (4 kg) in mean body weight from baseline to end of treatment in patients treated with panobinostat + bortezomib + dexamethasone.

Table 33 Change in body weight during trial D2308

Visit	Mean body weight Pan + BTZ + Dex (n=386)	Mean body weight Pbo + BTZ + Dex (n=372)
Baseline	72 kg	73 kg
End of treatment	68 kg	72 kg

Reviewer comment: It is likely that the high rate of gastrointestinal toxicity observed with panobinostat lead the finding of an overall decrease in body weight from baseline in patients who received panobinostat.

7.4.4 Electrocardiograms (ECGs)

As a class HDAC inhibitors are associated with QT prolongation and morphologic changes in ECG including T-wave and ST-segment changes. Isolated cases of QT-interval prolongation have also been observed with bortezomib. Therefore, it is important to evaluate the ECG findings from trial D2308 in order to determine if the addition of panobinostat to bortezomib and dexamethasone resulted in an increased incidence or severity of ECG adverse reactions. For trial D2308 ECGs were centrally reviewed by an independent reviewer.

7.4.4.1 QT interval abnormalities

The QT interdisciplinary review team (QT-IRT) was consulted to review the ECG results with regarding to QT prolongation from trial D2308.

A summary of the review is below:

The labeling language related to the QT risk appears to be adequate in mitigating risk after drug is approved to be marketed (please see our minor edits in the following). The sponsor's exposure-QTc analysis is not reliable because the QT prolongation is dose but not concentration dependent. Although the case of TdP was only noted with consecutive IV dosing, which has been discontinued, and plasma concentrations are lower with oral dosing, we would like to bring to the Division's attention that TdP risk has not been included in the proposed label. We defer final labeling decisions to the Division.

In the clinical study report for trial D2308 the Applicant states that "none of the patients who received panobinostat in trial D2308 had a QT interval $\geq$500 ms". In reviewing the ECG2 raw dataset this reviewer discovered that patient 0900_00002 had a QTc interval >500 ms at cycle 1 day 5. The QT-IRT team was asked to review and comment of this

case. At the time of this review the clinical team has not yet received a response from the QT-IRT team.

Reviewer comment: The case of Torsades de pointes the QT-IRT reviewer is referring to occurred in a patient in trial A2101 receiving the intravenous formulation of panobinostat at 20 mg/m^2 administered continuously on a daily basis. Exposures with this dosing regimen are significantly higher than that with oral dosing of panobinostat at the regimen investigated in patients with multiple myeloma.

7.4.4.2 Other ECG abnormalities

In the clinical study report for trial D2308 the Applicant presented the results of ECG abnormalities. Due to the complexity of recreating this analysis and the fact that the clinical study report safety population is similar to that used in the modified safety set 2, the Applicant's analysis from clinical study report table 12-17 was utilized and reviewed.

Below are the newly occurring ECG abnormalities that occurred at a rate >2 % higher in the panobinostat + bortezomib + dexamethasone arm. Event rates are presented due to the fact not all patients in each treatment arm were evaluable for developing a given event. For example, a patient with a baseline finding of sinus tachycardia would not be evaluable for a newly occurring post-baseline event. The N value presented is the number of patients at risk for developing the event.

The findings of increased rates of ST segment depression, flat T-waves and inverted T-waves in the panobinostat arm are suggestive and corroborate the adverse reaction findings of increased cardiac ischemic events. Flat T-waves can be a non-specific finding but can represent cardiac ischemia or hypokalemia. Therefore, the finding of a 20% increase in flat T-waves is consistent with the higher frequency of hypokalemia in patients treated with panobinostat.

Table 34 ECG abnormalities trial D2308

Abnormality type	**Pan + BTZ + Dex**	**Pbo + BTZ + Dex**
Ventricular premature complex	10% (n=370)	6% (n=368)
Sinus tachycardia	16% (n=373)	7% (n=369)
ST segment		
• Depressed ST segment	22% (n=373)	4% (n=363)
T-waves (any abnormality)	40% (n=381)	18% (n=377)
Flat T-waves	34% (n=358)	14% (n=348)
Inverted T-waves	13% (n=367)	6% (n=364)

Reviewer comment: In the proposed prescribing information for panobinostat the Applicant has included in section 6 language regarding ECG abnormalities and the findings of changes in T-wave and ST segment depression. It would be reasonable to describe the T-wave changes a (e.g., flat T-waves and inverted T-waves) to inform prescribers of the specific T-wave abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were submitted to this Application

7.4.6 Immunogenicity

No clinical data regarding immunogenicity were submitted to this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In a response to an IR (SD# 15) from the clinical pharmacology discipline the applicant completed a case-control assessment for FDA selected safety endpoints (thrombocytopenia, fatigue, diarrhea, anemia, neutropenia, hypokalemia, hemorrhage, and ischemic heart disease). The pharmacometrics review discipline is currently reviewing the data and will provide an analysis. Refer to the pharmacometrics review for this analysis.

The Applicant's executive summary of the response to IR is provided below:

Novartis has completed the case-control assessment for all selected safety endpoints (thrombocytopenia, fatigue, diarrhea, anemia, neutropenia, hypokalemia, hemorrhage, and ischemic heart disease) and PFS using the reference paper (Yang et al) in order to understand the relationship of dose intensity (DI) and clinical endpoints after adjusting for potentially unbalanced baseline risk factors. The potential relation between the respective endpoint and DI was explored by grouping patients within the panobinostat (PAN) arm by quartiles for DI.

In summary,

- Time to AEs by DI-quartiles showed a trend across all safety endpoints suggesting a possible association between Grade 3-4 AE and a higher DI. In addition, this trend was also observed for thrombocytopenia for all grades. Due to a very small number of events in each quartile of DI for all grades (n=10) and grade 3/4 (n=3) ischemic heart disease and grade 3/4 hemorrhage, no additional assessment was performed.

- After adjusting for baseline prognostic factors there appears to be a trend for higher risk in the high dose intensity case group for all grades and grade 3/4 thrombocytopenia, diarrhea, anemia and hypokalemia compared to the respective matched control group. In addition, there appears to be a trend for higher risk in the low DI PAN group for all grade and grade 3/4 for thrombocytopenia and diarrhea.
- For the PFS only 58 out of 207 PFS events from primary analysis were included in this analysis with a very limited number of PFS events per quartile (only 4 events in the fourth quartile). Although considering this limitation, there appears to be no effect of PAN DI on the occurrence of PFS events.
- No case control analysis was performed for fatigue (all grades and grade 3/4), neutropenia (all grades and grades 3/4), hemorrhage (all grades) and PFS as there was no significant difference in the prognostic factors across quartiles. For all other endpoints the case control analysis was performed.

7.5.2 Time Dependency for Adverse Events

The Applicant conducted a Kaplan Meier analysis to describe the time to onset of the first event of grade ≥3 thrombocytopenia in patients enrolled in trial D2308. This analysis included all 758 patients in the safety population. Patients who did not have an event of grade ≥3 were included in this analysis and censored. Based upon the Applicants analysis the median time to onset of grade ≥3 thrombocytopenia was 1.08 months for patients treated with panobinostat. The median was not able to be estimated for patients in the panobinostat arm (source table 14.3-3.4 of clinical study report). This reviewer did not agree with this analysis due to the fact that it includes patients that did no experience an event. The most clinically relevant time to event analysis should only include patients that experienced an event of grade ≥3 thrombocytopenia. Therefore, a reviewer analysis was conducted which only included patients that experienced an event. Based upon this analysis the median time to onset of first event of grade ≥3 thrombocytopenia was 31 days (95% CI: 29, 31) for the panobinostat arm compared to 28.5 days for the placebo arm (95% CI: 28, 31).

Reviewer comment: Based upon the reviewer analysis there is not clinically meaningful difference between to the time to onset of grade ≥3 thrombocytopenia between the treatment arms.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Age

Trial D2308 enrolled a significant number (n= 317, 42%) of patients age ≥65. In the panobinostat arm 42% of patients were age 65 years or older. With this number of

patients it is possible to conduct an analysis to compare the toxicity profile of panobinostat in patients age <65 years to patients age ≥65 years. Patients age ≥65 years old experienced higher rates of diarrhea, thrombocytopenia, anemia and fatigue. Most notably patients age ≥65 years experienced a 10% increase in grade ≥3 diarrhea, 17% increase in grade ≥3 thrombocytopenia, 5% increase in grade ≥3 anemia and 10% increase in grade ≥3 fatigue.

