CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205353Orig1s000

<u>CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)</u>

OFFICE OF CLINICAL PHARMACOLOGY
REVIEW ADDENDUM

NDA: 205353	**Submission Date:** 3/24/14 (SDN #1)
Brand Name:	FARYDAK®
Generic Name:	Panobinostat
Clinical Pharmacology (CP) Reviewers:	Joseph Grillo, Pharm.D.
CP Team Leader (TL):	Bahru Habtemariam, Pharm.D.
Pharmacometrics (PM) Reviewer:	Lian Ma, Ph.D.
PM TL:	Nitin Mehrotra, Ph.D.
OCP Division:	DCP-V and DPM
ORM division:	CDER/OND/OHOP/DHP
Sponsor:	Novartis Pharmaceuticals Corporation
Relevant IND	069862
Submission Type; Code:	NME Original NDA (Priority Review)
Formulation; Strength(s):	10 mg, 15 mg, or 20 mg hard gelatin capsules
Indication:	FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 2 prior therapies.

Background

The applicant provided the benefit risk analysis of a subset of the phase 3 patients who had received prior treatment with both bortezomib (BTZ) and an immunomodulatory agent. We have not received any new clinical pharmacology data or conducted any new analysis of the data related to the subset of the phase 3 population. We defer the recommendation of approvability of this application to the clinical review team. See CDTL review by Dr. Virginia Kwitkowski for more details. The objective of this addendum is to provide the justifications for the post-marketing dose finding and the confirmatory clinical trials.

After the completion of our review, the review timeline was extended by the Agency for further analysis of the phase 3 data. During the extended review period, additional clinical pharmacology evaluations were considered in order to determine panobinostat (PAN) dosing regimens for postmarking dose-optimization trial. This addendum is a repository of these evaluations and analyses that were not included in the original clinical pharmacology review of

1

panobinostat. Please refer to the original clinical pharmacology review by Dr. Joseph Grillo in DAARTs dated September 26 of 2014, for other details. OCP's recommendations for the dose finding PMR are also included in this addendum.
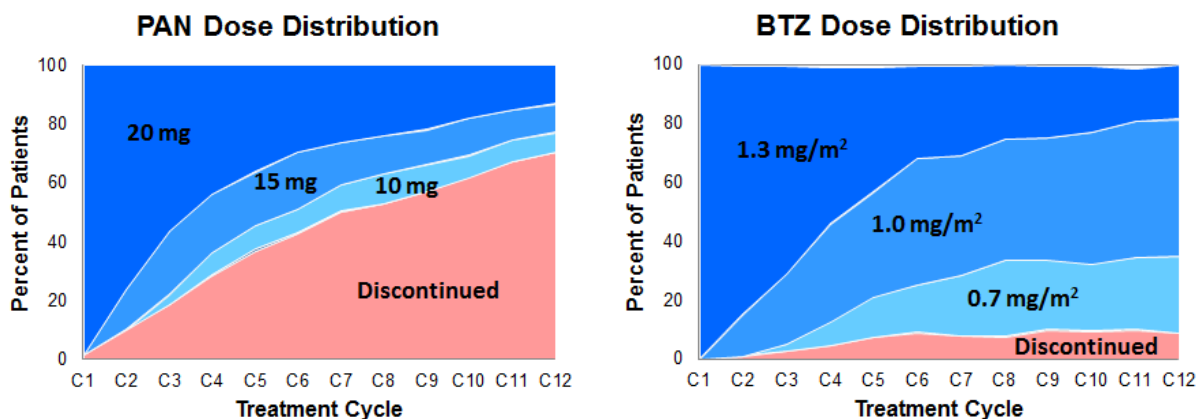
Executive Summary

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.

1 Dose distribution in Trial 2308

Based on the actual dosing data from individual patients in trial 2308, dose distribution plots was generated separately for panobinostat (PAN) and bortezomab (BTZ) to show the magnitude of dose reduction and drug discontinuations over time. As seen in **Figure 1**, the proportion of patients who stayed on the starting dose continuously declined over time for both PAN and BTZ. With the option of dose reduction to 1 or 0.7 mg/m^2, 90% of patients continued BTZ treatment throughout the 12 cycle trial period. In contrast, PAN dose reductions to 15 or 10 mg did not seem to address tolerability since 70% of patients discontinued PAN treatment by Cycle 12. The high rate of PAN treatment discontinuations, even after dose reduction, appears to show the dosing interval maybe contributing to the tolerability issues. These data indicate alternative dose schedule may help to address PAN tolerability issues and should be evaluated in a post marketing dose optimization study.

Figure 1. Percent of patients on Panobinostat and Bortezomab dose levels in Trial 2308
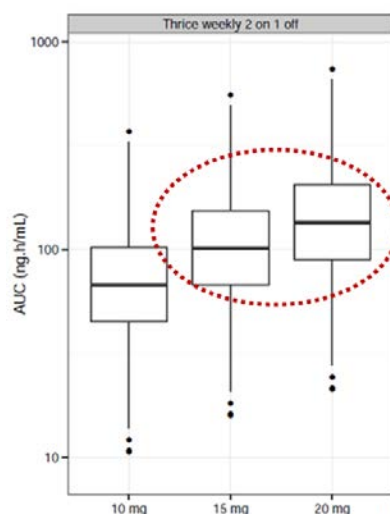

