CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205353Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Electronic Stamp
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA	205353
Applicant	Novartis
Date of Submission	03/24/14
PDUFA Goal Date	11/24/14 (Major Amendment on 11/21/14 extended to 02/24/15)
Proprietary Name / Established (USAN) names	FARYDAK / Panobinostat
Dosage forms / Strength	Capsules (10, 15, and 20 mg strengths)
Proposed Indication	In combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 1 prior therapy
Recommended:	*Accelerated Approval*

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1. Introduction

On March 24, 2014, Novartis Pharmaceuticals Corporation submitted New Drug Application (NDA) 205353 under section 505(b)(1) of the Food Drug and Cosmetic Act (21 USC §355) and 21 CFR §314.50 for panobinostat (previously known as LBH589), to the Division of Hematology Products.

Proposed Indication: FARYDAK® (panobinostat), in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma (MM), who have received at least 1 prior therapy

Panobinostat is an oral deacetylase inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds. Panobinostat has been in development for solid tumors and hematological malignancies since April 2003 as an intravenous formulation (under IND 67091) and as an oral capsule formulation since June 2004 (under IND 69862). The application was complete upon submission and was filed as a priority review because the topline data demonstrated an improvement in PFS over bortezomib and dexamethasone alone, which is one of the available therapies for this indication.

To support the proposed indication, Novartis conducted a single multi-national, Phase 3, double-blind, placebo-controlled, randomized trial (CLBH589D2308) [hereinafter referred to as D2308]. Trial D2308 enrolled 768 patients with multiple myeloma that had received 1 to 3 prior therapies whose disease has recurred or progressed and is not refractory to bortezomib. This trial was not conducted under Special Protocol Agreement.

Supportive data was provided from the following trials:

- CLBH589DUS71: Phase II, multicenter, single-arm, open-label trial of panobinostat in combination with bortezomib and dexamethasone in 55 patients with relapsed and bortezomib-refractory multiple myeloma.
- CLBH589B2207: Phase Ib, multicenter, open-label, dose-escalation study of oral LBH589 and intravenous bortezomib in adult patients with multiple myeloma

The Applicant requested regular approval.

The review team opted to take this application to the Oncology Drugs Advisory Committee (ODAC) because the benefit:risk assessment did not appear to be favorable and there were trial conduct issues that made it difficult to assess the true PFS benefit in trial D2308.

The Application was presented to the ODAC on November 6, 2014.

There was a single voting question:
VOTE: Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

The Advisory Committee voted 2 for "Yes" and 5 for "No" [no members abstained] to the question. See section 9 of this review for further details of the discussions at the Advisory Committee meeting.

After the Advisory Committee meeting, Novartis requested a meeting with the Agency to discuss whether a pre-specified subgroup population from Trial D2308 with limited treatment options, might support an Accelerated Approval. This meeting was conducted on November 19, 2014. At the outset of the meeting, the Agency advised Novartis that they were deeming the Novartis submission of the revised IRC analysis of PFS (submitted before the Late Cycle Meeting) as a Major Amendment to the NDA that would extend the review clock by 3 months.

During the meeting, Novartis presented slides that described a pre-specified subgroup of patients with relapsed MM who had received at least bortezomib and an immunomodulatory agent (IMiD) who are bortezomib-sensitive. They presented the efficacy and safety findings from this subgroup to discuss a path forward for the application. Novartis also presented a proposed confirmatory Phase 3 trial which would randomize patients with relapsed MM (1-3 prior lines of therapy) to two different doses of panobinostat (15 and 20 mg) or placebo in combination with subcutaneous bortezomib and dexamethasone. The proposed primary endpoint is PFS by investigator. Novartis stated that response and progression would be conducted by a central lab to ensure that the M-protein measurement methods were consistent across the trial. The need for a REMS was also discussed. At the conclusion of the meeting, the Agency stated that they would be sending Novartis a letter confirming the Major Amendment and PDUFA clock extension. The Applicant stated that they would submit a proposed complete REMS and a proposed confirmatory trial protocol and statistical analysis plan.

The team reviewed the information submitted with the major amendment that included new sensitivity analyses that took into account the need for confirmation of each disease progression. The team also reviewed multiple subset analyses to assess whether there was a subset of the ITT population for which panobinostat provided a favorable benefit to risk ratio.

This memo covers both the initial NDA review, the advisory committee meeting, and the review findings based upon the Major Amendment.

2. Background

Multiple Myeloma

Multiple myeloma (hereafter referred to as "MM") is a malignant condition of plasma cells that leads to a monoclonal gammopathy. The proliferation of clonal plasma cells in the bone marrow leads to high levels of circulating monoclonal-M-immunoglobulin (referred to as "M-protein"). The clinical manifestations of MM include hypercalcemia, renal dysfunction, anemia, and bone lytic lesions.

MM accounts for approximately 1% of all cancers and 10% of hematologic malignancies. An estimated 24,000 new cases of MM will occur in the U. S. in 2014 with an estimated 11,000 deaths. The diagnosis is most common in the 6th and 7th decades of life and approximately 75% of patients are over 70 years of age. Blacks account for twice as many new cases of multiple myeloma than Whites: 12.2 vs. 5.6 per 100,000 men and women per year (Howlader N, 2013)

There are two precursor conditions that can evolve into MM: monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. These conditions are characterized by the presence of abnormal plasma cells in the marrow, presence of an M-protein, but without the clinical manifestations (Benjamin M. Cherry, 2013).

Patients with MGUS and smoldering MM are estimated to have an average annual risk of transformation to multiple myeloma of 1% and 10% per year, respectively (Kyle RA, 2010) . There are no approved therapies for either MGUS or smoldering MM.

Treatment of newly diagnosed MM is typically initiated when the patient becomes symptomatic. The treatment of symptomatic multiple myeloma depends on their risk stratification and whether the patient is fit enough to be a candidate for autologous stem-cell transplantation (ASCT). Responses to primary therapy are often transient, and MM is not considered curable with the available treatments. Patients who have relapsed or failed to respond to both bortezomib and the immunomodulatory drugs prognosis is particularly poor, with a median overall survival (OS) of only 9 months, regardless of salvage regimen (Kumar SK, 2012).

Since this application is requesting a relapsed MM indication, only the management of relapsed MM will be discussed here.

Table 1 lists all products that have FDA approval for an indication similar to that proposed for panobinostat.

Table 1 FDA Approvals for Relapsed Multiple Myeloma

Drug Name ***Indication***	**Trial Type**	**Approval Date,** ***Type of Approval***	**Approval Basis**
Velcade (bortezomib) *For 3rd line MM*	Single arm trial (n=256)	2003 *Accelerated*	ORR 28%
Velcade (bortezomib) *For 2nd line MM*	RCT of Velcade vs. dexamethasone (n=669)	2005 *Regular*	Median TTP: Velcade 6.2 m. vs. dex 3.5 months ΔTTP 2.7 months
Revlimid (lenalidomide) *For 2nd line multiple*	Two RCTs of Revlimid + dex vs.	2006 *Accelerated* *	Trial 1: Median TTP: Rev+dex 8.5

myeloma, in combination with dexamethasone	dexamethasone alone (n=341, n=351)		m. vs. dex 4.6 m. Δ TTP 3.9 m. Trial 2: Median TTP Rev+dex NE vs. dex 4.6 months
Doxil (doxorubicin HCL liposome) *For 2nd line MM (no prior Velcade)*	RCT of Doxil + bortezomib vs. bortezomib alone (n=646)	2007 *Regular*	Median TTP Doxil+bort 9.3 months vs. bort 6.5 m. Δ TTP 2.8 m.
Kyprolis (carfilzomib) *For 3rd line MM*	Single arm trial (n=266)	2012 *Accelerated*	ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8 m.
Pomalyst (pomalidomide) *For 3rd line MM*	RCT of Pomalyst + dex vs. Pomalyst alone (n=221)	2013 *Accelerated**	PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.

*Remains under Subpart H because it has a REMS for restricted distribution

bort = bortezomib, dex = dexamethasone, mDOR = median duration of response, m = months, MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone, RCT = randomized controlled trial, TTP = time to progression, Δ = difference

The FDA has previously granted approval for a second line Multiple Myeloma indication to three drugs: bortezomib (2005), lenalidomide (2005), and liposomal doxorubicin (2007). Carfilzomib and pomalidomide were granted a 3rd line indication under the accelerated approval regulations. In addition to these three products, cyclophosphamide (1959), melphalan (1964), and carmustine (1977) have broad indications for the treatment of patients with multiple myeloma. Lenalidomide remains under Subpart H approval because it has a Risk Evaluation and Mitigation Strategy (REMS) attached to its approval. Bortezomib, lenalidomide, and liposomal doxorubicin were all granted their approvals in this indication based upon randomized, controlled trials. Prior approvals were based upon doublet therapies (adding on to single-agents), whereas this application is of triplet therapy (bortezomib + dexamethasone ± panobinostat).

Endpoints Accepted by FDA for Multiple Myeloma

The FDA has recently granted regular approvals for multiple myeloma indications based upon improvements in time-to-progression (TTP) or progression-free survival (PFS). Both include objective tumor progression in time from randomization; TTP is defined in various ways but

does not usually count deaths as progression events. Overall survival has not previously been required in approvals for Multiple Myeloma indications.

The improvements in PFS or TTP in the examples above for relapsed MM have ranged from 2.7-3.9 months (from prior doublet approvals supported by add-on design trials). The largest improvement in TTP (3.9 mos) occurred when lenalidomide was added on to dexamethasone (the least active comparator in these examples). It is not known how large of an improvement in PFS or TTP would be achieved by adding on to a doublet therapy.

The NCCN guidelines (NATIONAL COMPREHENSIVE CANCER NETWORK®, 2015) offer suggested regimens for the treatment of previously treated MM (see Table 2 below).

Table 2 NCCN Guidelines for Previously Treated Multiple Myeloma

Preferred Regimens
Repeat primary induction therapy (if relapse at >6 mos.)
Bortezomib (category 1)
Bortezomib± dexamethasone
Bortezomib/lenalidomide/dexamethasone
Bortezomib/liposomal doxorubicin (category 1)
Bortezomib/thalidomide/dexamethasone
Carfilzomib
Cyclophosphamide/bortezomib/dexamethasone
Cyclophosphamide/lenalidomide/dexamethasone
Dexamethasone/cyclophosphamide/etoposide/cisplatin
Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)
High-dose cyclophosphamide
Lenalidomide/dexamethasone (category 1)
Pomalidomide/dexamethasone
Thalidomide/dexamethasone

Regulatory Requirements

Per 21CFR §314.126, "reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."

For FDA approval of a new drug, the applicant must provide the results of two adequate and well-controlled studies. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

The Applicant has submitted the results from a single controlled trial and two uncontrolled single-arm trials (Phase Ib and II). Trial conduct for D2308 impacted the reliability of the results because of heavy censoring on the primary endpoint and a large number of protocol violations that affected the assessment of the trial primary endpoint. Despite Novartis' reassurances during their February 2012 Type C meeting that PFS in multiple myeloma was assessed primarily via laboratory tests and investigator sites would undergo training to ensure that they followed the protocol with regards to the primary endpoint measure, there were a significant number of protocol violations on the measurement of the primary endpoint.