Adverse reactions leading to treatment discontinuation occurred in 44% (n=71) of patients age ≥65 years compared to 30% (n=68) of patients age <65 years who received panobinostat. Adverse reactions leading to treatment interruption and/or dose modification occurred in 91% of patients age ≥65 years compared to 87% age <65 years who received panobinostat. There were 14 patients (9%) age ≥65 years compared 12 patients (5%) age <65 years who died due to a reason other than disease progression in the panobinostat arm.

Table 35 Most common adverse reactions in ≥20% of patients age ≥65 years compared to <65 years who received panobinostat trial D2308

	Age <65 years Pan + Bor + Dex (n=224)		**Age ≥65 years Pan + Bor + Dex (n=162)**	
Preferred term, n (%)	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea	142 (63)	48 (21)	122 (76)	50 (31)
Thrombocytopenia	132 (59)	111 (50)	117 (73)	108 (67)
Anemia	82 (37)	33 (15)	78 (48)	32 (20)
Fatigue	82 (37)	28 (13)	76 (47)	37 (23)
Nausea	87 (39)	17 (8)	52 (33)	4 (3)
Peripheral edema	60 (27)	4 (2)	51 (32)	4 (3)
Vomiting	52 (23)	16 (7)	47 (29)	12 (8)
Decreased appetite	64 (29)	6 (3)	46 (29)	6 (4)
Neutropenia	70 (31)	58 (26)	44 (27)	34 (21)
Hypokalemia	62 (28)	39 (17)	44 (27)	35 (22)
Pyrexia	57 (25)	2 (1)	42 (26)	3 (2)
Constipation	63 (28)	2 (1)	41 (26)	2 (1)
Asthenia	46 (21)	18 (8)	39 (24)	19 (12)
Peripheral neuropathy	83 (37)	15 (7)	36 (22)	11 (7)

Reviewer comment: These findings are concerning given that a significant number of patients with relapsed multiple myeloma are age ≥65 years. There is a considerable increase in the rate of death for patients age ≥65 years. In addition, the fact that 91% of

patients age ≥65 years required dose interruption/modification again calls into question whether the Applicant has selected the correct dose of panobinostat.

7.5.3.2 Race

The clinical pharmacology review notes that in the small subgroup of 13 Japanese patients for whom pharmacokinetic sampling was collected panobinostat exposure was higher compared to Caucasian patients. This finding coincides with the fact that there was a general tendency for a higher frequency of adverse event (AEs) for patients of Asian ethnicity than Caucasian ethnicity in the panobinostat arm of trial D2308 [i.e., thrombocytopenia (Caucasian vs. Asian: 60.7% vs. 70.1%), diarrhea (66.4% vs. 71.7%), fatigue (48.4% vs. 26.8%), hypokalemia (18.4% vs. 44.9%), decreased appetite (20.9% vs. 43.3%), pneumonia (12.7% vs. 26.0%), hypoesthesia (3.7% vs. 15.0%), hepatic function abnormal (0.0% vs. 3.9%), gastroenteritis (2.5% vs. 4.7%), and herpes zoster (2.9% vs. 8.7%].

To further explore this finding, a separate analysis of adverse events was conducted to determine whether there was a difference between the toxicity profile of panobinostat + bortezomib + dexamethasone in Asian patients compared to Caucasian patients that received panobinostat + bortezomib + dexamethasone. Overall Asian patients experienced a higher frequency of grade 1-4 and grade ≥3 adverse reactions compared to Caucasian patients. Most notably Asian patients experienced a 13% increase in grade ≥3 diarrhea, 11% increase in grade ≥3 thrombocytopenia and 20% increase in grade ≥3 hypokalemia. These findings are consistent with the clinical pharmacology findings in Japanese patients.

Table 36 Adverse events for Asian race compared to Caucasian race, trial D2308

	Asian patients Pan + Bor + Dex (n=129)		Caucasian Pan+ Bor + Dex (n=245)	
Preferred term, n (%)	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea	93 (72)	44 (34)	164 (67)	51 (21)
Thrombocytopenia	91 (71)	82 (64)	149 (61)	130 (53)
Hypokalemia	58 (45)	42 (33)	46 (19)	31 (13)
Decreased appetite	57 (44)	5 (4)	52 (21)	7 (3)
Anemia	53 (41)	27 (21)	101 (41)	35 (14)
Vomiting	46 (36)	12 (9)	50 (20)	16 (7)
Nausea	46 (36)	7 (5)	89 (36)	13 (5)
Peripheral neuropathy	44 (34)	7 (5)	67 (27)	16 (7)
Neutropenia	40 (31)	34 (26)	71 (29)	55 (22)
Constipation	39 (30)	1 (1)	62 (25)	3 (1)
Cough	38 (30)	2 (2)	43 (18)	2 (1)

Reviewer comment: These findings are quite profound and call into question the risk versus benefit of panobinostat in Asian patients. At minimum, the results of this AE analysis should be included in the prescribing information for panobinostat. A separate dose-finding trial for patients of Asian race may help to identify the correct dose for Asian patients.

7.5.4 Drug-Disease Interactions

All patients enrolled in trial D2308 had a diagnosis of relapsed/refractory multiple myeloma so no differences in safety variables can be assessed for different diagnoses.

7.5.5 Drug-Drug Interactions

Refer to clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the pooled safety analysis of 456 patients exposed to panobinostat at the recommended dose schedule of 20 mg of panobinostat 3 times a week on a 2 week on 1 week off schedule, a total of 8 patients (2%) reported events in the SOC neoplasms benign, malignant and unspecified compared to 11 patients (3%) who received placebo + bortezomib + dexamethasone. Among the 8 patients who received treatment with panobinostat + bortezomib + dexamethasone, 5 (1.1%) patients one case each of basal

cell carcinoma, endometrial cancer, lipoma, neoplasm malignant, and thyroid neoplasm. Among the 11 patients in who received treatment with placebo + bortezomib + dexamethasone, 10 patients (2.1%) reported different types of neoplasms which included 1 case of lipoma, 1 case of lung adenocarcinoma, 1 case of melanocytic naevus, 1 case of prostate neoplasm, 1 case of skin neoplasm, 1 case of prostate cancer, 2 cases of rectal cancer and 2 cases of small cell lung cancer.

Review of the integrated summary of safety dataset revealed that patient 0081_00002 enrolled in trial B2201 investigating single agent panobinostat in patients with refractory cutaneous T-cell lymphoma developed a thyroid neoplasm. This finding is relevant given the preclinical findings in animals of thyroid tumors.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of panobinostat in pregnant women. Studies conducted in animals with panobinostat have demonstrated reproductive and embryo-fetal toxicity.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of panobinostat have not been established in the pediatric population. Panobinostat was granted orphan drug designation on August 20, 2012. Products with orphan drug status are exempt from the requirements of the Pediatric Research Equity Act (PREA).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was one death due to drug overdose in trial D2308. A brief description of this event is provided in section 7.3.1 of this review. There were 2 patients in trial D2308 who had reports of an adverse reaction overdose. A summary of the narrative provided for these events is below.

Patient 0214_00001
In the narrative for this patient it explains that the patient reported taking 2 doses of panobinostat on [redacted] (b) (6) the same day the patient initiated therapy. The event of overdose was reported as resolved on [redacted] (b) (6). No treatment was reported for this event and the patient was not hospitalized due to this event. Adverse reactions of grade 3 lymphopenia and grade 3 hyponatremia were reported as starting on [redacted] (b) (6) Given the timing of the event in relation to initiation of therapy it is difficult to determine if the events lymphopenia and hyponatremia were due to overdose or a toxicity observed during prescribed therapy of 20 mg. Hyponatremia and lymphopenia are common toxicities associated with panobinostat.