2 Simulation for alternative dosing regimens

Upon request from the OCP, the sponsor conducted simulations for PK and platelet count profiles for the following single agent PAN regimens. The intention of requesting the simulations was to explore the doses/regimens that could be evaluated in the dose finding PMR (see section 3 below):

1. 20 mg three times per week (currently proposed dosing schedule)
2. 15 mg three times per week (currently proposed dosing schedule)
3. 10 mg three times per week (currently proposed dosing schedule)
4. 20 mg weekly
5. 15 mg weekly
6. 10 mg weekly

The simulation results in **Figure 2** indicated that the steady state AUC of PAN 15 and 20 mg with the currently proposed dosing schedule (thrice a week/2 on 1 off) was substantially overlapping. Therefore, due to high PK variability, doses of 15 and 20 mg will likely not provide useful information and thus may not be informative in differentiating efficacy or safety profile of PAN at 15 and 20 mg. There is value in studying a different regimen (for e.g. weekly regimen) since Q3W was not well tolerated in the trial 2308. It is also worth noting that 10 mg Q3W PAN with BTZ 1.3 was not evaluated as part of the clinical development program and could be one of the doses to be explored in the dose finding trial.

Figure 2. Box plots of simulated steady state AUC for 10, 15 and 20 mg PAN doses (thrice a week/2 on 1 off).

3

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Figure 3-2.

Based on the simulated platelet profiles, the grade 3/4 thrombocytopenia (TCP) rates for single agent PAN and combination of PAN+BTZ dosing regiments were also estimated (**Table 1**). Small increases in grade 3/4 TCP rates were associated with dose increments. However, for the same PAN dose, the estimated grade 3/4 TCP rates following weekly dosing were 13-15% lower than the currently proposed schedule.

Table 1. Predicted grade 3/4 thrombocytopenia rates

Regimen	PAN Dose (mg)	PAN Single Agent	PAN + BTZ (1.3 mg/m^2)
Thrice Weekly 2 on 1 off	20	27%	59%
Thrice Weekly 2 on 1 off	15	22%	53%
Thrice Weekly 2 on 1 off	10	16%	47%
Weekly	20	11%	43%
Weekly	15	8%	39%
Weekly	10	4%	36%

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Table 3-1.

3   Recommendations for Postmarketing Requirements

The first PMR's is a dose finding trial while the second PMR is a phase 3 trial. These PMRs should be conducted sequentially (not in parallel) such that results from the dose finding trial informs the dose selection and trial design for the phase 3 trial. These PMRs have been discussed internally with the clinical and biostatistics review team. The actual doses/regimens to be studied in dose-finding PMR will be decided at the protocol submission stage.

4

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.

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. The primary objective will be progression-free survival.

Signatures:

Lian Ma, Ph.D.	Nitin Mehrotra, Ph.D.
Reviewer	Team Leader
Division of Pharmacometrics	Division of Pharmacometrics

Bahru Habtemariam, Pharm.D.	NAM Atiqur Rahman, Ph.D.
Team Leader	Director
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DHP: CSO – **D Hanner**; MTL – **V Kwitkowski**; MO – **N Gormley**; MO – **B Miller**

DCP-5: Reviewer - **J Grillo**; TL – **B Habtemariam**; DD - **A Rahman**; DPM: Reviewer – **L Ma**; PMTL – **N Mehrotra**; DD – **V Sinha**

6

OFFICE OF CLINICAL PHARMACOLOGY
REVIEW ADDENDUM

NDA: 205353	**Submission Date:** 3/24/14 (SDN #1)
Brand Name:	FARYDAK®
Generic Name:	Panobinostat
Clinical Pharmacology (CP) Reviewers:	Joseph Grillo, Pharm.D.
CP Team Leader (TL):	Bahru Habtemariam, Pharm.D.
Pharmacometrics (PM) Reviewer:	Lian Ma, Ph.D.
PM TL:	Nitin Mehrotra, Ph.D.
OCP Division:	DCP-V and DPM
ORM division:	CDER/OND/OHOP/DHP
Sponsor:	Novartis Pharmaceuticals Corporation
Relevant IND	069862
Submission Type; Code:	NME Original NDA (Priority Review)
Formulation; Strength(s):	10 mg, 15 mg, or 20 mg hard gelatin capsules
Indication:	FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 2 prior therapies.

Background

The applicant provided the benefit risk analysis of a subset of the phase 3 patients who had received prior treatment with both bortezomib (BTZ) and an immunomodulatory agent. We have not received any new clinical pharmacology data or conducted any new analysis of the data related to the subset of the phase 3 population. See CDTL review by Dr. Virginia Kwitkowski for more details. The objective of this addendum is to provide the justifications for the post-marketing dose finding and the confirmatory clinical trials.