After all patients had enrolled, but while the trial was ongoing, the Applicant conducted an internal audit and identified that for 193 patients (25% of the total patients enrolled), non-protocol specified methods were used to assess myeloma protein. The protocol specified that myeloma protein should be assessed by protein electrophoresis (PEP) with quantification of M-protein spike. The protocol violations occurred when investigators used alternative (less specific) methods such as nephelometric methods, total globulin, turbidometric methods, or the gamma globulin fraction was used as an indicator for an IgG M-component. These assessments for myeloma protein are only recommended in the International Myeloma Working Group guidelines when SPEP is unavailable or unreliable (Durie BGM, 2006) and are not typically used in U.S. clinical practice. These potential modifications were not relevant to patients in trial D2308 because the inclusion criteria required that patients have monoclonal immunoglobulin (M-component) on electrophoresis.

Prior Regulatory History for (b) (4) **Panobinostat:**

(b) (4)

(b) (4)

3. CMC/Device

There are no outstanding issues for action from chemistry or biopharmaceutics reviews.

Chemistry

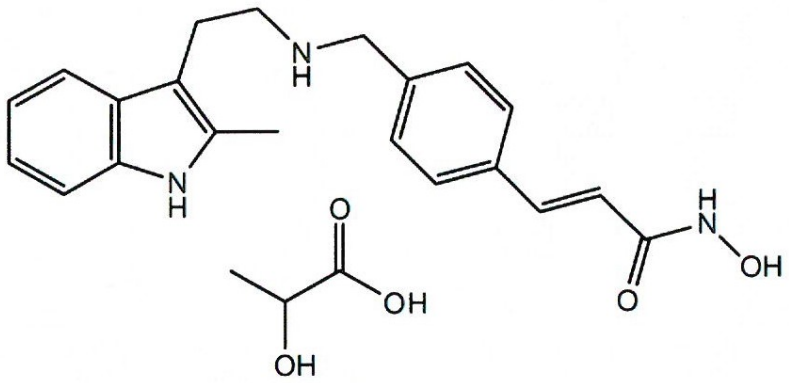
The primary chemistry review was conducted by Danuta Gromek-Woods, PhD of the Office of New Drug Quality Assessment, Division of New Drug Quality Assessment 1, Branch #2. Ali Al Hakim, Ph.D, Branch Chief, Branch 2, ONDQA provided concurrence on Dr. Gromek-Woods' review.

Per Dr. Gromek-Woods' review, the NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. From a CMC perspective, this NDA is recommended for "approval" pending an "acceptable" recommendation from the Office of Compliance and an "Adequate" recommendation from the Biopharmaceutics reviewer. The information in this section is summarized from Dr. Gromek-Woods' review.

The proposed dosage form is a hard gelatin capsule for oral administration with available strengths of 10 mg, 15 mg, and 20 mg.

Chemical Name: (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino} methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1)

Figure 1 Molecular Structure of Panobinostat



Molecular Formula: $C_{21}H_{23}N_3O_2 . C_3H_6O_3$
Relative molecular mass: 349.43 (free base) + 90.08 (lactic acid) = 439.51.
Salt/ base ratio: 1.258

The CMC review does not recommend any Post-Marketing Commitments, Agreements, and/or Risk Management Steps.

- General product quality considerations
  Drug Substance: Based on the drug substance stability data and ICH Q1E Guidance "Evaluation of Stability Data", a (b) (4) months re-test period for Panobinostat lactage, anhydrous when packed and stored in (b) (4) is granted.

  Drug Product: LBH589 was initially developed at Novartis Pharmaceuticals Corporation and (b) (4) The process was subsequently transferred to Novartis Barbera, Spain for scale-up and commercialization. LBH589 has been developed as an immediate release hard gelatin capsules for oral administration.

  FARYDAK hard gelatin capsules contain 10 mg, 15 mg, or 20 mg panobinostat free base. The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose and pregelatinized starch.

  Based on drug product stability data and statistical analysis, the expiration dating period for the Panobinostat capsules is 36 months. Product should be stored at 20 to 25 degrees C (68 to 77 degrees F), excursions permitted between 15 and 30 degrees C (59 and 86 degrees F).

Biopharmaceutics Review
The primary biopharmaceutics review was conducted by Elsbeth Chikhale, Ph.D. Her team leader was Angelia Dorantes, Ph.D. The biopharmaceutics Acting Supervisor is Paul Seo, Ph.D. The initial review was archived in DARRTS on 08/27/14 and an addendum was filed on 9/22/14.

The Biopharmaceutics review for this NDA focused on the evaluation and acceptability of:
1) The proposed dissolution methodology and dissolution acceptance criterion
2) The biowaiver request for the 10 and 15 mg strengths
3) The data supporting the bridging of the formulations

The text below is from Dr. Chikhale's reviews:

ONDQA-Biopharmaceutics had evaluated the information provided in NDA 205353 and concludes the following:

1) Dissolution method:
The following proposed dissolution method is **ACCEPTABLE**:
Apparatus 1 (basket), 900 mL 0.01 N HCl, pH ~2 at 100 rpm.
2) Dissolution acceptance criterion:
The revised dissolution acceptance criterion of QA= (b) (4) % at 15 minutes for Panobinostat was found acceptable.
3) Biowaiver request:
Based on the provided information, the request to waive the requirement for the submission of

in vivo bioavailability data for the proposed 10 mg and 15 mg capsules is **GRANTED**.

4) Bridging of the formulations:

Throughout the drug product's development, bridging of the formulations was adequately supported by dissolution and/or bioavailability data.

RECOMMENDATION:

From a Biopharmaceutics perspective NDA 205353 for Panobinostat Capsules (10, 15, 20 mg) is recommended for **APPROVAL**.

- Facilities review/inspection
  The FDA CDER EES Establishment Evaluation Request Summary Report Overall Recommendation was ACCEPTABLE on 09/11/14.

  There are no outstanding CMC/biopharmaceutics/or Inspection issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewers were Emily Place, PhD, MPH and Kimberly Ringgold, PhD. Their Supervisor/Team Leader is Haleh Saber, PhD who wrote the secondary review. The tertiary review was completed by John Leighton, PhD.

There are no outstanding issues identified by the Pharmacology Toxicology team. No PMRs or PMCs are suggested in their review.

The information below is from the Executive Summary of the combined primary review.

Panobinostat is a histone deacetylase (HDAC) inhibitor of both histone and non-histone proteins. The applicant is seeking approval for the oral route of administration and the proposed clinical dose is 20 mg once daily. Nonclinical pharmacology, pharmacokinetic, and toxicology studies have been submitted. Chronic toxicology studies in the rat and dog, genotoxicity, and reproductive toxicity studies were reviewed by Kimberly Ringgold, PhD (b) (4)

The pharmacology/toxicology studies conducted support approval of panobinostat for the proposed indication (in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma, who have received at least one prior therapy).

General nonclinical pharmacology/toxicology

Panobinostat is a histone deacetylase (HDAC) inhibitor with activity to HDAC isoforms in class I, II and IV at low nanomolar concentrations in vitro. Treatment of cells with panobinostat resulted in accumulation of acetylated histones and non-histone proteins as well as cell death and cell cycle arrest, including human multiple myeloma cells.

Panobinostat also caused cell death ex vivo in cells taken from patients with multiple myeloma and in both xenograft and disseminated mouse models of myeloma. Tumor tissues dissected from mice xenografts that were treated with panobinostat showed elevated levels of acetylated histones. Panobinostat in combination with bortezomib and dexamethasone reduced tumor burden and increased survival of animals.

Safety pharmacology studies showed no adverse respiratory findings. Neurological findings were evident in mice and presented as decreased motor activity, wobbly gait, convulsion, and decreased grip strength. The IC_{50}s in the hERG assay for panobinostat and a human metabolite BJB432 were 3.5 μM and 1.6 μM, respectively, suggesting week inhibition of the potassium channel. However, QTc prolongation was observed when panobinostat was given orally to dogs in a cardiovascular telemetry study.

The general toxicology studies were conducted in the rat and dog via oral (gavage), which is the intended route of administration. The 4, 13 and 26 week repeat dose toxicity studies in rat and 4 and 39 week repeat dose toxicity studies in dogs are reviewed. The 13 week repeat dose toxicity study in dogs was not reviewed but summarized to show findings related to thyroid toxicity and the male reproductive system. Nonclinical studies also included genotoxicity and developmental and reproductive toxicology studies. All appropriate studies were conducted in compliance with Good Laboratory Practice (GLP) regulations.

Nonclinical findings in the rat and dog show that panobinostat targets the bone marrow, hematopoietic/lymphatic systems, liver, lung, kidney, thyroid, mammary gland (atrophy; rat only) GI tract, skin (dog only) and male reproductive organs (dog only).

Genotoxicity

Panobinostat was mutagenic in the in vitro bacterial reverse mutation assay (AMES test). Panobinostat tested negative for chromosome aberrations; however, endoreduplication (increased number of chromosomes) in human peripheral blood lymphocytes in vitro was observed. Panobinostat also was positive for DNA damage in a COMET assay in mouse lymphoma cells.

Reproductive and Development Toxicity

Panobinostat may impair male and female fertility. Panobinostat elicited toxicity towards male reproductive organs in the dog in both the 4 and 13 week repeat dose studies. Toxicities included prostatic atrophy, reduced secretory granules in the prostate, testicular degeneration and oligospermia and epididymal debris. In a combined male and female fertility study in rats, females had reduced mating index, fertility index, and conception rate at 100 mg/kg (600 mg/m^2). Increased resorption and post-implantation loss were seen at ≥10 mg/kg (60 mg/m^2) and reduced number of live embryos was observed at doses ≥ 30 mg/kg (180 $mg/mg/m^2$). Panobinostat was teratogenic in the rat and rabbit. In the rat, embryo-fetal malformations (cleft palate and short tail), and variations or anomalies (e.g. incomplete ossifications, extra presacral vertebrae, and extra ribs) occurred at 30 mg/kg (180 mg/m^2) in the absence of maternal toxicities. There were no live fetuses at the 100 mg/kg dose. In the rabbit, maternal toxicity was observed at 80 mg/kg (960 mg/m^2). Embryo-fetal toxicities included decreased fetal

weight ≥40 mg/kg and malformations at 80 mg/kg. Malformations included absent digits, cardiac interventricular septal defects and aortic arch interruption, and missing gall bladder. Other skeletal variations or anomalies included incomplete ossification (≥10 mg/kg), and extra ribs (80 mg/kg). Thus, administration of panobinostat during pregnancy may pose a risk to the human fetus.

Secondary Review Comments:
Dr. Saber concurred with the primary review and states that a Pregnancy Category D is recommended for FARYDAK.

Tertiary Review Comments: Dr. John Leighton concurred with Dr. Saber's conclusion.