Patient 0338_00002
In the narrative for this patient it explains that on C1D15 ([redacted], C1D17 ([redacted] and C1D19 ([redacted]), the patient had taken extra doses of panobinostat. No treatment was reported for this event and the patient was not hospitalized due to this event. The event of overdose was reported as resolved on [redacted]. It is relevant to point out that 3 days later on [redacted] the patient had a grade 4 event of thrombocytopenia and a grade 4 event of pancytopenia. This patient did not have any prior adverse reactions of cytopenias prior to those experienced on [redacted]

Reviewer comment: As described in section 7.3.1 the death due to overdose is highly confounded. The adverse reactions of overdose for patients 0214_00001 and 0338_00002 are cases of medication administration errors. In this reviews opinion these events do not represent cases of drug overdose due to drug abuse or overdose with suicidal intent.

Given the case of overdose for patient 0338_00002 it may be helpful to describe in labeling that severe myelosuppression such as thrombocytopenia and pancytopenia have been observed within days after overdose with panobinostat. For this reason it would be reasonable to advise physicians to monitor patients closely for myelosuppression after overdose of panobinostat. In addition, the case of overdose for patient 0214_00001 suggests that it would also be reasonable to advise physicians to also monitor for electrolyte abnormalities.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 90 safety update to supplement 60 on January 16, 2014 (SD# 16). This update was reviewed and the findings were consistent with the safety findings discussed in this review.

8 Postmarket Experience

No post-market experience is available because panobinostat has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

The literature review consisted of evaluation of the current National Comprehensive Cancer Network (NCCN) guidelines on the treatment of multiple myeloma as well as review of the current prescribing information for Velcade®. The current prescribing information for Istodax® was also reviewed due to the fact that it is a HDAC inhibitor.

Velcade (bortezomib) for injection prescribing information, Millennium Pharmaceuticals, Inc. August 8, 2014

Istodax (romidepsin) for injection prescribing information, Celgene Corporation, June 13, 2013

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma, Version 1.2015, August 13, 2014

9.2 Labeling Recommendations

Discussed throughout review; labeling negotiations are ongoing at the time of this review finalization.

9.3 Advisory Committee Meeting

This application is being presented at the FDA Oncologic Drug Advisory Committee meeting in November 2014.

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/s/

ADAM N GEORGE
08/27/2014

VIRGINIA E KWITKOWSKI
08/27/2014

CLINICAL REVIEW OF EFFICACY

Application Type	NDA
Application Number	205353
Priority or Standard	Priority
Submit Date	March 22, 2014
Received Date	March 24, 2014
PDUFA Goal Date	November 24, 2014
Division / Office	Hematology Products/OHOP
Reviewer Name	Barry W. Miller, MSN, CRNP
Review Completion Date	August 26, 2014
Established Name	Panobinostat
(Proposed) Trade Name	Farydak
Therapeutic Class	Histone deacetylase inhibitor
Applicant	Novartis Pharmaceuticals, Corp.
Formulation(s)	10 mg, 15 mg, 20 mg capsules
Dosing Regimen	20 mg orally, once daily, 3 times a week for 2 weeks of eight repeated 3-week cycles, followed by eight additional cycles for patients with clinical benefit.
Indication	In combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 1 prior therapy
Intended Population	Adults

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6 Review of Efficacy

Efficacy Summary

The efficacy of Farydak (panobinostat) was principally evaluated in 768 patients with relapsed multiple myeloma enrolled in a 1:1 randomized, controlled, double-blinded, add-on design trial using bortezomib (B) and dexamethasone (D) as backbone therapy. The primary endpoint was investigator-assessed progression-free survival (PFS); the key secondary endpoint was overall survival (OS).

A summary of the key efficacy findings based on the data cut-off date of September 10, 2013 follows:

- Investigator-assessed median PFS difference was 3.9 months: 12.0 months in the panobinostat + BD arm vs. 8.1 months in the placebo + BD arm. The hazard ratio was 0.63 (95% CI: 0.52, 0.76), *p*-value <0.0001.

- An interim analysis for OS was not mature.

- Overall response rate (ORR) was 61% [11% complete response (CR)] on the panobinostat + BD arm with a median duration of response (DOR) of 13.1 months vs. 55% (6% CR) in the placebo + BD arm with median DOR of 10.9 months.

PFS was also assessed by independent review committee (IRC) in a sensitivity analysis due to large amounts of missing data.

- IRC-assessed median PFS difference was 2.2 months: 9.9 months in the panobinostat + BD arm vs. 7.7 months in the placebo + BD arm. The hazard ratio was 0.69 (95% CI: 0.58, 0.83), *p*-value <0.0001.

The supportive, single-arm trial CLBH589DUS71 enrolled 55 patients with relapsed and bortezomib-refractory multiple myeloma. All received panobinostat, bortezomib, and dexamethasone as given in the randomized trial. At the end of 8 cycles, the ORR was 34.5% with a median DOR of 6 months.

Limitations to confident interpretation of the randomized controlled trial include:

- Young age of enrolled patients compared to the U.S. myeloma population
- Few Blacks/African Americans compared to the U.S. myeloma population
- Fewer than 30% of patients completed treatment
- Missing baseline or response data for 25% of patients
- Missing patient reported outcome data for >70% of patients

Missing data contributed to the high proportion of censored events in the analysis of PFS; 47% of events were censored in the panobinostat + BD arm compared to 32% in the placebo + BD arm.

Barring these limitations of applicability and reliability, the question remains of whether the effect size of 2 to 4 months progression-free survival is sufficient to justify any risks identified in the trial. An analysis of Overall survival, when the data is mature, may be required to determine the clinical benefit to patients with relapsed multiple myeloma.

The final clinical assessment of benefit:risk will be discussed in the Cross-Discipline Team Leader review incorporating the separate reviews of efficacy and safety.

6.1 Indication

The Applicant's proposed indication is for Farydak, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

6.1.1 Methods

This review of efficacy primarily relies on the results of one randomized, placebo-controlled, double-blinded trial (CLBH589D2308, hereafter referred to as Trial 2308) of 768 patients with relapsed multiple myeloma. All patients were given bortezomib and dexamethasone; randomization was 1:1 to the panobinostat arm or placebo arm.

Treatment on protocol was 48 weeks duration split in two 24-week phases. Treatment phase 1 comprised eight 3-week cycles of panobinostat 20 mg orally 3 times a week for two weeks of 3-week cycles or identical placebo. All patients were given bortezomib 1.3mg/m^2 IV twice weekly for 2 of 3 weeks with dexamethasone 20 mg per day for two days with each dose of bortezomib.

After 24 weeks, patients with any treatment response or stable disease, and without Grade 2 or higher toxicity, could continue onto treatment phase 2. In treatment phase 2, bortezomib was reduced to two doses every 3 weeks with dexamethasone; panobinostat or placebo were continued as in treatment phase 1. Dose reductions of panobinostat, bortezomib, or dexamethasone were allowed. Refer to Section 5.3 of the full Clinical Review for details of the trial.

The primary endpoint was PFS based on investigator assessed EBMT criteria (Bladé, Samson, et al. 1998) modified to include near complete response (nCR). Near-complete response has been added to EBMT criteria in other drug trials in patients with relapsed multiple myeloma: a phase 2 trial of bortezomib (Richardson, Barlogie, et al. 2003), a phase 3 trial of bortezomib vs. high-dose dexamethasone (Richardson, Sonneveld, et al. 2005), and a randomized trial of pegylated liposomal doxorubicin with bortezomib vs bortezomib alone (Orlowski, Nagler, et al. 2007). The descriptive

differences of nCR and VGPR are seen in Table 1 and are practically the same. The International Myeloma Working Group integrated these two categories in 2006 (Durie, Harousseau, et al.).

Responses were confirmed after six weeks. VGPR and sCR were also determined based on IMWG criteria (Rajkumar, Harousseau, et al. 2011). All response criteria from the protocol are listed in Table 1.