After the completion of our review, the review timeline was extended by the Agency for further analysis of the phase 3 data. During the extended review period, additional clinical pharmacology evaluations were considered in order to determine panobinostat (PAN) dosing regimens for postmarking dose-optimization trial. This addendum is a repository of these evaluations and analyses that were not included in the original clinical pharmacology review of panobinostat. Please refer to the original clinical pharmacology review by Dr. Joseph Grillo in

1

DAARTs dated September 26 of 2014, for other details. OCP's recommendations for the dose finding PMR are also included in this addendum.
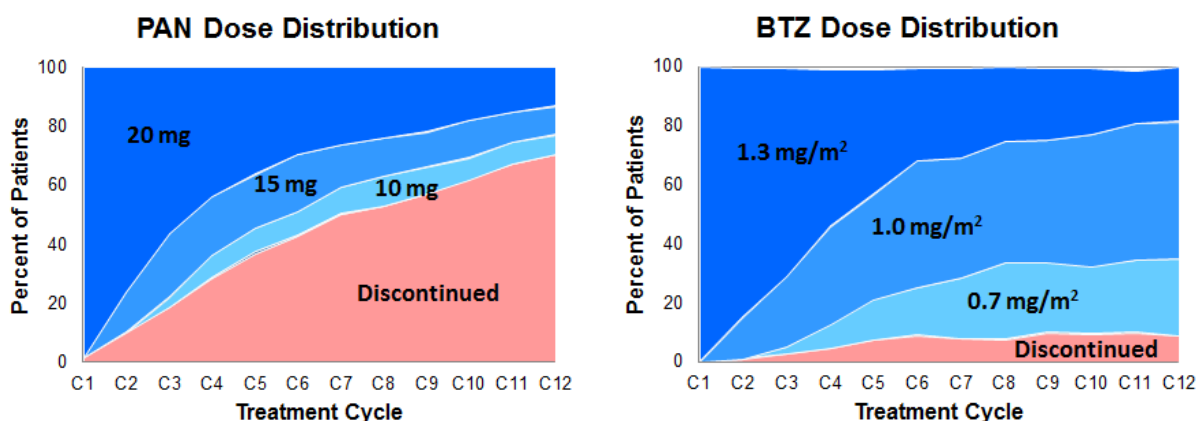

Executive Summary

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.

1   Dose distribution in Trial 2308

Based on the actual dosing data from individual patients in trial 2308, dose distribution plots was generated separately for panobinostat (PAN) and bortezomab (BTZ) to show the magnitude of dose reduction and drug discontinuations over time. As seen in **Figure 1**, the proportion of patients who stayed on the starting dose continuously declined over time for both PAN and BTZ. With the option of dose reduction to 1 or 0.7 mg/m^2, 90% of patients continued BTZ treatment throughout the 12 cycle trial period. In contrast, PAN dose reductions to 15 or 10 mg did not seem to address tolerability since 70% of patients discontinued PAN treatment by Cycle 12. The high rate of PAN treatment discontinuations, even after dose reduction, appears to show the dosing interval maybe contributing to the tolerability issues. These data indicate alternative dose schedule may help to address PAN tolerability issues and should be evaluated in a post marketing dose optimization study.

2

Figure 1. Percent of patients on Panobinostat and Bortezomab dose levels in Trial 2308
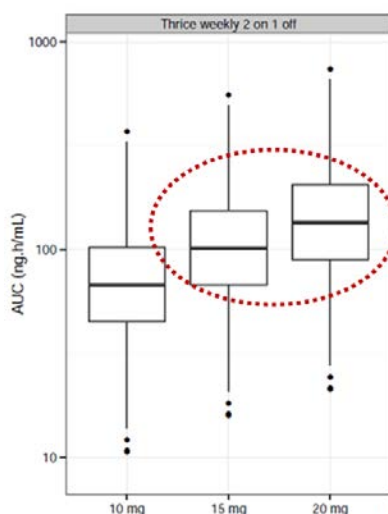

2   Simulation for alternative dosing regimens

Upon request from the OCP, the sponsor conducted simulations for PK and platelet count profiles for the following single agent PAN regimens. The intention of requesting the simulations was to explore the doses/regimens that could be evaluated in the dose finding PMR (see section 3 below):

1. 20 mg three times per week (currently proposed dosing schedule)
2. 15 mg three times per week (currently proposed dosing schedule)
3. 10 mg three times per week (currently proposed dosing schedule)
4. 20 mg weekly
5. 15 mg weekly
6. 10 mg weekly

The simulation results in **Figure 2** indicated that the steady state AUC of PAN 15 and 20 mg with the currently proposed dosing schedule (thrice a week/2 on 1 off) was substantially overlapping. Therefore, due to high PK variability, doses of 15 and 20 mg will likely not provide useful information and thus may not be informative in differentiating efficacy or safety profile of PAN at 15 and 20 mg. There is value in studying a different regimen (for e.g. weekly regimen) since Q3W was not well tolerated in the trial 2308. It is also worth noting that 10 mg Q3W PAN with BTZ 1.3 was not evaluated as part of the clinical development program and could be one of the doses to be explored in the dose finding trial.

Figure 2. Box plots of simulated steady state AUC for 10, 15 and 20 mg PAN doses (thrice a week/2 on 1 off).

3

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Figure 3-2.

Based on the simulated platelet profiles, the grade 3/4 thrombocytopenia (TCP) rates for single agent PAN and combination of PAN+BTZ dosing regiments were also estimated (**Table 1**). Small increases in grade 3/4 TCP rates were associated with dose increments. However, for the same PAN dose, the estimated grade 3/4 TCP rates following weekly dosing were 13-15% lower than the currently proposed schedule.

Table 1. Predicted grade 3/4 thrombocytopenia rates

Regimen	PAN Dose (mg)	PAN Single Agent	PAN + BTZ (1.3 mg/m^2)
Thrice Weekly 2 on 1 off	20	27%	59%
Thrice Weekly 2 on 1 off	15	22%	53%
Thrice Weekly 2 on 1 off	10	16%	47%
Weekly	20	11%	43%
Weekly	15	8%	39%
Weekly	10	4%	36%

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Table 3-1.