There are no outstanding Pharmacology Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The primary clinical pharmacology review was conducted by Joseph Grillo, PharmD.
The *in vitro* study review was conducted by Sarah Dorff, Ph.D.
The clinical pharmacology team leader (acting) was Bahru Habtemariam, PharmD.
The Pharmacometrics Reviewer was Lian Ma, PhD and her Team Leader was Nitin Mehrotra, PhD. The PBPK Reviewer was Ping Zhao, PhD.

The first review archived on 09/26/14 was based upon the initial NDA did not recommend approval. No PMRs or PMCs were recommended by the Clinical Pharmacology review team. The team archived a review addendum on 01/23/15 and in this review deferred the recommendation of approvability of this application to the clinical review team and recommended two PMRs.

At this time, there are no outstanding Clinical Pharmacology issues that would preclude approval (with PMRs).

The following information is from the Executive Summary of the Primary Clinical Pharmacology Review archived on 09/26/14.

Panobinostat (PAN) is a histone deacetylase inhibitor (HDACi). HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. FARYDAK (20 mg), in combination with bortezomib (1.3 mg/m2) and dexamethasone (20 mg), is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.

The review addressed three key questions.

1) *Does the dose/exposure-response relationship for efficacy and safety support the proposed combination dosing regimen?*
No. The totality of evidence based on efficacy and safety findings from phase 1b dose escalation trial and the registration trial does not support the proposed combination dosing

regimen. Both the dose escalation and pivotal trial results show the absence of acceptable therapeutic window for the overall clinical benefit at the proposed dose. Specific reasons are outlined below:
a) Dose escalation with expansion trial (B2207) showed that following treatment with the proposed treatment regimen (i.e., expansion phase), 87% of patients experienced Grade 3/4 adverse events (AEs), 73% of patients had dose interruptions or modifications, and 33% of patients were hospitalized due to adverse events.
b) Increased rate of serious adverse events and deaths were observed in the registration trial with the treatment arm compared to the active control group. The rates of death, Grade 3/4 AEs and dose interruptions or modifications in the Panobinostat arm were 7.9%, 96%, and 89% compared to 4.8%, 82.2%, and 76% for those in the control arm.
c) The efficacy was modest in terms of PFS [3.9 months based on investigator assessment (primary efficacy endpoint) and 2.2 months based on independent review assessment]. Interim analysis showed that overall survival (OS) was not significantly different between the two treatment arms with an estimated HR of 0.87 (95% CI: 0.70, 1.07), and a median OS of 38.2months for patients in the PAN arm compared to 35.4 months for patients in the control arm.
d) There was no exposure data available from the registration trial. Therefore the assessment of DI-efficacy or safety analysis to determine a better tolerated dose was found to be inconclusive due to multiple confounding factors. It was evident that earlier occurrences of adverse events were associated with higher dose-intensity of PAN, indicating lower average dose may provide a better safety profile. However, the effect of lower starting dose on safety cannot be determined from the current data since all the patients in the registration trials started on the same proposed dosing regimen of 20 mg every other day for three doses per week of weeks 1 and 2 of each 21 day cycle.
e) Due to lack of dose/exposure-response data for efficacy, it is not possible to determine if a lower starting dose would provide similar efficacy and thus may offer a better benefit-risk profile.
f) Overall survival data when mature may be useful to better assess the benefit risk of the proposed PAN combination dosing regimen in the treatment of patients with relapsed multiple myeloma.

2) *What is an appropriate dose for patients with baseline hepatic impairment?*
In patients with NCI-CETP class mild and moderate hepatic impairment AUC0-inf increased 43% and 105% compared to patients with normal hepatic function, respectively. The effect of severe hepatic impairment was indeterminate in this study due to the small sample size (n=1). Based on these findings, a dose modification is required in patients with mild or moderate hepatic impairment; however, a specific dose cannot be recommended because there is no reference dose available as discussed above. FARYDAK doses of 15 and 10 mg in patients with mild and moderate hepatic impairment provide comparable systemic exposure as a 20 mg dose of FARYDAK in patients with normal hepatic function. There was insufficient PK data in patients with severe impairment to make a reliable comparative PK assessment.

3) *What is an appropriate dose for patients taking a strong CYP3A inhibitor or inducer?*
a) CYP3A inhibitors: Coadministration of a single 20 mg FARYDAK dose with ketoconazole (200 mg twice daily for 14 days) increased the Cmax and AUC0-48 of PAN by 67% and 73%

respectively. When given concomitantly with strong CYP3A4 inhibitors, FARYDAK dose of 10 mg will provide comparable systemic exposure as 20 mg of FARYDAK in the absence of concomitant CYP3A4 inhibitors b) *CYP3A inducers:* The sponsor did not characterize the influence of CYP3A4 inducers on the PK of PAN. PBPK simulations suggest coadministration of PAN with strong CYP3A4 inducers could reduce exposure of PAN by in approximately 70%. The simulation results suggest there is no practical FARYDAK dose that will provide exposure matching when given concomitantly with strong CYP3A4 inducers.

Recommendation
The Office of Clinical Pharmacology (OCP) has determined the sponsor has not identified an acceptable dose in this NME NDA to support a recommendation of approval of FARYDAK. The primary reason for this decision is that that the proposed dosing regimen has major safety concerns and does not provide a favorable benefit risk from a clinical pharmacology perspective. The acceptability of specific drug information is provided below.

- Absorption: The mass balance (ADME) trial B2108 reports that the extent of PAN absorption following oral administration of [14C]-PAN is ≥ 87% of radioactivity associated with PAN and its metabolites recovered in excreta. Unchanged PAN in the feces accounted for <3.5% of the administered dose which further suggests absorption.
- Distribution: In vitro, PAN is 89.6% bound to plasma proteins (88.2% in human serum). In the normal group of the special population trials X2101 and X2105, where PK sampling was collected over 96 hours the mean (%CV) terminal volume of distribution (Vz/F) of single agent PAN from the noncompartmental analysis was 9318.2 (50.3) and 6092.8 (43.3) liters, respectively (see Table 7). This finding was consistent with the median (range) Vz/F estimate of 9464 (5178; 9867) liters from the ADME trial B2108 and suggests extensive tissue distribution. The central volume of distribution reported from the pop-PK analysis of PAN single agent was 24.8 liters. In vitro studies suggest that the substantial P-gp mediated efflux ratios for PAN may hypothetically limit its exposure in tissues that are protected by high levels of P-gp expression such as the brain and testis, but this has not been evaluated clinically.
- Metabolism: Based on the results of the ADME trial above and in vitro studies using pooled human liver microsomes, recombinant human cytochrome P450 (CYP) enzymes, and human liver slices, the metabolism of PAN appears to be extensive. This includes both CYP mediated oxidative metabolism and non-CYP mediated processes, including reduction, hydrolysis, one- and two-carbon shortening of the hydroxyamic acid side chain, and glucuronidation. CYP3A4, CYP2D6 and CYP2C19 metabolized PAN above control levels, with kinetic parameters predicting the contributions to be 0.603, 0.174 and 0.0466 mL*h-1*mg protein-1, respectively. The relative contribution of these CYP isozymes was explored in human liver microsomes in the presence and absence of inhibitors of CYP3A4, CYP2D6, CYP2C19, CYP1A2, CYP2C8, and CYP2C9. Dr. Grillo agreed with the applicant's position that CYP3A4 is likely the predominant CYP isozyme responsible for the metabolism of PAN.
- Drug-Drug Interactions: Panobinostat is a CYP3A substrate and inhibits CYP2D6. Panobinostat is a P-glycoprotein (P-gp) transporter system substrate.
- Elimination: The elimination of PAN was primarily in the form of metabolites with unchanged PAN in feces and urine accounting for median (range) of 0 (0 – 3.3%) and

2% (1.1 – 2.4%) of dose, respectively.

- PK changes with chronic dosing: Steady-state should theoretically be achieved after the third dose of a TIW FARYDAK dosing regimen, but it is not maintained due to the 72-hour rest after the 3rd dose on Day 5.
- Intrinsic Factors: Results from a pop-PK analysis and two dedicated organ dysfunction trials suggest that age, body surface area (BSA), hepatic dysfunction, and possibly Japanese race may influence PAN exposure. Of these, the magnitude of the effect of hepatic impairment on exposure requires a dose modification to match exposure in patients with normal hepatic function.
- Extrinsic Factors: Inhibition or induction of the CYP3A4 metabolic pathway will likely impact PAN exposure to a degree that requires intervention by the prescriber. A semi-mechanistic indirect PKPD model reports that there is a dose and schedule dependent relationship between single agent PAN exposure and thrombocytopenia. Considering the risk of overlapping toxicities with BTZ, the risk of thrombocytopenia may be even greater with combination therapy. The exposure safety of other risk parameters is not known. Patients receiving FARYDAK concurrently with a strong inhibitor or CYP3A4 should receive a starting dose of 15 mg with frequent monitoring. FARYDAK should be avoided in patients that require coadministration with a strong inducer of the CYP3A4 metabolic pathway given the potential reduction in exposure estimated by PBPK modeling simulations.
- Food Effect: The product may be administered without regard to food.
- Demographic interactions/special populations:
    1. Hepatic Impairment: Given the ADME profile of single agent PAN combined with the less than optimal exposure results from trial X2101due to high variability and the exposure and safety profile of FARYDAK, a dose modification is recommended for patients with mild to moderate hepatic impairment to match exposure to patients with normal hepatic function. Because the selected dose for the general population was found unacceptable we are we cannot recommend a dose for special population without a reference dose.
    2. Renal Impairment: The PAN geometric mean $AUC0_{-inf}$ in the mild, moderate and severe groups were 64%, 99% and 59%, of the normal group, respectively. The geometric mean values of Cmax followed a similar pattern.
    3. Elderly: The pop-PK analysis reported that younger patients with a median age of 30 years are predicted to have 12% slower clearance and 25% lower central volume of distribution than patients with a median age of 61 years old. In addition, patients at age 80 are predicted to have 5% faster PAN clearance than patients 61 years old. The age effect did not appear to be confounded by the BSA effect. Based on these findings it is unlikely that older patients are at risk of having a potential higher systemic exposure that would require a dose modification.
    4. Pediatrics: The expected exposure and PK in pediatrics is not known. Given this is an orphan drug it is excluded from PREA requirements.
    5. Gender: The pop-PK analysis of single agent PAN showed no effect by gender on PAN clearance.

6. Body Weight and BSA: The BSA effect on systemic exposure is unlikely to require a dose modification or a weight based dosing scheme.
7. Race: The race effect on systemic exposure of PAN is not considered clinically relevant. There were no apparent differences in efficacy parameters between Caucasian and Japanese patients however there appears to be a trend towards higher frequency of AEs for Asian than Caucasian patients in the PAN+ BTZ+DEX arm. The ClinPharm reviewer defers whether the increased frequency of AEs in Asian patients should be communicated in labeling.
8. Thorough QT study or other QT assessment: Administration of panobinostat by intravenous and oral routes causes a dose-related increase in the QT interval. There has been one case of TdP with the 20 mg/m2 consecutive IV dosing regimen that has since been discontinued. This property is probably a class effect of HDAC inhibitors. The QT effect appears to occur hours after tmax of the parent drug, so the effect is not dependent on the concentration of the parent drug.