Table 1 Response criteria from Trial 2308

Category	Definition
Stringent complete response (sCR) *IMWG*	• All criteria met for CR (see below) • Normal observed FLC ratio • Absence of phenotypically aberrant plasma cells in bone marrow analyzed by multiparametric flow cytometry
Complete response (CR) *EBMT*	• Absence of M-protein in serum and urine by immunofixation, maintained ≥ 6 weeks (presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR), AND • < 5% plasma cells in bone marrow. No confirmation on bone marrow plasma cell (additional assessment) is needed to document CR except patients with non-secretory myeloma where the bone marrow examination must be repeated after an interval of at least 6 weeks, AND • In case of presence of lytic bone lesion(s) at baseline, no increase in size or number of lytic bone lesions (development of a compression fracture does not exclude CR), AND • Disappearance of any soft tissue plasmacytoma, if present at baseline.
Near-complete response (nCR) *EBMT*	• All criteria of CR apply except that absence of serum and urine M-protein cannot be confirmed by immunofixation.
Very good partial response (VGPR) *IMWG*	• Serum and/or urine M-protein detectable by IFE but not by PEP or ≥ 90% reduction from baseline in serum AND urine M-protein <100 mg/24h • Disappearance of any soft tissue plasmacytomas, if present at baseline
Partial response (PR) *EBMT*	• If disease was measurable based on serum M-protein at baseline, then ≥ 50% reduction from baseline in serum M-protein as determined by PEP, maintained for ≥ 6 weeks; otherwise, serum M-protein < 1 g/dL, AND • Reduction in 24h urine M-protein as measured by PEP from baseline either by ≥ 90% or to < 200 mg, maintained ≥ 6 weeks, AND • ≥ 50% reduction from baseline in the size of soft tissue plasmacytomas (by CT/MRI), AND • No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude PR) • For patients with non-secretory myeloma, in addition to the above, ≥ 50% reduction from baseline in plasma cells in a bone marrow aspirate and/or on biopsy (if both available then “and”, otherwise “or”), maintained for ≥ 6 weeks

Category	Definition
Minimal response (MR) *EBMT*	• If disease was measurable based on serum M-protein at baseline then 25 to <50% reduction from baseline in serum M-protein measured by PEP, maintained for ≥ 6 weeks; otherwise serum M-protein <1 g/dL AND • 50 to < 90% reduction from baseline in 24h urine M-protein as measured by PEP and absolute value is still ≥ 200 mg/24h, maintained for ≥ 6 weeks, AND • 25 to < 50% reduction from baseline in the size of soft tissue plasmacytomas (by CT/MRI) AND • No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude MR) • For patients with non-secretory myeloma, in addition to the above, 25 to <50% reduction from baseline in plasma cells in a bone marrow aspirate and/or on biopsy, maintained for ≥ 6 weeks
No change (NC)	• Not meeting any other criteria
Relapse from CR *EBMT*	• Reappearance/presence of serum or urine M-protein on immunofixation or PEP confirmed by ≥ one further investigation and excluding oligoclonal immune reconstitution, OR • ≥ 5% plasma cells in a bone marrow aspirate or on bone biopsy, OR • Development of new soft tissue plasmacytoma(s),or definite increase in the size of soft tissue plasmacytomas, OR • Development of new lytic bone lesions or increase in the size of lytic bone lesions (development of a compression fracture does not exclude continued response and hence does not indicate PD), OR • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) not attributable to any other cause. In case of preexisting hypercalcemia at baseline, this criterion applies only in case the corrected serum calcium level was ≤11.5 mg/dL during the course of the study. This criterion does qualify for relapse even if no previous calcium assessment. There is no given time frame for the confirmation measurement of serum or urine M-protein. A repetition and confirmation at any time qualifies for relapse.

Category	Definition
Progressive disease (PD) from any response but CR	• 25% increase from nadir in the serum M-protein as measured by PEP which must also be an absolute increase from nadir of at least 0.5 g/dL and absolute value of serum M-protein ≥ 1.0 g/dL, and confirmed by at least one repeated investigation, OR • 25% increase from nadir in the 24h urine M-protein as measured by PEP which must also be an absolute increase from nadir of at least 200 mg/24h and confirmed by at least one repeated investigation, OR • 25% increase from nadir in plasma cells in a bone marrow aspirate or on biopsy which must also be an absolute increase from nadir of at least 10%, OR • Increase from baseline in size of existing lytic bone lesions, OR • Development of new lytic bone lesion (development of a compression fracture does not exclude continued response and does not indicate PD), OR • Definite increase from nadir in size of existing soft tissue plasmacytomas, OR • Development of new soft tissue plasmacytomas, OR • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will only be assessed due to the hypercalcemia criterion in case the corrected serum calcium level was ≤ 11.5 mg/dL post-baseline and increased thereafter beyond 11.5.g mg/dL.
EBMT	There is no given time frame for the confirmation measurement of serum or urine PEP. A repetition and confirmation at any time qualifies for PD.

Overall Survival was the key secondary endpoint. Additional secondary endpoints included:

- Overall response rate, based on the proportion of patients with CR, nCR, or PR
- near CR/CR rate
- MR rate
- Time to response (TTR), from randomization to first documented response
- Time to progression (TTP) or relapse, from randomization to documented PD, relapse, or death due to multiple myeloma
- Duration of response (DOR), from first documented response to documented PD, relapse, or death due to multiple myeloma
- Safety of the combination therapy
- Health related quality of life and symptoms of multiple myeloma
- PK of panobinostat and bortezomib in a subset of Japanese patients

Exploratory endpoints included sCR, CR, and VGPR rates based on IMWG criteria. The data cut-off date for the efficacy analysis was 10 September 2013.

The protocol was amended five times. All protocol amendments occurred prior to study un-blinding. The following amendments are relevant to the review of efficacy.

- After 668 patients were randomized to the trial, the Applicant identified a higher than expected drop-out rate (20% compared to 10%) mostly due to consent withdrawal after discontinuing treatment. The sample size was increased to attain the targeted number of PFS events while maintaining the original statistical

assumptions. The Independent Data Monitoring Committee assessed the drop-outs and did not identify a safety issue.

- After 742 patients were randomized to the trial, the protocol was amended to increase the PFS event fraction for the second interim analysis from 67% to 80%. This was done to provide a better estimate of a treatment effect and increased the probability of detecting a treatment effect. A secondary objective to compare CR and nCR between arms was added. The definition of PFS was clarified as an event of progression, relapse, or death; the definition of an event and the statistical methodology were not changed.
- After all patients had enrolled and completed treatment, the Applicant identified missing baseline and response assessments of M-protein as specified in the protocol. This amendment provided for additional data collection of other methods of M-protein monitoring that were done and established an IRC to perform independent response assessments.

Supporting this application is the multi-center, single arm open label trial CLBH589DUS71 (hereafter referred to as Trial 71) of panobinostat with bortezomib and dexamethasone in 55 patients with relapsed and bortezomib-refractory multiple myeloma. Treatment dosing, schedule, and modifications were similar to that of the randomized Trial 2308. The primary endpoint was ORR, defined as the proportion of patients with CR, nCR, or PR per investigator-assessment based on modified EBMT criteria at the end of 8 cycles. Responses were confirmed after six weeks. Secondary endpoints included MR rate, TTR, DOR, PFS, TTP, and OS.

The following items from Trials 2308 and 71 submitted by the Applicant were reviewed:

- Clinical study report (CSR)
- Protocol and statistical analysis plan
- Raw and derived datasets (not CDISC standard)
- Case report forms
- Patient narratives
- Applicant responses to FDA information requests
- Proposed labeling for Farydak

6.1.2 Demographics

Efficacy analyses of Trial 2308 were performed with the intent-to-treat (ITT) population of 768 patients.

Of the 768 randomized patients, only 54 (7%) were from the United States. Enrollment occurred primarily in European and Asian countries (43% and 29% of patients, respectively). The demographic characteristics in the treatment arms were well balanced.

Race and ethnicity differed from the U.S. myeloma population. NCI SEER estimates that Black or African Americans account for twice as many new cases of multiple myeloma than White or Caucasian Americans: 12.2 vs. 5.6 per 100,000 men and women per year (Howlader, Noone, et al. 2013). Considering the 24,000 new cases of myeloma this year, Black or African American patients are under-represented in this trial. Trial 2308 enrolled 22 Black or African American patients and 499 White or Caucasian patients. Six of the Black or African American patients were from U.S. sites.

The median age of patients in the trial was 63 years, six years younger than the median age (69 years) at myeloma diagnosis in the U.S. expected from SEER statistics. The expected median age for a patient at relapse would be approximately 70 years.