3   Recommendations for Postmarketing Requirements

The first PMR's is a dose finding trial while the second PMR is a phase 3 trial. These PMRs should be conducted sequentially (not in parallel) such that results from the dose finding trial informs the dose selection and trial design for the phase 3 trial. These PMRs have been discussed internally with the clinical and biostatistics review team. The actual doses/regimens to be studied in dose-finding PMR will be decided at the protocol submission stage.

4

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.

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. The primary objective will be progression-free survival.

5

Signatures:

Lian Ma, Ph.D.	Nitin Mehrotra, Ph.D.
Reviewer	Team Leader
Division of Pharmacometrics	Division of Pharmacometrics

Bahru Habtemariam, Pharm.D.	NAM Atiqur Rahman, Ph.D.
Team Leader	Director
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DHP: CSO – **D Hanner**; MTL – **V Kwitkowski**; MO – **N Gormley**; MO – **B Miller**
DCP-5: Reviewer - **J Grillo**; TL – **B Habtemariam**; DD - **A Rahman**; DPM:
Reviewer – **L Ma**; PMTL – **N Mehrotra**; DD – **V Sinha**

6

Reference ID: 3691251

OFFICE OF CLINICAL PHARMACOLOGY
REVIEW ADDENDUM

NDA: 205353	**Submission Date:** 3/24/14 (SDN #1)
Brand Name:	FARYDAK®
Generic Name:	Panobinostat
Clinical Pharmacology (CP) Reviewers:	Joseph Grillo, Pharm.D.
CP Team Leader (TL):	Bahru Habtemariam, Pharm.D.
Pharmacometrics (PM) Reviewer:	Lian Ma, Ph.D.
PM TL:	Nitin Mehrotra, Ph.D.
OCP Division:	DCP-V and DPM
ORM division:	CDER/OND/OHOP/DHP
Sponsor:	Novartis Pharmaceuticals Corporation
Relevant IND	069862
Submission Type; Code:	NME Original NDA (Priority Review)
Formulation; Strength(s):	10 mg, 15 mg, or 20 mg hard gelatin capsules
Indication:	FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 2 prior therapies.

Background

After the phase 3 trial failed to demonstrate acceptable benefit risk profile in the overall phase 3 trial population, a subset of the phase 3 population, patients who had received prior treatment with both bortezomib (BTZ) and an immunomodulatory agent, were found to benefit from panobinostat treatment. See CDTL review by Dr. Virginia Kwitkowski for more details.

After the completion of our review, the review timeline was extended by the Agency for further analysis of the phase 3 data. During the extended review period, additional clinical pharmacology evaluations were considered in order to determine panobinostat (PAN) dosing regimens for postmarking dose-optimization trial. This addendum is a repository of these evaluations and analyses that were not included in the original clinical pharmacology review of panobinostat. Please refer to the original clinical pharmacology review by Dr. Joseph Grillo in DAARTs dated September 26 of 2014, for other details. OCP's recommendations for the dose finding PMR are also included in this addendum.
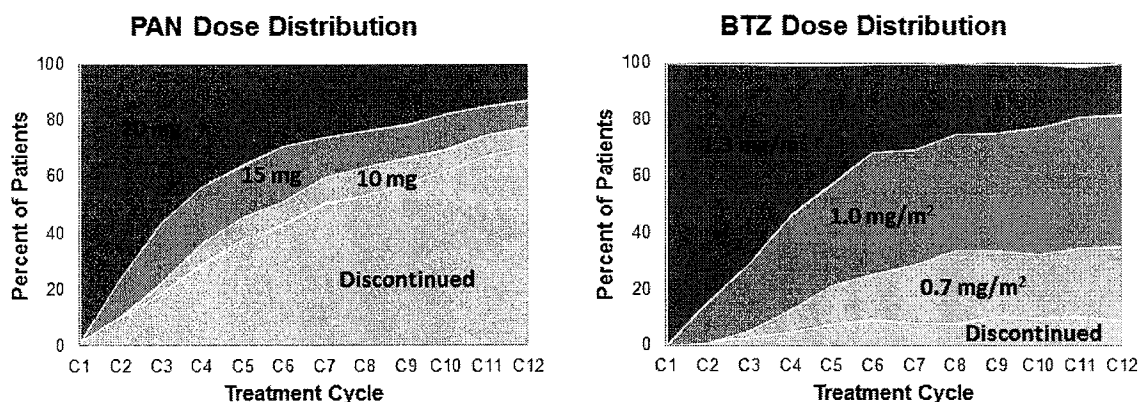
1

Executive Summary

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.

1   Dose distribution in Trial 2308

Based on the actual dosing data from individual patients in trial 2308, dose distribution plots was generated separately for panobinostat (PAN) and bortezomab (BTZ) to show the magnitude of dose reduction and drug discontinuations over time. As seen in **Figure 1**, the proportion of patients who stayed on the starting dose continuously declined over time for both PAN and BTZ. With the option of dose reduction to 1 or 0.7 mg/m^2, 90% of patients continued BTZ treatment throughout the 12 cycle trial period. In contrast, PAN dose reductions to 15 or 10 mg did not seem to address tolerability since 70% of patients discontinued PAN treatment by Cycle 12. The high rate of PAN treatment discontinuations, even after dose reduction, appears to show the dosing interval maybe contributing to the tolerability issues. These data indicate alternative dose schedule may help to address PAN tolerability issues and should be evaluated in a post marketing dose optimization study.