Review Addendum

The dose distribution data obtained from the trial 2308 indicated that PAN dose was not well tolerated even after dose modifications. Approximately 70% of the patients discontinued the PAN treatment by cycle 12 indicating that the dose reduction schema did not address the safety/tolerability issues with PAN+BTZ combination. On the other hand, < 10% of the patients in the BTZ control arm discontinued the treatment indicating majority of the patients were able to tolerate and continue BTZ treatment with appropriate dose reduction strategy. Therefore, a lower dose or an alternate dosing regimen of PAN in combination with BTZ may offer a better safety/tolerability profile.

To test the hypothesis that a lower dose or alternate dosing regimen may offer a better tolerability profile, two PMRs are being recommended. A dose- finding PMR to evaluate various dose(s)/regimen(s) to adequately characterize the dose-response relationship of PAN. The results for this dose finding PMR should inform the dose selection for the phase 3 trial (second PMR). Therefore, it is important that the two PMR trials should be conducted sequentially, not in parallel. Furthermore, it is important to note that there exists significant variability in pharmacokinetics (CV% for Clearance: 65%) of PAN and therefore the doses for the dose finding trial should be selected to maximize the likelihood of differentiating efficacy and safety between doses. For e.g., doses of 15 and 20 mg PAN Q3W are unlikely to be informative for selection of the dose of the phase 3 trial. The final dose(s)/regimen(s) to be studied in dose-finding PMR will be discussed and finalized at the protocol submission stage.

The review concluded that the recommendation on approvability is deferred to the Clinical Review Team. The PMRs suggested by the Agency are listed in Section 13 below.

6. Clinical Microbiology

Not relevant: Panobinostat is an oral anti-cancer agent.

7. Clinical/Statistical- Efficacy

The initial submission of NDA 205353 (Farydak, panobinostat) was co-reviewed by Adam George, PharmD and Barry Miller, MS, CRNP. They archived separate reviews. Dr. George reviewed the safety portion and Mr. Miller reviewed the efficacy portion. Dr. George transferred out of the Division during the review clock, and Dr. Nicole Gormley presented the safety findings at the ODAC meeting and contributed to a co-authored review of the Major Amendment with Mr. Miller. The biostatistics review was conducted by Chia-Wen Ko, PhD and archived on 08/26/14. The biostatistical team leader is Lei Nie, PhD.

In his primary NDA review, Mr. Miller, clinical efficacy reviewer, deferred the final clinical assessment of benefit:risk to the CDTL review. Dr. George recommended not approving the application due to the increased rate of severe adverse reactions, serious adverse reactions, and toxicity-related deaths in patients who received panobinostat. He concluded that the toxicity observed is not outweighed by a 3.9 month improvement in investigator assessed median Progression Free Survival. Dr. Ko stated in her review that she did "not have a definite recommendation on whether or not this product should be approved for the proposed indication based on data submitted for this application."

The *italicized* information in this and subsequent sections below is from Mr. Miller's Clinical Review--Efficacy Summary, Dr. George's Clinical Review—Safety, and Dr. Ko's Biostatistics review.

In support of the proposed indication, Novartis conducted one randomized trial and two single-arm trials. Trial D2308 was a randomized, placebo-controlled, double-blinded trial of 768 patients with relapsed multiple myeloma that were randomized in a 1:1 fashion to treatment with bortezomib (B) and dexamethasone (D) ± panobinostat.

Supportive data was provided from the following trials:

- CLBH589DUS71: Phase II, multicenter, single-arm, open-label trial of panobinostat in combination with bortezomib and dexamethasone in 55 patients with relapsed and bortezomib-refractory multiple myeloma.
- CLBH589B2207: Phase Ib, multicenter, open-label, dose-escalation study of oral LBH589 and intravenous bortezomib in adult patients with multiple myeloma

Regulatory Background of Panobinostat

Regulatory Milestones:

03/14/03 Novartis submitted initial IND for intravenous formulation of LBH589

05/17/04 Novartis submitted initial IND for the oral formulation of LBH589.

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
SPA-4 for multiple myeloma

SPA-4 proposed a single arm trial (CLBH589B2203) 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 (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.

11/22/10 FDA notified the Sponsor that their proposed trade name "(b) (4) was unacceptable.

01/25/12 FDA notified the Sponsor that their proposed trade name "Farydak" was acceptable.

02/29/12 Type C meeting to discuss the statistical and clinical issues related to the Phase 3 study CLBH589D2308. A summary of the discussions are summarized below:

- The Agency agreed that a clinically meaningful and statistically significant improvement in PFS (primary endpoint) may serve as the basis for approval for patients with relapsed MM, but that the evaluation of risk and benefits for any labeling claims will be a review issue. The Agency also stated that PFS assessment should be based on an Independent Review Committee Assessment.

• 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.

Novartis stated in their response that "with regards to the need for an independent review of PFS data, the following should be considered:

-The assessment of response is multiparametric, mostly based on laboratory testing (e.g. electrophoresis, calcium)
-All the investigators are provided with detailed guidance and specific training modules to ensure that the investigator assessments are consistent with the protocol defined response criteria.
-Disease status as assessed by the investigator is reviewed by the sponsor, in a blinded fashion, by using a computer algorithm, according to the protocol defined criteria, as a tool to check validity and integrity of the data

-Current blinded assessment of PFS data for IA1 shows approx. 95% concordance between Investigator's assessment and sponsor's assessment

-The discordant cases (approximately 5% of patients) will be reviewed by an external independent blinded expert panel. As there are no anticipated major differences in toxicity over bortezomib and dexamethasone that could compromise the blind, this plan is considered adequate to ensure the validity of the data."

They also stated that this "plan *will ensure the validity of the data in the double blind study"*.

• 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.

08/20/12 Panobinostat was granted Orphan Drug Designation (12-3762) for the treatment of multiple myeloma.

02/05/14 Type B meeting 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:

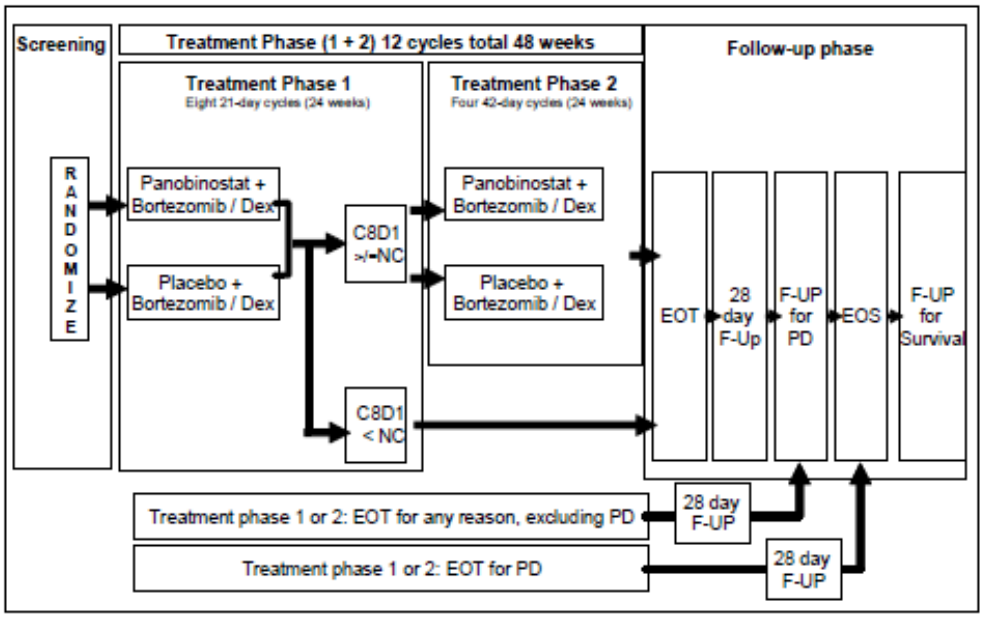
- We agreed to the proposed content and format of the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) and to waive the requirement for providing an Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS)
- We recommended that diarrhea be included in the 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

03/24/14 Novartis submitted New Drug Application 203353 for Relapsed Multiple Myeloma

Primary Efficacy Trial (CLBH589D2308) of Panobinostat in Combination with Bortezomib and Dexamethasone:

Trial CLBH589D2308 was a Novartis-sponsored, phase 3, double-blind, placebo-controlled, double-blind, randomized 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 (1-3 prior therapies). The trial planned to randomize 762 patients 1:1 stratified by number of prior lines of therapy (1 vs. 2 or 3) and prior use of bortezomib (yes or no). Trial D2308 was discussed with FDA but was not conducted under Special Protocol Assessment.

Figure 2 Trial Schema of D2308



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.

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

Trial Objectives

[Source: Section 8, LBH589D2308 Clinical Study Report]

Primary Objective: To compare PFS in patients treated with panobinostat in combination with bortezomib/dexamethasone vs. patients treated with placebo in combination with bortezomib/dexamethasone.

PFS was defined as the time from randomization to the date of the first documented PD or relapse or death due to any cause based on mEBMT criteria and assessed by the Investigator.

Analysis of the primary endpoint

The primary comparison in PFS between treatment arms was based on a 2-sided stratified (by randomization factors) log-rank test. The HR estimation for the effect of PAN+BTZ+DEX over PBO+BTZ+DEX was based on a proportional hazards model including treatment arm and the randomization factors. The study had several pre-specified sensitivity analyses for PFS with respect to censoring rules, handling of missing M-protein assessments, and impact of prognostic factors. Please refer to Table 5 of Dr. Ko's review and Table 3 below for the description of the sensitivity analyses.

For the protocol-specified primary analysis of PFS, PFS was censored at the date of the last adequate response assessment prior to the data cut-off or start of new antineoplastic therapy if a patient had not experienced a PFS event by the date of the analysis cut-off, had started

another antineoplastic therapy, or had an event after more than two missing adequate assessments. [Source: Dr. Chia Wen Ko, Statistical Review; Section 3.2.4.1.1]

During the NDA review, and before the AC meeting (on 10/07/14), the Applicant submitted a Response to FDA information request which described a new sensitivity analysis for the IRC results. The response stated that "subsequent to the submission of the response to FDA [IR-32], it was realized that IRC assessment of progression, or relapse from complete response (CR), did not take into account a confirmation assessment as required by modified EBMT criteria (for patients progressing due to an increase in serum or urine m-protein), as specified in the protocol, and mandated for the primary PFS analysis. To correct this incorrect assessment, Novartis performed an IRC PFS sensitivity analysis that considered progression, or relapse from CR, only when confirmed by a subsequent IRC assessment of progression or relapse. Table 3 below compares the different PFS sensitivity analyses conducted by Novartis.