Table 2 Demographic characteristics of patients in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Age, years		
Mean (SD)	62 (9)	62 (9)
Median	63	63
Range	28-84	32-83
Groups		
<40	6 (1.6%)	8 (2.1%)
40-64	219 (56.6%)	212 (55.6%)
≥65	162 (41.9%)	161 (42.3%)
Sex		
Male	202 (52.2%)	205 (53.8%)
Female	185 (47.8%)	176 (46.2%)
Race		
White or Caucasian	249 (64.3%)	250 (65.6%)
Asian	128 (33.1%)	104 (27.3%)
Black or African American	5 (1.3%)	17 (4.5%)
Other	5 (1.3%)	10 (3.8%)
Ethnicity		
Chinese	42 (10.9%)	38 (10.0%)
Hispanic or Latino	29 (7.5%)	51 (13.4%)
Japanese	18 (4.7%)	16 (4.2%)
Mixed	2 (0.5%)	5 (1.3%)
Indian	1 (0.3%)	2 (0.5%)
U.S.	22 (5.7%)	32 (8.4%)

BD = bortezomib + dexamethasone, SD = standard deviation

Prior exposure to individual agents is provided in Table 3. Treatment history was comparable in the two arms. The use of bortezomib appears low compared to current use in the U.S. which may reflect the period of enrollment: years 2010 to 2012.

Thalidomide as prior therapy rather than lenalidomide is consistent with a non-U.S. population.

Table 3 Treatment history of patients in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Time from initial diagnosis, years		
Mean (SD)	3.9 (3.2)	4.1 (2.9)
Median	3.1	3.2
Range	0.2-25.7	0.2-25.0
Number of prior antineoplastic regimens		
Mean (SD)	1.7 (0.76)	1.7 (0.78)
Median	1	1
Range	1-4	1-3
Prior chemotherapy		
Corticosteroids[1]	347 (89.7%)	341 (89.5%)
Melphalan	310 (80.1%)	301 (79.0%)
Thalidomide	205 (53.0%)	188 (49.3%)
Cyclophosphamide	182 (47.0%)	166 (43.6%)
Bortezomib	169 (43.7%)	161 (42.3%)
Doxorubicin	146 (37.7%)	153 (40.2%)
Lenalidomide	72 (18.6%)	85 (22.3%)
Other prior therapy		
Stem cell transplant	215 (55.6%)	224 (58.8%)
Radiation	93 (24%)	73 (19.2%)

BD = bortezomib + dexamethasone, SD = standard deviation
[1] Includes Preferred Terms: dexamethasone, prednisolone, betamethasone, corticosteroids, and methylprednisolone

The pathologic features of myeloma in patients on trial are comparable to the current understanding of the disease and are fairly balanced between arms. The percentage of missing SPEP and UPEP results is high. Refer to Table 4. As in many oncologic drug trials, the performance status of patients is high at baseline. Patients in the community requiring treatment for multiple myeloma are likely to have a worse performance status than patients enrolled on the trial.

Table 4 Baseline disease characteristics of patients in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Immunoglobulin class		
IgG	252 (65.1%)	251 (65.9%)
IgA	90 (23.3%)	86 (22.6%)
IgM	4 (1.0%)	1 (0.3%)
IgD	3 (0.8%)	3 (0.8%)
IgE	0	1 (0.3%)

	Panobinostat + BD n=387	Placebo + BD n=381
Involved light chains at initial diagnosis		
Kappa	241 (62.3%)	219 (57.5%)
Lambda	126 (32.6%)	137 (36.0%)
Light chain only	24 (6.2%)	19 (5.0%)
Renal impairment[1]	265 (68.5%)	249 (65.4%)
Serum M-protein by PEP (g/dL)	n=300 (77.5%)	n=317 (83.2%)
Mean (SD)	2.4 (1.6)	2.6 (1.7)
Median	2.2	2.5
Range	0-8.3	0-8.4
Urine M-protein by PEP (mg/24 h)	n=278 (71.8%)	n=264 (69.3%)
Mean (SD)	696.3 (2091.6)	754.3 (1815.1)
Median	10.5	0
Range	0-21720	0-16050
Bone marrow plasma cell count (%)	n=347 (89.7%)	345 (90.6%)
Mean (SD)	28.3 (24.2)	30.3 (23.8)
Median	20.0	25.0
Range	0-100	0-99.0
Soft tissue plasmacytoma present	21 (5.4%)	19 (5.0%)
Lytic bone lesions present	180 (46.5%)	193 (50.7%)
ECOG Performance Score		
0-1	366 (94.6%)	348 (91.3%)
2	19 (4.9%)	29 (7.6%)

BD = bortezomib + dexamethasone, SD = standard deviation
[1] baseline CrCl 60-90 mL/min
[CSR CLBH589D2308, pp. 177-179, 181-184]

Trial 71 enrolled 55 U.S. patients with a median age of 61 years (range 41-88); 62% were less than 65 years of age, and 53% were male. Most patients (92%) were considered ECOG performance status 0 or 1. All patients had received bortezomib and were considered refractory to it as defined by progressive disease within 60 days of the last bortezomib-containing therapy. Additional patient characteristics are listed in Table 5.

Table 5 Demographic, treatment history, and baseline disease characteristics of patients in Trial 71

	n=55
White or Caucasian	43 (78.2%)
Black or African American	12 (21.8%)
Time from initial diagnosis, years, range	4.6 (0.6-22)
Number of prior antineoplastic regimens, median, range	4 (2-11)
Prior lenalidomide	54 (98.2%)
Prior thalidomide	38 (69.1%)
Prior melphalan	24 (43.6%)
Prior stem cell transplant	45 (81.8%)
Prior radiation	26 (47.3%)

[CSR CLBH589DUS71, pp. 78-84]

The most common M-protein was IgG in 64% of patients followed by IgA in 22%.

6.1.3 Subject Disposition

During evaluation of eligibility for the randomized trial, 294 patients failed screening. The primary reasons for non-randomization are listed in Table 6.

Table 6 Screening failures in Trial 2308

Reason	n=294
Unacceptable laboratory value	123 (41.8%)
Unacceptable test procedure result	48 (16.3%)
Did not meet diagnostic/severity criteria	39 (13.3%)
Other	30 (10.2%)
Unacceptable past medical history/concomitant diagnosis	25 (8.5%)
Patient withdrew consent	15 (5.1%)
Intercurrent medical event	8 (2.7%)
Unacceptable use of excluded medication/therapies	6 (2.0%)
Unknown	1 (0.3%)

[CSR CLBH589D2308, p. 268]

To continue protocol treatment after the first 8 cycles (24 weeks), a response to treatment or stable disease was required, as was no Grade 2 or higher toxicity. Only 44% of patients on the panobinostat + BD arm and 50% of patients on the placebo + BD arm started Treatment Phase 2.

Notable differences between the two arms are noted in the disposition of patients on trial. A greater percentage of patients (34% vs. 17%) stopped treatment for an adverse event or withdrew consent on the panobinostat + BD arm compared to the placebo + BD arm. Nearly half the percentage of patients (21% vs. 40%) stopped treatment in the panobinostat + BD arm for progression of their disease compared to the placebo + BD arm. Refer to Table 7 for additional disposition of patients.

Table 7 Disposition of patients in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Treated	382 (98.7%)	376 (98.7%)
Treatment ongoing	0	0
Started Treatment Phase 2	169 (43.7%)	192 (50.4%)
Completed Treatment Phases 1 and 2	102 (26.4%)	102 (26.8%)
Discontinued treatment	280 (72.4%)	274 (71.9%)
Adverse event	130 (33.6%)	66 (17.3%)
Progressive disease	82 (21.2%)	153 (40.2%)
Consent withdrawal	34 (8.8%)	18 (4.7%)
Death	21 (5.4%)	17 (4.5%)
Completion of end of study evaluation	346 (89.4%)	364 (95.5%)
Progressive disease	206 (53.2%)	268 (70.3%)
Consent withdrawal	72 (18.6%)	44 (11.5%)
Death	28 (7.2%)	19 (5.0%)
New treatment	27 (7.0%)	19 (5.0%)

BD = bortezomib + dexamethasone
[CSR CLBH589D2308, pp. 174-175]

The majority of treated patients (96%) in Trial 71 ended treatment. Primary reasons for the end of treatment are listed in Table 8.

Table 8 Reasons for end of treatment in Trial 71

	n=55
Adverse event	10 (18.2%)
Progressive disease	36 (65.5%)
Consent withdrawal	5 (9.1%)
Death	1 (1.8%)
New treatment	1 (1.8%)

[CSR CLBH589DUS71, pp.73-75]

6.1.4 Analysis of Primary Endpoint

For clinical trials of new drugs for patients with relapsed multiple myeloma, recommended clinically relevant endpoints include PFS, TTP, and OS (Anderson, et al, 2008). Recent FDA approvals for myeloma treatments are consistent with this advice. Improved response rates have also supported accelerated approvals which require additional confirmation of clinical benefit for continued approval.