Figure 1. Percent of patients on Panobinostat and Bortezomab dose levels in Trial 2308

2

PAN Dose Distribution
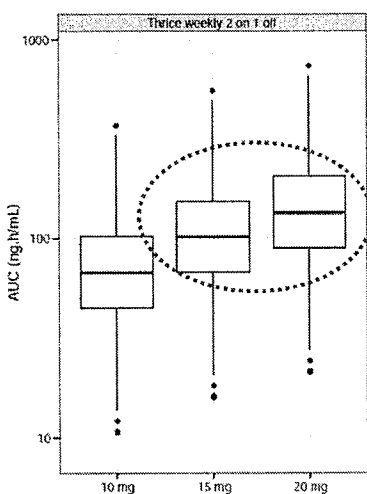
BTZ Dose Distribution

2   Simulation for alternative dosing regimens

Upon request from the OCP, the sponsor conducted simulations for PK and platelet count profiles for the following single agent PAN regimens. The intention of requesting the simulations was to explore the doses/regimens that could be evaluated in the dose finding PMR (see section 3 below):

1. 20 mg three times per week (currently proposed dosing schedule)
2. 15 mg three times per week (currently proposed dosing schedule)
3. 10 mg three times per week (currently proposed dosing schedule)
4. 20 mg weekly
5. 15 mg weekly
6. 10 mg weekly

The simulation results in **Figure 2** indicated that the steady state AUC of PAN 15 and 20 mg with the currently proposed dosing schedule (thrice a week/2 on 1 off) was substantially overlapping. Therefore, due to high PK variability, doses of 15 and 20 mg will likely not provide useful information and thus may not be informative in differentiating efficacy or safety profile of PAN at 15 and 20 mg. There is value in studying a different regimen (for e.g. weekly regimen) since Q3W was not well tolerated in the trial 2308. It is also worth noting that 10 mg Q3W PAN with BTZ 1.3 was not evaluated as part of the clinical development program and could be one of the doses to be explored in the dose finding trial.

Figure 2. Box plots of simulated steady state AUC for 10, 15 and 20 mg PAN doses (thrice a week/2 on 1 off).

3

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Figure 3-2.

Based on the simulated platelet profiles, the grade 3/4 thrombocytopenia (TCP) rates for single agent PAN and combination of PAN+BTZ dosing regiments were also estimated (**Table 1**). Small increases in grade 3/4 TCP rates were associated with dose increments. However, for the same PAN dose, the estimated grade 3/4 TCP rates following weekly dosing were 13-15% lower than the currently proposed schedule.

Table 1. Predicted grade 3/4 thrombocytopenia rates

Regimen	PAN Dose (mg)	PAN Single Agent	PAN + BTZ (1.3 mg/m^2)
Thrice Weekly 2 on 1 off	20	27%	59%
Thrice Weekly 2 on 1 off	15	22%	53%
Thrice Weekly 2 on 1 off	10	16%	47%
Weekly	20	11%	43%
Weekly	15	8%	39%
Weekly	10	4%	36%

Source: Sponsor's Response to FDA Information Request (IR-45), December 12, 2014. Table 3-1.

3 Recommendations for Postmarketing Requirements

The first PMR's is a dose finding trial while the second PMR is a phase 3 trial. These PMRs should be conducted sequentially (not in parallel) such that results from the dose finding trial informs the dose selection and trial design for the phase 3 trial. These PMRs have been discussed internally with the clinical and biostatistics review team. The actual doses/regimens to be studied in dose-finding PMR will be decided at the protocol submission stage.

4

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.

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. The primary objective will be progression-free survival.

5

Reference ID: 3689704
Reference ID: 3709088

Signatures:

Lian Ma, Ph.D.	Nitin Mehrotra, Ph.D.
Reviewer	Team Leader
Division of Pharmacometrics	Division of Pharmacometrics

Bahru Habtemariam, Pharm.D.	NAM Atiqur Rahman, Ph.D.
Team Leader	Director
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DHP: CSO – **D Hanner**; MTL – **V Kwitkowski**; MO – **N Gormley**; MO – **B Miller**
DCP-5: Reviewer - **J Grillo**; TL – **B Habtemariam**; DD - **A Rahman**; DPM:
Reviewer – **L Ma**; PMTL – **N Mehrotra**; DD – **V Sinha**

6

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIAN MA
01/20/2015

NITIN MEHROTRA
01/20/2015

BAHRU A HABTEMARIAM
01/20/2015

NAM ATIQUR RAHMAN
01/20/2015
I agree with the recommendation.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	205353	**Submission Date:**	3/24/14 (SDN #1)
Brand Name:		FARYDAK®	
Generic Name:		Panobinostat	
Clinical Pharmacology (CP) Reviewers:		Joseph Grillo, Pharm.D. (primary) Sarah Dorff, Ph.D. (in vitro study review)	
CP Team Leader (TL) [Acting]:		Bahru Habtemariam, Pharm.D.	
Pharmacometrics (PM) Reviewer:		Lian Ma, Ph.D.	
PM TL:		Nitin Mehrotra, Ph.D.	
PBPK Reviewer:		Ping Zhao, Ph.D.	
OCP Division:		DCP-V and DPM	
ORM division:		CDER/OND/OHOP/DHP	
Sponsor:		Novartis Pharmaceuticals Corporation	
Relevant IND		069862	
Submission Type; Code:		NME Original NDA (Priority Review)	
Formulation; Strength(s):		10 mg, 15 mg, or 20 mg hard gelatin capsules	
Indication:		FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.	