Table 3 Comparison of Primary Analysis and Sensitivity Analyses Conducted by Applicant on Primary Endpoint of PFS

Name of Analysis	Timing	Rationale for Analysis	Definitions	PFS (mos) Pan+ Bortez+ Dex Arm	PFS (mos) Placebo+ Bortez+ Dex Arm
Primary	Submitted with NDA	Primary	Investigator-assessed PFS by mEBMT criteria (required confirmation of M-protein progression events)	12	8.1
IRC Analysis	Prior to database lock; after audit of study results; submitted with NDA	During audit of data protocol violations noted; Novartis found 177 (23%) patients had non-PEP methods used to measure M-protein; IRC convened to conduct blinded assessment of all pts enrolled. The	IRC convened to perform an independent review of disease response data for all randomized patients in a blinded manner based on modified EBMT criteria, as well as dates of response assessments. They had no knowledge of investigator assessment. Key Rules: Pts with PEP M-protein assessments were eval for response according to mEBMT criteria.	9.9	7.7

		charter required confirmation of M-protein progressions. After NDA submission, and in response to an FDA IR, Novartis discovered that statistician did not conduct the correct analysis and had counted unconfirmed PFS events.	Pts w/o available M-protein (whose disease was monitored using total globulins and/or nephelometrric or turbidometric quantification of immunoglobulin levels, the IRC assessed responses based on principles and intensions of mEBMT criteria. They counted the non-prespecified methods.		
IRC without PD confirmation	Submitted to Agency on 10/07/14	To evaluate the impact of the lack of confirmation of PD in original IRC analysis	PFS using the first report of PD irrespective of the confirmation of PD	9.95	7.66
"Updated IRC Analysis" IRC with PD confirmation, as per mEBMT criteria	Submitted to Agency on 10/07/14	To evaluate the impact of the lack of confirmation of PD in original IRC analysis	PFS using the first report of progression with confirmation by at least one repeat assessment or first report of PD without confirmation if PD was identified due to a reason other than M-protein	11.99	8.31

The treatment effect on median PFS for all of the analyses above ranged from 2-4 months.

Issues identified with IRC analysis:

- IRC called some progression events earlier than INV based on rising M protein without meeting the threshold for progression.

- Some patients who were considered to have non-measurable disease as per mEBMT or with missing baseline data, IRC provided responses other than 'unknown' or 'progressive disease' using post-baseline M-protein values and immunofixation data. This is contrary to the INV assessment where all patients with non-measurable disease as per mEBMT or with missing baseline data were assessed for 'unknown' or 'progressive disease' responses only.
- IRC called some patients as having adequate assessments where investigators called them "unknown" due to missing individual efficacy data. This led to censoring due to missing adequate assessments being observed more frequently in the analysis by investigator assessment compared to the IRC assessment.

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

Responses were confirmed after six weeks. VGPR and sCR were also determined based on IMWG criteria (Rajkumar SV, 2011).

The response criteria are nearly the same and are further discussed in Section 6.1 of Mr. Miller's review. Because the same response criteria were used for both arms of Trial D2308, they will not be further discussed in this review.

Statistical Assumptions

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. [Source: Mr. Miller's Review, Page 16]

Interim analyses

Two interim analyses for PFS were planned after observing 33% and 80% of the 460 events targeted for the final analysis. The first interim analysis was for testing futility, while the second interim analysis was intended to test for treatment efficacy. OS would be tested if the primary endpoint PFS was statistically significant for efficacy. [Source: Dr. Chia Wen Ko, Statistical Review; Section 3.2.2]

Type I error control

The Type I error control for multiple testing in PFS was done through the O'Brien-Fleming alpha spending function approach. For the key secondary endpoint OS, a separate pre-planned O'Brien-Fleming function was utilized for alpha spending based on anticipated

number of OS events at the planned PFS analyses and the final targeted 415 OS events for the final OS analysis. This strategy, as shown in Glimm et al (Glimm E, 2009) *and Tamhane et al* (Tamhane AC, 2010)*, utilized a hierarchical testing procedure allowing for the testing of OS after PFS was statistically significant without inflating the study Type I error, because alpha sharing in OS was done based on a separate alpha spending function for all possible planned interim analyses of OS irrespective of whether the analysis was performed.* [Source: Dr. Chia Wen Ko, Statistical Review; Section 3.2.2]

Secondary Objectives:

Key Secondary Objective: To compare overall survival (OS) between treatment arms.

Other Secondary Objectives:

- To compare ORR (overall response rate) comprising Complete Response (CR), near CR
  (nCR) and Partial Response (PR)
- To compare nCR plus CR rate
- To compare Minimal Response rate (MRR)
- To compare time to response (TTR)
- To compare time to progression (TTP)
- To assess duration of response (DOR) from first occurrence of PR or better
- To assess safety of the combination therapy
- To assess health-related quality of life (QoL) and symptoms of multiple myeloma
- To evaluate the pharmacokinetics (PK) of panobinostat and bortezomib in a subset of Japanese patients

Note: All secondary efficacy endpoints related to objective disease response were based on mEBMT criteria

Statistical Analysis of secondary endpoints:[Source: Dr. Ko's review, Section 3.2.2]
OS was the only secondary endpoint with pre-specified testing using stratified log-rank test. For other secondary time-to-event endpoints, the analysis included estimation of median times with 95% confidence intervals using the Kaplan-Meier product-limit method. Secondary response rate endpoints were estimated along with 95% exact confidence intervals as derived by the Clopper-Pearson method for each treatment arm.

Trial D2308 Key Landmarks: (complete landmarks are in section 5.3.1.3 of Dr. George's review)

- The first patient enrolled on January 29, 2010.
- June 30, 2010: Amendment 1 (after 34 patients randomized) was a Japanese country-specific amendment with limited impact to the overall trial results.
- December 22, 2011: Amendment 2 (after 668 patients had been randomized) increased the sample size to compensate for a higher-than-expected drop-out rate (in the absence of

safety concerns). The main reason for dropout was that patients who discontinued treatment withdrew their consent to be followed for response per protocol.

- March 7, 2012: Amendment 3 (after 742 patients were randomized) increased the PFS event fraction for Interim Analysis 2 from 67% to 80% (306 to 368 events). This amendment was intended to reduce the risk of an overestimation of the treatment effect. 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 rate was unchanged. Based upon the Study Steering Committee recommendations, 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.
- October 2, 2012: Amendment 4 (with 87 patients remaining on treatment) specified that collection of serum calcium variables (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 (after 768 patients randomized) was instituted because the Sponsor determined that though the protocol required measurement of M-protein spikes by protein electrophoresis (PEP) in serum and urine as per mEBMT criteria, they found 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). The Applicant stated that "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 amendment was to document PEP results without specific M-spike measurement and to document the 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 primary analysis continued to be PFS based upon Investigator's response following the ITT principle. The newly collected data was used in sensitivity analyses of PFS and other efficacy-related endpoints, including an analysis using independent response assessment in patients for whom M-protein spike was not measured by PEP or PEP was used without measurement of the M-protein spike. This sensitivity analysis was to be conducted by an Independent Review Committee.

- September 10, 2013: Data cutoff for clinical study report.

Trial Population:

Eligible patients were:

- *Adults with a previous diagnosis of multiple myeloma (MM) based on IMWG 2003 definitions. All three of the following criteria were needed for enrollment:*
  1) Monoclonal immunoglobulin (M-component) on electrophoresis, and on immunofixation on serum or on total 24-hr urine (or demonstration of M-protein in cytoplasm of plasma cell for non-secretory myeloma);
  and

2) Bone marrow (clonal) plasma cells ≥10% or biopsy proven plasmacytoma; and
3) Related organ or tissue impairment (CRAB symptoms: anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis, or recurrent infections.

- *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*

- *Patient has measureable disease at study screening defined by at least one of the following measurements as per IMWG 2003 criteria:*
  Serum M-protein ≥1 g/dL or Urine M-protein ≥200 mg/24 hour
- *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*
- *ECOG of ≤2*
- *Minimum laboratory values within 3 weeks before starting study drug:*
  - *Absolute neutrophil count (ANC) ≥1.5 x 10^9/L*
  - *Platelet count ≥100 x 10^9/L*
  - *Serum potassium, magnesium, phosphorus, within normal limits (WNL) for institution*
  - *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*
  - *AST/SGOT and ALT/SGPT ≤2.5 x ULN*
  - *Serum total bilirubin ≤1.5 x ULN (or ≤3 x ULN if patient has Gilbert syndrome)*
  - *Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥60 ml/min*
- *Provided written informed consent*
- *Able to swallow oral capsules*
- *Able to adhere to study visit schedule and other protocol requirements*
- *Women of childbearing potential must have negative serum pregnancy test at baseline.*

Key Exclusion Criteria

- *Primary refractory disease (progressed under all prior lines of anti-MM therapy)*
- *Bortezomib-refractory (did not achieve at least a MR, or have progressed under it or within 60 days of last dose)*
- *Recipient of allogeneic stem cell transplant with graft versus host disease (active or requiring immunosuppression)*
- *History of intolerance to bortezomib or dexamethasone or any components of these drugs or has a contraindication to receiving one of these drugs.*
- *Grade ≥2 peripheral neuropathy of grade 1 peripheral neuropathy with pain on clinical examination within 14 days before randomization.*
- *Patients who have received prior treatment with deacetylase inhibitors including panobinostat*
- *Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment*
- *Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period).*
- *Patients with secondary malignancies < 3 years of first dose of study treatment*
- *Prior anti-myeloma chemotherapy or medications including IMiDs and dexamethasone ≤3 weeks prior to start of study; experimental therapy or biologic immunotherapy ≤4 weeks prior to start of study; prior radiation therapy ≤4 weeks or limited field radiotherapy ≤2 weeks prior to start of study.*
- *Patient not recovered from therapy-related toxicities to < grade 2 CTCAE.*
- *Patient has undergone major surgery ≤2 weeks prior to starting study drug or who have not recovered from effects of surgery to < grade 2 CTCAE*
- *Patients with mucosal or internal bleeding, unresolved diarrhea ≥grade 2*
- *Impaired cardiac function (see Dr. George's review section 5.3.1.2 for details)*
- *Use of concomitant medications with relative risk of QT prolongation interval or inducing Torsades de pointes.*
- *Impairment of GI function or disease that may impair the absorption of panobinostat*
- *Concurrent severe and/or uncontrolled medical conditions*
- *Known history of HIV seropositivity or history of active/treated hepatitis B or C*
- *Women who are pregnant, breastfeeding, or of childbearing potential and unwilling to use a double method of contraception (one must be a barrier method) during the study and 3 months after the study evaluation.*
- *Males who are not willing to use a barrier method of contraception during the study and for 3 months after the study*

Treatments Administered

Table 4 D2308 Treatment Doses and Regimens

Treatment phase 1: Cycles 1-8, 3 week cycles			
Drug	**Panobinostat/Placebo**	**Bortezomib**	**Dexamethasone**
Dose	20 mg orally	1.3 mg/m^2 IV	20 mg orally
Regimen	Days: 1, 3, 5 8, 10, 12	Days: 1, 4 8, 11	Days: 1, 2, 4, 5 8, 9,11, 12
Cycle duration	21 days	21 days	21 days
Treatment phase 2: Cycles 9-12, 6 week cycles			
Drug	**Panobinostat/Placebo**	**Bortezomib**	**Dexamethasone**
Dose	20 mg orally	1.3 mg/m^2 IV	20 mg orally
Regimen	Days: 1, 3, 5 8, 10, 12 22, 24, 26 29, 31, 33	Days: 1 8 22 29	Days: 1, 2 8, 9 22, 23 29, 30
Cycle duration	42 days	42 days	42 days

[Source: Table 9-2 Applicant D2308 Clinical Study Report]

[Source: Dr. George's review, page 22]
Treatment on protocol was 48 weeks in duration split in two 24-week 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/m2 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. The treatment regimens are described in Table 4 above.