Bortezomib and dexamethasone as the backbone therapy in this clinical trial is considered an effective treatment for patients with relapsed multiple myeloma. Bortezomib has also been used safely and effectively in trials in combination with other chemotherapeutics and with immunomodulating agents.

In Trial 2308, PFS was defined as the time from the date of randomization to the date of the first documented PD or relapse, or death due to any cause. PFS was censored at the date of the last response assessment prior to the data cut-off date or start of new treatment for patients who had not progressed or died.

The analysis plan assumed a median PFS of 10.2 months in the panobinostat + BD arm and 7.5 months in the placebo + BD arm; a difference of 2.7 months with a hazard ratio of 0.74. The planned sample size was 762 subjects to test superiority on 460 events with a stratified log rank test considering a cumulative type 1 error rate of α=0.05, 2-sided. Final enrollment included 768 patients who experienced 467 events at the pre-specified data cut-off date.

Efficacy analyses were primarily performed on the intent-to-treat (ITT) trial population of this randomized controlled trial. This analysis minimizes bias due to noncompliance, patient withdrawals, and protocol deviations and more closely models real-world clinical practice. A limitation of ITT analysis is that the observed treatment effect can be diluted by missing outcome data.

During an internal audit while the trial was ongoing, the Applicant identified that not all investigation sites used protocol-defined methods for measuring M-protein: protein electrophoresis (PEP) with quantification of M-protein spike. In 193 patients (25% of the total enrolled) alternative methods were used such as nephelometry or total globulin, or the gamma globulin fraction was used as an indicator for an IgG M-component. Missing assessments occurred in both arms: M-protein measurement was missing in 25% of patients on the panobinostat + BD arm and 26% on the placebo + BD arm.

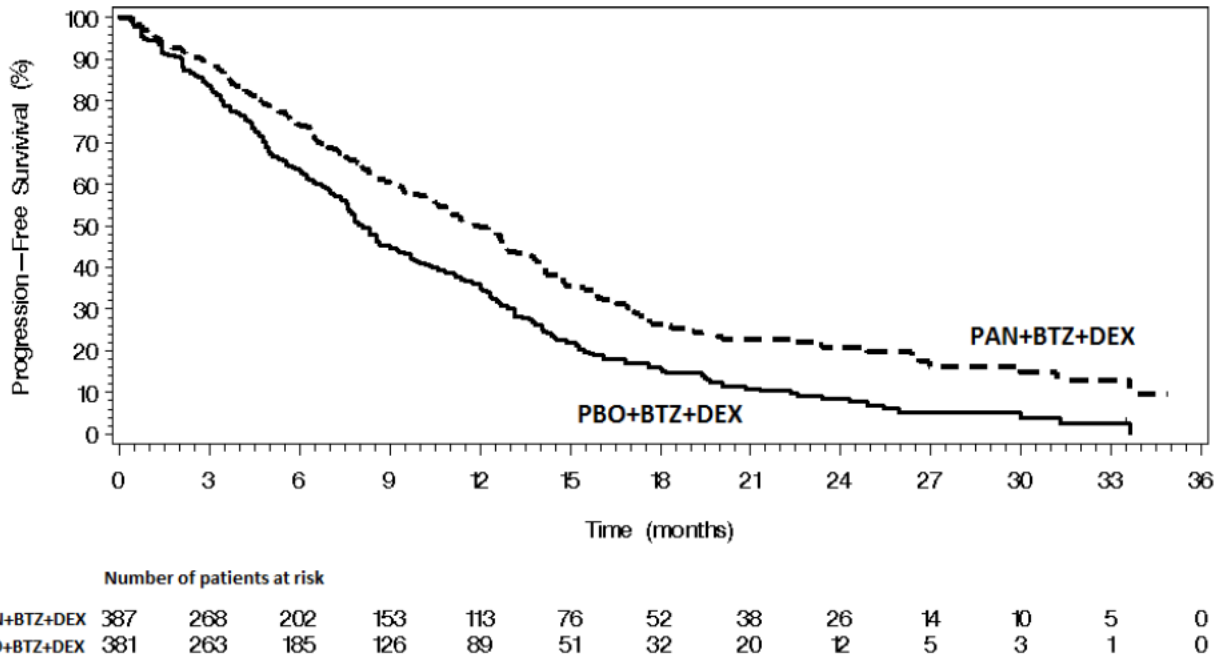
In the primary endpoint analysis of PFS, shown in Table 9 and Figure 1, patients with unavailable M-protein measurements by PEP were assessed for 'unknown' or 'progressive disease' responses only. The difference in median PFS was 3.9 months favoring the panobinostat + BD arm.

Table 9 Progression-free Survival (PFS) analysis of Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
PFS events, n	207 (53.5%)	260 (68.2%)
Censored[1], n	180 (46.5%)	121 (31.8%)
Median time to event, months[2]	12.0 (10.3, 12.9)	8.1 (7.6, 9.2)
Hazard ratio, 95% CI	0.63 (0.52, 0.76)	
p-value	<0.0001	

BD = bortezomib + dexamethasone, CI = confidence interval
[1] Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation
[2] Kaplan-Meier estimates

Figure 1 Kaplan-Meier estimates of Progression Free Survival in Trial 2308



Nearly half of patients on the panobinostat + BD arm were censored in the analysis for PFS. Table 10 lists the reasons for PFS censoring by arm. Censoring occurred more often in the panobinostat + BD arm, primarily due to missing assessments: 31% vs. 22%.

Table 10 PFS censoring in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Censored patients	180 (46.5%)	121 (31.8%)
Inadequate response assessment	86 (22.2%)	54 (14.2%)
≥2 missing assessments prior to event	36 (9.3%)	28 (7.3%)
Ongoing (in follow-up)	35 (9.0%)	15 (3.9%)
New cancer therapy added	23 (5.9%)	24 (6.3%)

BD = bortezomib + dexamethasone,

Identification of these protocol deviations prompted the Applicant's Study Steering Committee to recommend IRC assessment of response data. This sensitivity analysis and others were performed by FDA biostatistics review team and are summarized here in Table 11. The difference in IRC-assessed median PFS was 2.2 months favoring the panobinostat + BD arm.

Another sensitivity analysis of PFS considered patients without PEP and quantification of M-protein spike as non-responders, i.e. progressive disease on the date of randomization. This analysis demonstrates a median difference of 3.4 months when using investigator assessed responses and a difference of 2.5 months when using IRC

assessed responses. All reasonable sensitivity analyses for PFS favored the panobinostat + BD arm over the placebo + BD arm.

Table 11 Summary of PFS sensitivity analyses of Trial 2308

Analysis	Event/censored		Median, months (95% CI)		Δ	Hazard Ratio (95% CI)	p-value
	PAN+BD n=387	PBO+BD n=381	PAN+BD n=387	PBO+BD n=381			
Primary (INV)[1]	207/180	260/121	12.0 (10.3, 12.9)	8.1 (7.6, 9.2)	3.9	0.63 (0.52, 0.76)	<0.0001
Actual event[2]	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
Backdating[3]	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
Drop-out[4]	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
IRC assess[5]	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

PAN = panobinostat, BD = bortezomib + dexamethasone, PBO = placebo, CI = confidence interval, INV = investigator, IRC = Independent Review Committee
[1] Primary INV-assessed endpoint analysis
[2] Included the event whenever it occurred even after ≥2 missing assessments
[3] Used date of next scheduled assessment for events occurring after ≥1 missing assessment
[4] Considered next therapy and PD without documentation or after ≥2 missing assessments as events
[5] IRC assessment of all patients

In Trial 71, 35% of patients achieved a PR or nCR at the end of 8 cycles; there were no complete responses. The median duration of response, a secondary endpoint, was 6 months (range 1.9-21.5).