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

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/m^2) 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 regiment (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 AUC_{0-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 AUC_{0-48} 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.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has determined the sponsor has not identified 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.

Decision	Acceptable to OCP?			Comment
	Yes	No	NA	
Overall	☐	☒	☐	The proposed dosing regimen is not acceptable.
Evidence of Effectiveness†	☒	☐	☐	1 positive registration trial. Dose-response supportive.
Proposed dose for general population	☐	☒	☐	The proposed dosing regimen is not acceptable due to safety concerns including excessive rates of serious AE, AE related treatment discontinuation, and AE related hospitalization.
Proposed dose selection for others	☐	☒	☐	Since there is no reference dose for the general population, we cannot recommend doses for special populations and for concomitant CYP3A4 inhibitor uses.
Pivotal BE	☒	☐	☐	The FMI formulation was used for the pivotal phase III trial D2308
Labeling	☒	☐	☐	Pending satisfactory agreement with applicant

†This decision is from a clinical pharmacology perspective only. The overall safety and effectiveness determination is made by the Clinical reviewer.
FMI = Final Market Image

1.2 Post Marketing Requirements

None

1.3 Post Marketing Commitments

None

1.4 Comments to the Applicant

1.4.1

1.4.2 Consider evaluating the impact of UGT inhibition on panobinostat and BJB432 and the potential for panobinostat to inhibit UGT in vitro.

1.4.3 If you intend to develop panobinostat for use in populations where hepatico-jejunostomy is common (e.g., pancreatic cancer) you should further evaluate the impact of this procedure on panobinostat exposure given a patient in your ADME trial B2108 with a history of this procedure had a substantial discrepancy in panobinostat parent and metabolite elimination.

1.5 Summary of Important Clinical Pharmacology Findings

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. In vitro, PAN caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy. It is formulated as a hard gelatin capsule containing 10 mg, 15 mg, or 20 mg of PAN free base. The OCP review team has determined that the proposed dosing regimen is not acceptable. Based on information provided by the applicant, the OCP review team is also not able to recommend an a potentially acceptable dosing regimen. Therefore, the OCP review team finds the proposed dosing regimen unacceptable and cannot recommend approval of the NDA.

The proposed dosing regimen is based on the MTD (20 mg PAN TIW and 1.3 mg/m^2 bortezomib (BTZ)). The dosing schedule (2 weeks on/ 1 week off) was introduced to manage thrombocytopenia and to allow for accelerated platelet recovery. The applicant did not provide an analysis of exposure response or exposure safety for the proposed combination therapy PAN+BTZ+ dexamethasone (DEX). A visual analysis of the best overall response (Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR) or Stringent Complete Response (sCR)) following PAN+BTZ therapy suggests a trend toward increased response with increased dose. However, this analysis also showed a trend toward increased serious adverse events (SAEs) and an increased rate of AE related drug discontinuation with increased dose. At the proposed dose, 94% of patients experienced Grade 3/4 AEs, 77% of patients had dose interruptions or modifications, and 59% of patients were hospitalized due to AEs.

The safety and efficacy of FARYDAK is based primarily on a multicenter, randomized, double-blind, placebo (PBO) controlled phase 3 trial (D2308) of PAN in combination with BTZ and DEX in patients with relapsed multiple myeloma. A total of 768 patients were enrolled and randomized to receive PAN+BTZ+DEX (n=387 patients) or PBO+BTZ+DEX (n=381 patients). Progression-free survival (PFS), using modified European Bone Marrow Transplant Group (EBMT) criteria, was assessed by the investigators as the primary

endpoint. PFS was statistically significantly different between the treatment arms (HR: 0.63 [0.52, 0.76]) in favor of the PAN+BTZ+DEX arm. Median PFS was prolonged by 3.9 months (from 8.1 months to 12.0 months) with the addition of PAN to BTZ+DEX. Similarly, in the phase 3 trial D2308, high toxicity was observed in PAN+BTZ+DEX arm as compared to PBO+BTZ+DEX arm. The rate of adverse reactions leading to dose modification or interruption was 89% with PAN versus 76% with PBO respectively. Treatment discontinuation rates due to AEs were 36% in patients treated with PAN compared to 20% in the PBO arm. Death rate was also higher in PAN treated patients (8% versus 5%). Kaplan-Meier Curves of time to AEs also showed that the occurrences of severe event were earlier in PAN+BTZ+DEX group compared to the PBO+BTZ+DEX group. A time to event analysis of AEs by DI quartiles showed a trend across all safety endpoints (thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia) suggesting possible relationship between AEs and higher PAN DI. An increasing risk of thrombocytopenia (all grades and grade 3/4) with increasing PAN DI was identified based on Cox proportional hazards model.

During development, administration of PAN by intravenous and oral routes caused a dose-related increase in the QT interval. There was one case of TdP with the 20 mg/m^2 consecutive intravenous dosing regimen which has been discontinued. In the current NDA submission, the incidence of grade 3 QTc prolongation (QTcF > 500 ms) with intermittent dosing is about 1% with the highest frequency of <5% seen in patients treated with the 60-mg oral dose. The effect of PAN on QT appears to occur hours after Tmax of the parent drug, so the effect is probably not dependent on the concentration of the parent drug. The FDA Interdisciplinary Review Team (QT-IRT) for QT Studies reviewed this information and found that the labeling language related to the QT risk appeared to be adequate in mitigating risk after FARYDAK is approved to be marketed with minor edits.