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 >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/m2 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.

Comment: I agree with Dr. George that the dosing regimen of bortezomib used for trial D2308 does not meaningfully differ from the dosing regimen of bortezomib recommend in the prescribing information. I agree with Mr. Miller that 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.

Dose reductions of panobinostat, bortezomib, or dexamethasone were allowed for toxicity. The reader is referred to Dr. George's review Section 5.3.1.2 for details of the dose adjustments. Because this was a blinded trial, the plans were equal between treatment arms.

Trial D2308 Primary Efficacy Results

(Source: Mr. Miller's Efficacy Review; Section 6)

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

Trial D2308 randomized 768 patients (387 to panobinostat and 381 to placebo). All patients were scheduled to receive bortezomib and dexamethasone. These patients are included in the ITT population (as randomized).

• 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.

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. This IRC assessment was included in the trial as a sensitivity analysis due to the 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.

In the primary endpoint analysis of PFS, shown below in Table 4, *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.*

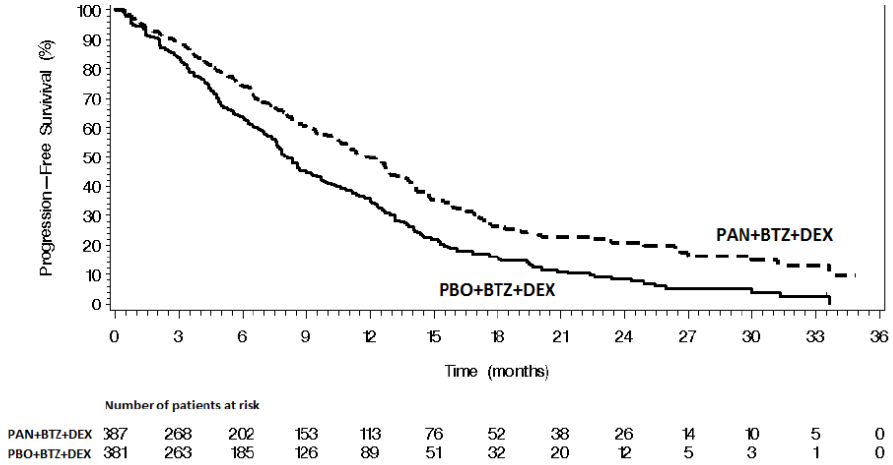
Table 5 Progression-Free Survival Analysis of Trial D2308 by Investigator

	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

[Source: Mr. Miller's Review; Table 9]

Figure 3 Kaplan-Meier Estimates of Progression-Free Survival in Trial D2308



[Source: Mr. Miller's Review; Figure 1]

Excessive censoring is noted in this analysis. *Nearly half of patients on the panobinostat + BD arm were censored in the analysis for PFS. Censoring occurred more often in the panobinostat + BD arm, primarily due to missing assessments: 31% vs.22%.* Table 5 *below, describes the main reasons for censoring of PFS by treatment arm.*

Table 6 Reasons for Censoring in Trial D2308

	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,

[Source: Mr. Miller's Review; Table 10]

The Applicant conducted several sensitivity analyses to assess robustness of the primary PFS analysis, with respect to the censoring rule, handling of missing PEP M-protein assessments, protocol violations, potential imbalance in baseline factors, and a possible worse-case scenario [See Table 6 below].

All the sensitivity analyses suggested a statistically significant difference between the treatment arms in PFS distribution; however, there was a wide range in the estimated benefit by panobinostat with the estimated improvement in median PFS from some sensitivity analyses to be only half of the one from the primary analysis. *[Source: Dr. Chia Wen Ko's Statistical Review, Section 3.2.4.1.2]*.

Table 7 Summary of PFS Sensitivity Analyses for Primary Endpoint in Trial D2308

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

The limitations of the PFS endpoint have been described in written FDA guidance as well as in publications. "Missing data and loss to follow-up can be informative and can introduce bias, thus affecting the interpretation and validity of an analysis (Rothmann M, 2013)."

Secondary Endpoints

[Source: Mr. Miller's Clinical Efficacy Review, Section 6.1.5]

Overall survival was the key secondary endpoint in Trial D2308. 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.

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 7*).*

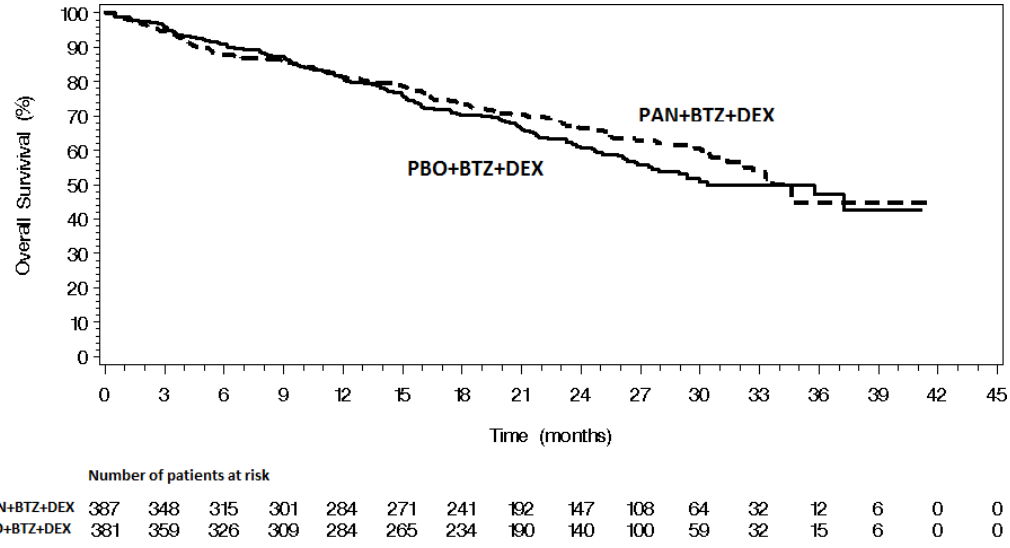
Table 8 Overall Survival Interim Analysis of Trial D2308

	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

[Source: Mr. Miller's Clinical Efficacy Review, Section 6.1.5]

Figure 4 Kaplan-Meier Estimates of Interim Analysis of Overall Survival in Trial D2308



[Source: Mr. Miller's Clinical Efficacy Review, Section 6.1.5]

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 9 Response Rates from Trial D2308

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.

By the modified EBMT criteria, panobinostat appears to add very little to the response rate (6%).

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.
[Source: Mr. Miller's Clinical Efficacy Review, Table 14]

Review of pre-specified subset analysis proposed by Applicant (Major Amendment to NDA)

As previously stated, the review team and ODAC members did not feel that patients in the overall (ITT) population had a positive benefit/risk assessment for panobinostat added to bortezomib and dexamethasone. A protocol specified subgroup analysis of patients enrolled on Trial D2308 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.

I agree with the primary reviewers that 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.

The population proposed by the Applicant were:
Patients with relapsed/refractory multiple myeloma who had received prior bortezomib and an immunomodulatory agent (n=193).

The key efficacy findings for this subset of patients are:

- *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.*

Demographics of Subpopulation:
*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 9 *).*

Table 10 Demographic characteristics of patients in Trial D2308 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

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.

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 10 *and* Figure 5 *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.*

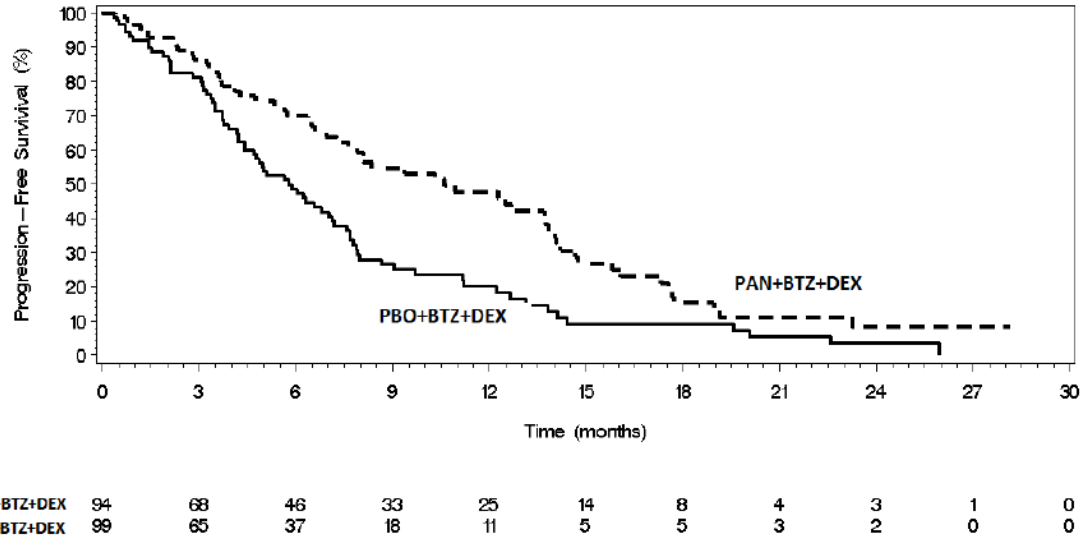
Table 11 Investigator-assessed Progression-free Survival (PFS) analysis of Trial D2308: Prior bortezomib and an immunomodulatory agent

	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)	0.56 (0.39, 0.79)	
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

Secondary Endpoints for Subgroup

Figure 5 Kaplan Meier plot of investigator-assessed Progression-free Survival (PFS) from Trial D2308 subgroup: Prior bortezomib and an immunomodulatory agent



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

Table 12 Response rate and duration of response in Trial D2308 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

Overall responses were observed more frequently in the panobinostat + BD arm compared to the placebo + BD arm.

Protocol Deviations

Major protocol deviations occurred in 25.3% of patients on the panobinostat arm and 28.1% of patients on the control arm. The largest portion of protocol deviations had an impact on the assessment of the primary endpoint, which were "missing efficacy baseline assessment", which may have included missing serum M-protein, urine M-protein, soft tissue plasmacytoma, bone lesion. These deviations included the patients without M-protein assessment as per mEBMT criteria. Missing efficacy baseline assessments occurred in 19.9% of patients in the panobinostat arm and 22.6% of the control arm. The rest of the deviations occurred in <5% of patients in either arm, so will not be discussed here. [Source: Applicant CSR for D2308; Section 11].

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. Blacks (or African Americans) were underrepresented in trial D2308. The trial population median age of 63 years was somewhat younger than the historical age for patients with Multiple Myeloma at relapse (70 years). Further details of the demographic characteristics of the trial patients can be found in Table 2 of Mr. Miller's review.