Table 12 Response rate analysis of Trial 71

	n=55
ORR[1]	19 (34.5%)
CR	0
nCR	1 (1.8%)
PR	18 (32.7%)
MR	10 (18.2%)
NC	20 (36.4%)
PD	3 (5.5%)
Unknown	3 (5.5%)

[1] Includes CR, nCR, PR

6.1.5 Analysis of Secondary Endpoints(s)

In Trial 2308, OS was defined as the time from the date of randomization to the date of death due to any cause. If it was not known whether a patient died, survival was censored at the date of last contact.

Overall Survival

OS was the key secondary endpoint and was only tested after a significant PFS result. The plan for final OS analysis was based on 415 events, testing a difference of 5.4 months with a hazard ratio of 0.73. At the pre-specified data cut-off date for final PFS analysis, an interim analysis for OS was done.

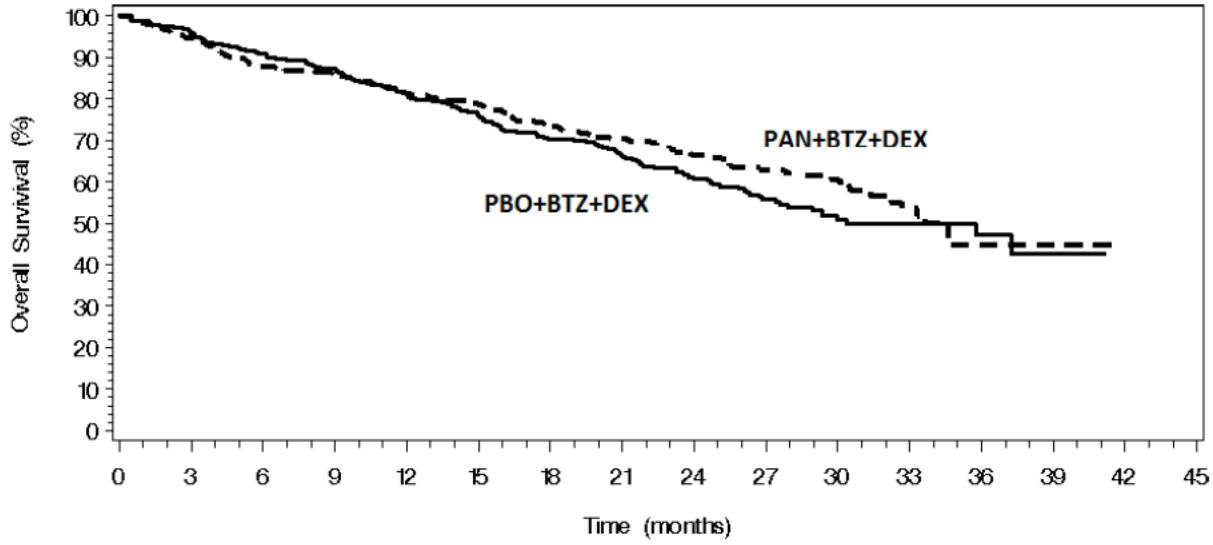
The interim data is not mature: 286 events (69%) were observed, 134 in the panobinostat + BD arm and 152 in the placebo + BD arm. There were fewer deaths reported in the panobinostat + BD arm compared to the placebo + BD arm. At this time, 416 of the 482 censored patients continued to be followed for survival. There is a non-statistically significant difference of 3 months between arms.

Table 13 Overall Survival (OS) interim analysis of Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
OS events, n	134 (34.6%)	152 (39.9%)
Censored, n	253 (65.4%)	229 (60.1%)
Median time to event, months[1]	33.6 (31.3, NE)	30.4 (26.9, NE)
Hazard ratio, 95% CI	0.87 (0.69, 1.10)	
p-value	0.2586	

BD = bortezomib + dexamethasone, NE = not evaluable, CI = confidence interval
[1] Kaplan-Meier estimates

Figure 2 Kaplan-Meier estimates of interim analysis of Overall Survival in Trial 2308



Response Rates

Response rates, including the exploratory endpoint of responses assessed by IMWG criteria, are provided in Table 14 to facilitate comparisons with other recent drug approval trials. Incomplete post-baseline assessments contributed to the inability to assess response using IMWG criteria in 24% of patients. Overall response rates favored the panobinostat + BD arm over placebo.

Table 14 Response rates in Trial 2308

Response criteria	mEBMT		IMWG	
	PAN + BD n=387	PBO + BD n=381	PAN + BD n=387	PBO + BD n=381
ORR[1]	235 (60.7%)	208 (54.6%)	223 (57.6%)	90 (23.6%)
sCR			5 (1.3%)	0
CR	42 (10.9%)	22 (5.8%)	31 (8.0%)	12 (3.1%)
nCR	65 (16.8%)	38 (10.0%)		
VGPR			105 (27.1%)	78 (20.5%)
PR	128 (33.1%)	148 (38.8%)	82 (21.2%)	96 (25.2%)
MR	23 (5.9%)	42 (11.0%)	13 (3.4%)	27 (7.1%)
NC or SD	65 (16.8%)	74 (19.4%)	25 (6.5%)	36 (9.4%)
PD	21 (5.4%)	32 (8.4%)	29 (7.5%)	43 (11.3%)
Unknown[2]	43 (11.1%)	25 (6.6%)	97 (25.1%)	89 (23.4%)

PAN = panobinostat, BD = bortezomib + dexamethasone, PBO = placebo
[1] Includes CR, nCR, PR or sCR, CR, VGPR, PR
[2] Mostly due to incomplete post-baseline assessments

The median DOR was 13.1 months on the panobinostat + BD arm vs. 10.9 months on placebo.

Table 15 Duration of response analysis of Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Median DOR, months	13.1	10.9
95% CI	11.8, 14.9	9.2, 11.8

BD = bortezomib + dexamethasone, CI = confidence interval

Patient-reported Outcomes

Three quality-of-life (QOL) instruments were used in Trial 2308.

1. The Quality of Life Questionnaire (QLQ)-C30 was released in 1993 by the European Organization for Research and Treatment of Cancer (EORTC) to assess health-related QOL of cancer patients participating in international clinical trials.
2. QLQ-MY20, a patient self-reporting module developed by EORTC to complement the QLQ-C30 for patients with multiple myeloma
3. Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group (GOG)-Neurotoxicity (Ntx) Subscale Score, a patient self-reporting questionnaire which was developed by GOG to assess platinum/paclitaxel-induced neurologic symptoms

All three instruments have been used in clinical trials with patients with multiple myeloma.

Missing data prohibits a meaningful understanding of available quality-of-life data. Analysis of inadequate data is prone to bias and unfortunately is uninterpretable. Baseline data is incomplete for 10-17% of all patients, by instrument. By the end of study, 27-29% of patients completed the questionnaires with 7-10% disparity between arms. Completion rates at intended collections points can be seen in Table 16.

Table 16 QOL assessment completion rates in Trial 2308

QOL instrument	QLQ-C30		QLQ-MY20		FACT/GOG-Ntx	
	PAN + BD n=387	PBO + BD n=381	PAN + BD n=387	PBO + BD n=381	PAN + BD n=387	PBO + BD n=381
Baseline, %	93	92	91	89	83	84
Week 6, %	71	77	68	74	64	73
Week 12, %	54	60	50	59	51	57
Week 18, %	47	55	46	51	44	49
Week 24, %	38	45	35	42	34	41
Week 30, %	36	39	34	37	34	37
Week 36, %	31	32	29	29	29	30
Week 42, %	27	29	26	26	25	27
Week 48, %	10	7	10	7	8	6
Week 54, %	2	1	2	1	2	1
Week 60, %	0	1	0	1	0	1
End of Study, %	25	33	23	33	23	30

PAN = panobinostat, BD = bortezomib + dexamethasone, PBO = placebo

6.1.6 Other Endpoints

The exploratory endpoint of response determined by IMWG criteria is included in Table 14 in Section 6.1.5. Missing data limits the comparability of the two response criteria.

6.1.7 Subpopulations

No significant difference in PFS was observed between patients who were 65 years of age and older and those who were less than 65 years old in either treatment arm. There is a trend towards shorter progression-free survival in older patients who received panobinostat which may be clinically relevant.