Using a population based approach PAN PK was characterized by a 3-compartment model with data from 581 patients across 14 phase 1/2 studies in solid tumors or hematological malignancies receiving oral or intravenous administration of PAN. Body surface area at baseline, age and race were statistically significant covariates on the clearance and central volume of distribution. However, the extent of these covariate effects were small as compared to the large (~65%) inter-individual variability of PAN and were not deemed sufficient to require a dosing modification.

The absolute oral bioavailability of FARYDAK is approximately 21%. Peak concentrations of PAN are observed within 2 hours (Tmax) of oral administration in patients with advanced cancer. FARYDAK exhibits an approximately dose proportional increase in both C_{max} and AUC over the dosing range. When given with food, plasma PAN C_{max} and AUC_{0-48} were approximately 44% and 15% lower compared to fasting conditions. The median T_{max} was also delayed by 2.5 hours in these patients. The aqueous solubility of PAN is pH dependent, with higher pH resulting in lower solubility. Coadministration of FARYDAK with drugs that elevate the gastric pH was not evaluated in vitro or in a clinical trial; however, altered PAN absorption was not observed in simulations using mechanistic models.

PAN has extensive tissue distribution following oral administration. The oral terminal volume of distribution ranged from approximately 6 to 10000 L in clinical trials of single agent FARYDAK where sampling was sufficient to characterize the terminal phase. PAN is approximately 90% bound to human plasma proteins in vitro and is independent of concentration. FARYDAK is a P-gp substrate, but not subject to MRP mediated efflux.

PAN undergoes extensive systemic metabolism. Pertinent metabolic pathways involved in the biotransformation of PAN are reduction, hydrolysis, oxidation, and glucuronidation processes. In vitro, PAN is primarily (~40%) metabolized by CYP3A4 and to a lesser extent

by CYP2D6 and 2C19. In vitro, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, and UGT2B4 contribute to the glucuronidation of PAN.

In an in vivo evaluation, coadministration of a single 20 mg FARYDAK dose with the strong CYP3A4 inhibitor ketoconazole (200 mg twice daily for 14 days) increased the C_{max} and AUC_{0-48} of PAN by 67% and 73% respectively, compared to when FARYDAK was given alone in 14 advanced cancer patients. 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.

A mass balance trial with orally administered [^{14}C]-PAN was conducted in 4 patients with advanced cancer. Mass balance was achieved with ≥ 87% of the radioactive dose being recovered from the excreta of all patients after 7 days either in the feces (44%-77%) or urine (29%-51%). Unchanged PAN accounted for < 2.5% of the dose in urine and < 3.5% of the dose in feces.

The PK characteristics of PAN were evaluated in patients with renal and hepatic impairment. In a dedicated trial, mild, moderate or severe renal impairment did not alter PAN plasma exposure. PAN was not tested in patients with end stage renal disease or undergoing dialysis. In a dedicated trial, mild and moderate hepatic impairment increased the plasma exposure of PAN by 43% and 105, respectively. FARYDAK doses of 15 and 10 mg in patients with mild and moderate hepatic impairment, respectively, provide comparable systemic exposure as a 20 mg dose of FARYDAK in patients with normal hepatic function. There is insufficient PK in patients with severe hepatic impairment in order to conduct comparative exposure determination.

PAN is a competitive CYP2D6 inhibitor and a weak time-dependent inhibitor of CYP3A4 in vitro. The coadministration of a single 60 mg dextromethorphan (DM) dose with FARYDAK (20 mg once per day, on Days 3, 5, and 8) increased the C_{max} and $AUC_{0-\infty}$ of DM by 20% to 200% (interquartile range)and 20% to 130% (interquartile range), respectively, compared to when DM was given alone in 14 advanced cancer patients. These DM observations were extremely variable (CV% >150%). Based on these findings coadministration of FARYDAK with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index should be avoided.

Additional DDI related assessments were conducted using physiologic based pharmacokinetic (PBPK) modeling methods. PBPK simulation results show that the PAN systemic exposure could be decreased by approximately 70% when PAN is coadministered with rifampin, a strong CYP3A4 inducer. Therefore, the concomitant use of strong CYP3A4 inducers should be avoided. Simulations also show systemic concentrations of midazolam, a CYP3A4 substrate, could by increased by < 20% when coadministered with PAN. This finding will be confirmed in a planned clinical drug interaction trial.