Disease Characteristics

Patients enrolled to the panobinostat arm and the control arm had a median of 3.1 and 3.2 years, respectively, in time from their initial myeloma diagnosis. Both treatment arms had a median of 1 prior antineoplastic regimens. Prior treatments for myeloma in these patients included (from most frequently reported to least) corticosteroids, melphalan, thalidomide,

cyclophosphamide, bortezomib, doxorubicin, and lenalidomide. The prior usage of each product was well balanced between treatment arms.

The most frequent immunoglobulin class for the enrolled patients' myeloma was IgG, followed by IgA, IgM, IgD, and IgE (only one patient in the control arm). The most frequently reported light chains at baseline were Kappa at 62% for the panobinostat arm and 58% for the placebo arm versus 33% and 36% respectively for lambda light chains. The median serum and urine M-protein by PEP, bone marrow plasma cell count, presence of soft tissue plasmacytoma, and lytic bone lesions were well balanced between treatment arms.

The pathologic features of myeloma in patients on trial are comparable to the current understanding of the disease and are fairly balanced between arms.

As in many oncologic drug trials, the performance status of patients is high at baseline. Patients in the community requiring treatment for multiple myeloma may have a worse performance status than patients enrolled on the trial. Baseline renal impairment was balanced between arms.

The percentage of patients with missing M-protein by SPEP and UPEP results is excessive and limits the reliability of the trial from a conduct perspective.

Table 13 Figure 6 Disposition of patients randomized 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]

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. Similar numbers of patients (26% per arm) completed Treatment Phases 1 and 2 (Table 12).

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.

Mr. Miller identified the following limitations in the reliability of the results from Trial D2308:

- *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*
- *Excessive censoring on PFS: 47% of events in the panobinostat arm vs. 32% of events in the control arm.*

Barring these limitations, there remains a question as to whether a 2 or 4 month (depending upon which assessment is used) improvement in progression-free survival is sufficient to justify the risks of panobinostat for patients with relapsed multiple myeloma. It is not known whether overall survival will ever reach statistical significance when the data is mature.

Additional Supportive Trials

Phase 2 Trial

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. This trial enrolled 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. At the end of 8 cycles, the ORR was 34.5% with a median DOR of 6 months. No patients achieved a Complete Response.

Table 14 Response Rate Analysis of Trial DUS71

	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

Trial LBH589B2207 (Phase Ib dose-escalation trial)
The trial enrolled 47 patients who had received at least one prior therapy for MM.
Based on the results of adaptive Bayesian logistic model integrated with information from clinical assessment of the toxicity profiles observed, the dose of PAN 20 mg + BTZ 1.3 mg/m2 was considered as MTD. In the 3 times weekly, two weeks on/one week off schedule, PAN 20 mg + BTZ 1.3 mg/m2 + DEX 20 mg was considered as the recommended dose.
[Source: LBH589B2207 Clinical Study Report]

8. Safety

Adam George, PharmD conducted the safety review for the panobinostat NDA. The safety review was primarily based upon the data from trial D2308 with supportive data provided from B2207 and DUS71.

Dr. George's review conclusion was that he recommended against the approval of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. He concluded that 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. He also recommended 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. [Source: Clinical Safety Review by Adam George, PharmD]

Dr. George recommended the following PMRs:

- 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.

A summary of his review conclusions is provided below:

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 Dr. George's review for further discussion.

Relevant Class Effects
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.

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 application 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.

<u>Deaths in Trial D2308</u>

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 14*).*

Table 15 Deaths within 28 days of last panobinostat 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

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. Detailed descriptions of the deaths on study can be located in Section 7.3.1 of Dr. George's review.

Table 16 Serious Adverse Events 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.

*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 15*).*

Table 17 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 16*).*

Severe Adverse Reactions

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.

Common Adverse Events

*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 (*Table 17*). 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 18 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.

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 more 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. Details of the laboratory abnormalities can be found in Tables 31 and 32 in Dr. George's review.

I concur with Dr. George's conclusion that the laboratory adverse events are consistent with the fact that panobinostat is associated with severe vomiting, diarrhea, and dehydration.

Risk conclusion [Source: Adam George, Safety Review]
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.

I agree with Dr. George's conclusion that 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. However, with adequate communications in place to prescribers, the risks may be tolerable.

Submission Specific Primary Safety Concerns with Panobinostat

Gastrointestinal Toxicity-*Severe gastrointestinal toxicity manifesting as nausea, vomiting, and diarrhea occurred more frequently in the panobinostat arm than the placebo arm. The addition of panobinostat to bortezomib and dexamethasone increased the rate of all grade diarrhea by 27% and the grade ≥ grade 3 by 17%. The addition of panobinostat to bortezomib and dexamethasone increased the rate of all grade nausea by 15% and the grade ≥ grade 3 by 4%. The addition of panobinostat to bortezomib and dexamethasone increased the rate of all grade vomiting by 13% and the grade ≥ grade 3 by 6%. Diarrhea and vomiting may lead to electrolyte abnormalities which may lead to ECG changes and cardiac arrhythmias.*

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. 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. In trial D2308 management of diarrhea included instructing patients to initiate loperamide at the first episode of poorly formed or loose 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). There was no clinically relevant difference in the events of colitis or ileus in the D2308 trial arms. I agree with Dr. George's conclusion that the need for adequate management of gastrointestinal toxicity should be clearly communicated in labeling.

Cytopenias-

Thrombocytopenia: The addition of panobinostat to bortezomib and dexamethasone increased the rate of grade ≥ 3 thrombocytopenia by 27%. Severe thrombocytopenia is of clinical concern as it because it increases the risk of bleeding and may lead to 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. Additionally, 31% of patients in the panobinostat arm required dose modification/interruption due to thrombocytopenia compared to 11% of patients in the placebo arm. 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. There was no clinically meaningful difference between arms in the time to onset of grade ≥3 thrombocytopenia.

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. The addition of panobinostat to bortezomib and dexamethasone increased the rate of severe neutropenia (grade 3-4) by 16%. 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 than the placebo arm (13% vs. 4%). Pancytopenia was rare and not different between arms (1% vs. <1%). There was no clinically relevant difference between the two arms in incidence of all grade infections. There was a modest increase in severe (grade ≥3) infections with the addition of panobinostat to bortezomib and dexamethasone (from 24% to 31%). The rate of deaths due to infection were similar between arms (3% for panobinostat vs. 2% for placebo).

Cardiac Toxicity-

Ischemia: 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, three patients in the panobinostat arm died due to cardiac ischemia and none in the placebo arm. All grade ischemic events were increased by 3% by the addition of panobinostat to bortezomib and dexamethasone in trial D2308. The difference of severe (grade 3-4) ischemic events was minimal (2% for panobinostat vs. <1% for placebo).

ECG Changes: 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. Though the clinical study report states that "none of the patients who received panobinostat in trial D2308 had a QT interval of 500 ms or more", a review of the ECG2 raw dataset identified a patient who received panobinostat (0900_00002) had a QTc interval measured at >500 ms at cycle 1 day 5. There was also a single case of *Torsades de pointes* in trial A2101 (intravenous formulation of panobinostat) dosed at 20 mg/m^2 continuously on a daily basis. Exposures with this dosing regimen are much higher than in Trial D2308. The QT-IRT reviewer stated that "the sponsor's exposure-QTc analysis is not reliable because the QT prolongation is dose but not concentration dependent".

The addition of panobinostat to bortezomib and dexamethasone increased the rate of ST segment depression by 18%, any T-wave abnormalities by 28%, flat T-waves by 20%, and inverted T-waves by 7%.

Arrhythmias: The addition of panobinostat to bortezomib and dexamethasone increased the rate of PVCs by 4% and sinus tachycardia by 9%.

Asthenic conditions- The addition of panobinostat to bortezomib and dexamethasone in Trial D2308 produced a 12% increase in the all grade asthenic conditions and an 11% increase in the grade ≥3. Asthenic conditions lead to treatment discontinuation in 6% of patients in the panobinostat arm compared with 3% in the placebo arm. Asthenic conditions can negatively impact patient quality of life and physical function.

Dr. Gormley conducted additional safety analyses on the main ITT population. Her summary of ECG changes is as follows:
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.

Safety Evaluation of Subpopulation:

Dr. Nicole Gormley conducted the safety analysis of the pre-specified subgroup of patients. 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.).

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 (Table 18).

Table 19 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

Serious adverse events that were more frequently reported (2% or more difference) in the panobinostat arm were thrombocytopenia, anemia, diarrhea, nausea, vomiting, asthenia/fatigue, pneumonia, gastroenteritis, and renal failure. Table 19 below presents the SAEs in the subgroup population.

Table 20 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

Common Adverse Reactions in the Subgroup

Adverse reactions that occurred in ≥10% of patients with a ≥ 5% incidence in the panobinostat arm compared to the placebo arm are shown in Table 20. 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 21 Adverse reactions 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

9. Advisory Committee Meeting

The Oncologic Drugs Advisory Committee was convened on November 6, 2014.

In planning for the AC meeting, contact was attempted or made with over 20 physicians with expertise in the care of patients with Multiple Myeloma but none were able to be seated on the committee for the meeting for the following reasons:

- No response to communication from FDA
- Not available on meeting date
- Not responsive to contacts from Advisor's and Consultants staff after original contact with review division

- Conflict of interest
    - Investigator on D2308
    - Financial conflict of interest
    - Investigator on competing trial, another panobinostat trial, or another Novartis trial

The FDA reviewers presented the Agency's concerns regarding the results of Trial D2308, specifically with regards to the lack of reliability of the PFS results because of the use of non-protocol specified techniques for measuring M-protein in 25% of the patients as well as the excess toxicity experienced by the patients in the panobinostat arm.

There were five speakers during the open public hearing portion of the meeting.

The following question was posed to the Advisory Committee:

Question to the Committee:
Trial 2308 is a randomized, placebo-controlled, double-blinded trial, with an add-on treatment design using bortezomib and dexamethasone as backbone therapy. 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.

1. **VOTE:** Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

   Vote Result: Yes: 2 No: 5 Abstain: 0

   Committee Discussion: *The majority of the committee voted "no." 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: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.*
   Those committee members who voted "yes" described a judgment that the demonstrated magnitude of improvement in PFS was sufficient to support a positive benefit:risk profile for the use of panobinostat in this complex and challenging population of patients.

10. Pediatrics

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).

11. Other Relevant Regulatory Issues

Consults:

OSE/DRISK: Suzanne Robottom—"DRISK defers a recommendation on a risk management approach pending further discussions with DHP regarding the risk benefit of this product and after the ODAC meeting". The REMS is still in development at the time of finalization of this review.