Table 17 PFS analysis of Trial 2308, by age <65 vs ≥65 years

	Panobinostat + BD n=387		Placebo + BD n=381	
Age, years	<65 n=225	≥65 n=162	<65 n=220	≥65 n=161
PFS events, n	120 (53.3%)	87 (53.7%)	156 (70.9%)	104 (64.6%)
Censored[1], n	105 (46.7%)	75 (46.3%)	64 (29.1%)	57 (35.4%)
Median time to event, months[2]	12.5 (10.3, 13.8)	11.4 (8.4, 14.7)	7.9 (6.6, 9.0)	8.6 (7.6, 11.2)
Hazard ratio, 95% CI	0.93 (0.71, 1.23)		1.10 (0.86, 1.41)	

BD = bortezomib + dexamethasone
[1] Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation
[2] Kaplan-Meier estimates

No significant difference in PFS within arms was noted for patients of Asian race compared to non-Asian patients. The similar proportion of censored events to actual events does not allow meaningful clinical interpretation.

Table 18 PFS analysis of Trial 2308, by Asian race

Race	Panobinostat + BD n=387		Placebo + BD n=381	
	Asian n=128	Non-Asian n=259	Asian N=104	Non-Asian n=277
PFS events, n	62 (48.4%)	145 (55.9%)	71 (68.3%)	189 (68.2%)
Censored[1], n	66 (51.6%)	114 (44.0%)	33 (31.7%)	88 (31.8%)
Median time to event, months[2]	12.7 (7.7, 16.5)	12.0 (10.2, 12.9)	8.1 (6.1, 9.7)	8.3 (7.4, 9.5)
Hazard ratio, 95% CI	0.81 (0.59, 1.08)		1.06 (0.80, 1.39)	

BD = bortezomib + dexamethasone
[1] Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation
[2] Kaplan-Meier estimates

Too few patients (n=54) were enrolled at U.S. sites to perform meaningful analysis of efficacy. Too few Black or African American patients (n=22) enrolled globally to perform meaningful analyses of efficacy; all 6 from the U.S. were randomized to the placebo + BD arm.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose escalation Trial CLBH589B2007 combined panobinostat and bortezomib, in doses ranging from 10-30 mg and 1-1.3 mg/m^2 in 47 patients with relapsed multiple myeloma. There were 14 patients in 2 lower dose cohorts; 3 patients had a response (1 VGPR, 2 PR). At the MTD in 17 patients, 9 had a response (1 sCR, 2 CR, 2 VGPR, 4 PR). Of the 15 patients in the expansion phase using the selected dose, 11 had a response (3 VGPR, 8 PR).

No pharmacokinetic data were collected in Trial 71. All patients were started on the same dose. Even though dose reductions occurred in 64% of patients, the limited number of patients at varying doses and time points does not allow for dose related analyses of efficacy.

In Trial 2308, panobinostat dose reductions occurred in 51% of patients compared to 23% receiving placebo. Bortezomib dose reductions occurred in 61% of patients on the panobinostat + BD arm and 42% on the placebo + BD arm. Dexamethasone dose reductions occurred in 24% of patients on the panobinostat + BD arm and 17% on placebo + BD arm. Most dose reductions occurred within the first 8 cycles of treatment phase 1.

As noted in Section 6.1.3, less than half of patients received more than 8 cycles of treatment. Only a quarter of patients completed all 12 cycles. More patients stopped treatment on the panobinostat + BD arm for toxicity while more patients on the placebo + BD arm stopped for lack of efficacy. The median duration of exposure to panobinostat was 6 months (and to placebo was 5 months). The median relative dose intensity of panobinostat by treatment phase was 80% for the first 8 cycles and 75% for the second 4 cycles.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term use of panobinostat is not expected.

6.1.10 Additional Efficacy Issues/Analyses

Treatment exposure and compliance were assessed at each patient visit using pill counts. Missed study drug doses occurred 75 times in 34 patients (9%) on the panobinostat + BD arm and 65 times in 33 patients (9%) on the placebo + BD arm. As the occurrence was balanced in both arms, study drug effects were unlikely to be the cause. A more likely cause was the complexity of the dosing schedule. The Dosage and Administration section of the Prescribing Information will need to be clear to minimize missed doses in practice.

Major protocol violations in the randomized trial are iterated in Table 19. Other than the deviations for missing baseline assessments, the incidence is low and does not change the overall assessment of Zydelig.

Table 19 Major protocol deviations in Trial 2308

	Panobinostat + BD n=387	Placebo + BD n=381
Total	98 (25.3%)	107 (28.1%)
Missing baseline assessment for serum or urine M-protein, soft tissue plasmacytoma, or bone lesion	77 (19.9%)	86 (22.6%)
Inclusion criteria		
M-protein, serum <1 g/dL or urine <200mg/24h	10 (2.6%)	13 (3.4%)
Never reached MR with any prior therapy	6 (1.6%)	2 (0.5%)
Untreated multiple myeloma	1 (0.3%)	1 (0.3%)
Did not relapse after last therapy	0	3 (0.8%)
ECOG PS >2	0	1 (0.3%)
Exclusion criteria		
Was refractory to bortezomib	6 (1.6%)	6 (1.6%)
Had prior HDAC treatment	0	1 (0.3%)
Conduct of Trial		
Un-blinded patient for reason other than emergency, interim analyses, or regulatory reporting	2 (0.5%)	1 (0.3%)

BD = bortezomib + dexamethasone

In Trial 71, 13 patients were exposed to 17 major protocol violations. Four patients remained on treatment despite dose delays > 21 days, 2 other patients had errors in dexamethasone dosing, and 1 other patient took consecutive daily doses of panobinostat. In addition, 8 patients continued on treatment when they should have been discontinued: 6 for progressive disease and 2 for adverse events. The two other major protocol violations involved safety reporting requirements.

9 Appendices

9.1 Literature Review/References

Anderson KC, Kyle RA, Rajkumar SV, et al. (2008) Clinically relevant end points and new drug approvals for myeloma. Leukemia; 22(2):231-9.

Bladé J, Samson D, Reece D, et al. (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. Brit J Haematol;102(5):1115.

Dimopoulos M, Kyle R, Fermand JP, et al. (2011) Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood; 117:4701.

Dispenzieri A, Kyle R, Merlini G, et al. (2009) International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia; 23:215.

Durie BG, Harousseau J-L, Miguel JS, et al (2006) International uniform response criteria for multiple myeloma. Leukemia; 20(9):1467.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

International Myeloma Working Group. (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol; 121:749.

Kumar SK, Lee JH, Lahuerta JJ, et al. (2012) Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. Leukemia: 26: 149.

Kyle RA, Gertz MA, Witzig TE, et al. (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc; 78:21.

Kyle RA, Rajkumar SV. (2009) Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia; 23:3.

Ocio EM, Richardson PG, Rajkumar SV, et al. (2014) New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). Leukemia; 28: 525.

Orlowski RZ, Nagler A, Sonneveld P, et al. (2007) Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol; 25(25):3892.

Rajkumar SV, Harousseau J-L, Durie B, et al. (2011) Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood; 117: 4691.

Richardson PG, Barlogie B, Berenson J. (2003) A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med; 348(26):2609.

Richardson PG, Sonneveld P, Schuster MW, et al. (2005) Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med; 352(24):2487.

SEER Cancer Statistics Factsheets: Myeloma. National Cancer Institute. Bethesda, MD (accessible at http://seer.cancer.gov/statfacts/html/mulmy.html).

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9.

Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008.

U.S. Census Bureau. USA Quickfacts. Revised July 8, 2014 (accessible at http://quickfacts.census.gov/qfd/states/00000.html).

Waxman AJ, Mink PJ, Devesa SS, et al. (2010) Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood; 116:5501.

9.2 Abbreviations

BD	bortezomib and dexamethasone
BTZ	bortezomib
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CSR	Clinical Study Report
CT	computed tomography
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
FLC	free light chain
HDAC	histone deacetylase inhibitor
IFE	immunofixation electrophoresis
IMWG	International Myeloma Working Group
INV	Investigator
IRC	Independent Review Committee
ITT	intent-to-treat
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NC	no change
NCI	National Cancer Institute
nCR	near-complete response
NE	not evaluable
OS	overall survival
PAN	Panobinostat
PBO	placebo
PD	progressive disease
PEP	protein electrophoresis
PFS	progression free survival
PR	partial response
PS	performance status
QLQ	Quality of Life Questionnaire
QOL	quality of life
sCR	stringent complete response
SD	standard deviation
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results program
TTP	time to progression
VGPR	very good partial response

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/s/

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