Office of Scientific Investigations (Anthony Orencia)-- A single adequate and well-controlled clinical trial was submitted in support of the applicant's NDA. A single domestic and a single foreign clinical study site were selected for audit, since these sites represented the largest enrolling sites. Clinical trial sites # 561 (Robert Schlossman, MD at Dana Farber Cancer Institute) and #262 (Vania Hungria, MD at Irmandade da Santa Casa de Misericordia de Sao Paulo in Sao Paulo, Brazil) were inspected on June 18-24, 2014 and July 28-August 1, 2014, respectively. An inspection of the Sponsor (Novartis Pharmaceuticals in East Hanover, NJ) was also conducted from July 15-August 5, 2014. Site # 561 was given a NAI classification, indicating that there were no deviation from regulations and the data is acceptable. Site #262 and the Sponsor's site were given a VAI classification meaning that there were noted deviations from the regulations, but the data is acceptable. One sub-investigator was dismissed from participation in the study because an SAE in a hospitalized patient was not reported. Novartis was notified and they monitored the site more closely and provided retraining. There were apparently data discrepancies between source documents and case report forms reported to Novartis. Novartis unlocked the database and made changes to the raw data to correct some details of safety reporting and a single instance of M-protein electrophoresis results that had not previously been reported in CRFs was added to the database.

OSI reviewer comments:
As far as drug safety assessment is concerned, the recently identified discrepancies in AE reporting appear to be minor. Adverse event information has been conveyed by the site to the sponsor who has reportedly updated the database and provided the adverse events report to FDA. The DHP review team concurs with OSI.

12. Labeling

Proprietary name: FARYDAK

The following are recommendations from the review team 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 reactions for cytopenias and blood chemistries.

I concur with their recommendations.

13. Recommendations/Risk Benefit Assessment

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.

- Recommended Regulatory Action

Accelerated approval in a more limited indication than proposed by the Applicant, is recommended. I concur with the primary clinical review team that panobinostat should receive approval under Subpart H (21 CFR314.510), 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 and are bortezomib sensitive. Accelerated approval is based on the finding of prolonged progression-free survival and an acceptable safety profile in a subgroup population of patients from Trial D2308. Confirmation of clinical benefit is required.

Section 505-1 of the Food Drug and Cosmetic Act (FDCA) authorizes FDA to require NDA applicants to submit a proposed REMS as part of such application if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug. The review team has concluded that a communication plan REMS is necessary to ensure that the benefits of panobinostat outweigh the risks of severe diarrhea and cardiac toxicities.

Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of Evidence:** Relapsed or refractory multiple myeloma is a malignant condition of plasma cells that leads to a monoclonal gammopathy. An estimated 24,000 new cases of MM will occur in the U. S. in 2014 with an estimated 11,000 deaths. The proliferation of clonal plasma cells in the bone marrow leads to high levels of circulating monoclonal-M-immunoglobulin (referred to as "M-protein"). The diagnosis is most common in the 6th and 7th decades of life and approximately 75% of patients are over 70 years of age. The clinical	**Conclusions (implications for decision):** Relapsed or refractory multiple myeloma is a serious, incurable condition that leads to death if untreated and when the disease fails to respond to the available therapies.

	manifestations of MM include hypercalcemia, renal dysfunction, anemia, and bone lytic lesions. Patients who have relapsed or failed to respond to both bortezomib and the immunomodulatory drugs prognosis is particularly poor, with a median overall survival (OS) of only 9 months, regardless of salvage regimen (Kumar SK, 2012)	
Unmet Medical Need	**Summary of Evidence:** There are no available therapies for patients who have received at least two prior regimens that included bortezomib and an immunomodulatory agent. This is an area of unmet medical need. Kyprolis and Pomalyst have third line indications, but they both remain under accelerated approval and not considered as available therapies.	**Conclusions (implications for decision):** Patients who have received at least 2 prior regimens that included bortezomib and an immunomodulatory agent have no available therapies.
Clinical Benefit	**Summary of Evidence:** Trial D2308 was a Randomized, blinded, placebo-controlled trial that randomized 768 patients with relapsed or refractory MM to receive bortezomib with dexamethasone and panobinostat (or placebo). The trial design was agreeable to the Agency as it isolated the treatment effect of panobinostat and utilized a blinded placebo control. The primary endpoint was Progression Free Survival (PFS) which was acceptable to the Agency and has been utilized by other Applicants to obtain MM indications. During discussions with the Applicant about the trial, the Agency recommended the use of centralized, blinded review of PFS but the Sponsor disagreed because they claimed that since the endpoint was based upon objective laboratory values, this was not needed. For the overall ITT population, the hazard ratio was 0.63 (mPFS was 12 mos for the panobinostat arm and 8.1 mos. for placebo arm). A four month improvement in PFS would be considered an acceptable improvement, if there had not been so many protocol violations (specifically on the assessment of the primary endpoint) and the safety profile had been more tolerable with less severe and fatal adverse reactions. There was excessive censoring of	**Conclusions (implications for decision):** Clinical benefit has not been established for panobinostat in combination with bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. There was uncertainty in trial D2308 with regard to the magnitude of improvement in PFS because of the protocol violations and missing data. The review team concludes that accelerated approval is recommended for the indication of: "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

	the PFS data. The results of subgroups were robust in several sensitivity analyses. There were trial conduct issues that led to some uncertainties with regards to the magnitude of the treatment effect because 25% of patients had myeloma protein measurements conducted using a non-protocol approved methodology. This was the major source of protocol violations. Trial D2308 may have been considered acceptable if the primary endpoint had been evaluated by the protocol-specified methods and the safety profile was more tolerable. The secondary endpoints included overall survival, overall response rate, and median duration of response. The interim analysis of 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. The 6% improvement in ORR demonstrates a very modest improvement over placebo. For the pre-specified subset that the review team agreed to grant an indication for, the Hazard Ratio for PFS was 0.56 for a 4.8 month improvement in median PFS between arms for panobinostat. 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.	immunomodulatory agent". Accelerated approval requires confirmation of benefit through a confirmatory trial.
Risk	**Summary of Evidence:** From the 758 patients (ITT population) 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	**Conclusions (implications for decision):** The safety profile for panobinostat in combination with bortezomib and dexamethasone appears acceptable for a more heavily pretreated population of patients with multiple myeloma than the Applicant originally proposed, as long

	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. The safety profile for panobinostat appears acceptable for a more heavily pretreated population of patients with multiple myeloma than the Applicant originally proposed, as long as the risks are adequately communicated in labeling and through a Risk Evaluation and Mitigation Strategy. The risks that are recommended for enhanced communication are severe diarrhea and cardiac toxicities (ischemia, arrhythmias, and ECG changes).	as the risks are adequately communicated in labeling and through a Risk Evaluation and Mitigation Strategy.
Risk Management	**Summary of Evidence:** Community oncologists are accustomed to managing the toxicities of cytotoxic chemotherapeutic agents. These therapies typically induce cytopenias and nausea/vomiting. The potential cardiac and diarrhea risks may not be anticipated by community oncologists unless clearly communicated. A communication plan REMS is necessary to ensure that the benefits of panobinostat outweigh the risks for the approved indication. The communication should include a clear description of the risks and the recommendations of the steps that should be taken to monitor for and mitigate the risks.	**Conclusions (implications for decision):** The applicant should develop a communication plan Risk Evaluation and Mitigation Strategy (REMS) to inform healthcare professionals about the risks of cardiac events (ischemia, EKG changes and arrhythmias) and diarrhea in patients taking panobinostat as well as mitigation factors that should be in place.

- Recommendation for other Postmarketing Requirements and Commitments

The Applicant is required to conduct a confirmatory trial in a Multiple Myeloma population because Trial D2308 was not well-conducted. Because of the questions that remain about the correct dose of panobinostat in combination with bortezomib and dexamethasone, the Applicant should conduct a dose-finding trial that evaluates the 20 mg dose and a lower dose (possibly 15 mg) prior to initiating the confirmatory trial. In order to enhance enrollment, this trial should be conducted in a slightly different population than for which the indication is being granted and conducted internationally. The Applicant should conduct efficacy analyses centrally to avoid the risk of protocol violations on the primary endpoint (as occurred in Trial D2308). The Post-Marketing requirement trials are under negotiation at the time of this review finalization. On 1/20/15 the Agency sent the revised version (below) of the PMRs (with a preamble to explain our edits) to Novartis 01/20/15. On 1/21/15, we held a

teleconference with Novartis to discuss the revised PMRs and preamble. During this meeting Novartis stated that they agreed to the FDA proposal (above) for PMR-1 to expand the sample size and perform an interim analysis for the phase 2 study evaluating 15 mg vs 20 mg panobinostat which will now be a global study. Novartis proposed (b) (4) The Agency initially agreed but then after internal discussion expressed concern that the (b) (4) , so that ORR is the preferred endpoint (b) (4) . Novartis agreed on use of ORR as the primary endpoint. FDA informed Novartis that they should be sure to enroll an adequate number of US patients so that the results will be applicable to a US population. Novartis agreed to provide further details on expected percentage of US patients within the trial at the time of preliminary protocol submission).

Novartis agreed to the two PMRs (as written below) but requested the opportunity to revise the milestone dates because the trials will now be run sequentially. The Agency and Novartis agreed that Novartis can get these revised dates back to us this Friday, January 23 at 10am. (b) (4) The Agency stated that they would entertain such a change in the future with adequate justification for the rationale.

Preamble to Novartis:

- The Division is concerned that you plan to proceed with the Phase 3 confirmatory trial (we will call PMR-2) concurrently with your proposed Phase 2 dose-finding trial [we will call PMR-1].
- We believe that you will need at least interim efficacy/safety data from PMR-1 before beginning enrollment in PMR-2.
- We are also concerned that the proposed US dose-finding trial, [PMR-1] is underpowered (at (b) (4) patients) to result in the identification of a safe and effective dose for the Phase 3 confirmatory trial [PMR-2]. We would like to recommend that you increase the sample size of PMR-1. To accomplish this, you can consider making it an international trial (open enough US sites to gain some experience in US patients).
- If you increase the sample size of PMR-1 and wait for interim results before starting PMR-2, you could conduct PMR-2 with only one treatment arm and one control arm, because you should already know the optimal dose of the combination of panobinostat + subcutaneous bortezomib and dexamethasone.

PMR #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 once weekly 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 all treatment arms according to IMWG criteria by investigator assessment. The results of this trial will be used to

inform the dose selection for the confirmatory Phase 3 trial. Submit a final study report with full datasets.

PMR Schedule Milestones:
Preliminary Protocol Submission to Include SAP: April 2015
Final Protocol Submission: September 2015
First Patient Enrolled: December 2015
50% Trial Accrual: October 2016
Trial Fully Accrued: August 2017
Study/Trial Completion: August 2018
Final Report Submission: August 2019

PMR #2
Conduct a multicenter, randomized, three-arm, placebo-controlled phase 3 trial of two different
doses of panobinostat to placebo in combination with subcutaneous bortezomib and dexamethasone in
patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The panobinostat dose selection will be based upon at least preliminary results from the trial described in PMR-1. Eligible patients will have previously treated multiple myeloma,
1-3 prior lines of therapy, prior immunomodulatory agent exposure (either thalidomide, lenalidomide, or pomalidomide), and measurable disease.

PMR Schedule Milestones:
Preliminary Protocol Submission to Include SAP Apr 2015
Final Protocol Submission Sep 2015
First Patient Enrolled Dec 2015
50% Trial Accrual June 2017
Trial Fully Accrued Mar 2018
Study/Trial Completion Feb 2020
Final Report Submission Dec 2020

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/s/

VIRGINIA E KWITKOWSKI
01/25/2015