Signatures

_____
Joseph Grillo, Pharm.D.
Primary Clinical Pharmacology Reviewer
PBPK Secondary Reviewer
Division of Clinical Pharmacology V

_____
Sarah Dorff, Ph.D.
Clinical Pharmacology Reviewer (in vitro studies)
Genomics and Targeted Therapy Group

_____
Lian Ma, Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics

_____
Nitin Mehrotra, Ph.D.
Pharmacometrics Team Leader
Division of Pharmacometrics

_____
Ping Zhao, Ph.D.
PBPK Primary Reviewer and Scientific Lead
Division of Pharmacometrics

_____
Bahru Habtemariam, Pharm.D.
Clinical Pharmacology Team Leader (Acting)
Division of Clinical Pharmacology V

_____
Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology V

2   QUESTION BASED REVIEW

2.1   General Attributes

2.1.1   What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?
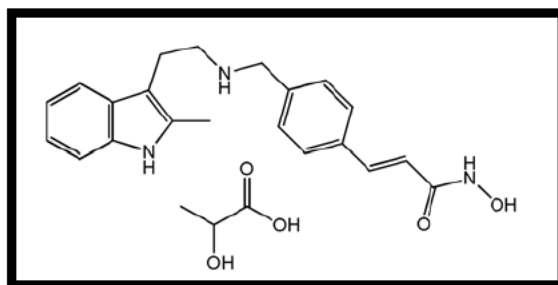
Established Name:	Panobinostat (PAN)
Molecular Weight:	349.43 (free base) + 90.08 (lactic acid) = 439.51 (Salt/ base ratio: 1.258)
Molecular Formula:	$C_{21}H_{23}N_3O_2 . C_3H_6O_3$
Chemical Name:	(2E)-N-Hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino} methyl)phenyl]prop-2-enamide 2-hydroxypropanoate
Description:	White to slightly yellowish or brownish powder
Chirality:	Panobinostat (free base) is not chiral and shows no specific optical rotation.
Solubility:	Solubility is pH dependent. At 37 °C anhydrous Panobinostat lactate is slightly soluble to pH 6 then very slightly soluble to insoluble at pH 6.8 and 7.6, respectively.
Log P:	Approximately 2.7 (estimated)
pKa-Values:	8.4 and 9 within a pH of approximately 6

FARYDAK hard gelatin capsules contain 10 mg, 15 mg, or 20 mg PAN free base. The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose and pregelatinized starch. The capsules contain gelatin, FD&C Blue 1 (10 mg), yellow iron oxide (10 mg and 15 mg), red iron oxide (15 mg and 20 mg) and titanium dioxide.

2.1.2   What are the proposed mechanism(s) of action and therapeutic indication?

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. In vitro, PAN caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Increased levels of acetylated histones were observed in xenografts from mice that were treated with PAN. PAN inhibited the enzymatic activity of histone deacetylases at nanomolar concentrations. PAN shows more cytotoxicity towards tumor cells compared to normal cells in preclinical studies.

The proposed indication for FARYDAK is as part of combination with bortezomib (BTZ) and dexamethasone (DEX) for the treatment of patients with multiple myeloma (MM), who have received at least 1 prior therapy.

2.1.3   What are the proposed dosage(s) and route(s) of administration?

The recommended starting dose of FARYDAK is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10 and 12, of a 21 day cycle. Patients should be treated initially for 8 cycles. The applicant recommended that patients with clinical benefit continue the treatment for 8 additional cycles. The total duration of treatment is up to 16 cycles (48 weeks). FARYDAK is administered in combination with BTZ and DEX as shown in Table 1. The recommended dose of BTZ is 1.3 mg/m^2 given as an injection. The recommended dose of DEX is 20 mg taken orally per scheduled day, on a full stomach.

Table 1: Recommended Posology and Dosing Schedule of FARYDAK in Combination with BTZ and DEX

Cycles	Drug	Week 1 Days						Week 2 Days						Week 3
1-8	FARYDAK	1		3		5		8		10		12		Rest period
	BTZ	1			4			8			11			Rest period
	DEX	1	2		4	5		8	9		11	12		Rest period
9-16	FARYDAK	1		3		5		8		10		12		Rest period
	BTZ	1						8						Rest period
	DEX	1	2					8	9					Rest period

Source: Applicant's proposed labeling document

2.2   General Clinical Pharmacology

2.2.1   What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

PAN has not been evaluated in healthy volunteer subjects because of the observed genotoxicity (see Section 2.2.5.2). The applicant submitted twenty-one clinical trials in support of dosing and other clinical pharmacology related claims in this application (Table 2). Pharmacokinetic (PK) sampling was collected in seventeen of these trials (See Appendix Section 4.1, Table 30). The majority of these trials evaluated the single agent use of FARYDAK in various advanced solid tumor and hematologic cancers. Four trials specifically evaluated patients with MM (i.e., Trials B2203, B2207, D2308, and DUS71) and three of these used combination therapy (i.e., Trials B2207, D2308, and DUS71). The applicant also submitted eighteen in vitro study reports, three physiologic based PK (PBPK) modeling reports, three population based PK reports (pop-PK), and four bioanalytical reports in support of the clinical pharmacology claims in this application.

Table 2: Clinical trials in support of dosing and other clinical pharmacology related claims in this application

Trial	Trial Description
A2101	A phase IA, four-arm, multicenter, dose-escalating trial of PAN administered intravenously according to four different schedules in adult patients with advanced solid tumors, Hodgkin's lymphoma, or non-Hodgkin's lymphoma
A2102	A phase IA/II, two-arm, multicenter, dose-escalation trial of LBH589 administered intravenously on two dose schedules in adult patients with advanced hematologic malignancies
B1101	A phase I dose-escalation trial of LBH589 administered orally in adult patients with advanced solid tumors or Cutaneous T-cell lymphoma
B1201	A phase II trial of oral LBH589 in patients with cutaneous T-cell lymphoma and adult T-cell leukemia/lymphoma
B2101	A phase IA, 2-arm, multicenter, dose-escalation trial of LBH589B administered orally on two dose schedules in adult patients with advanced solid tumors or non-Hodgkin's lymphoma
B2102	A phase IA/II, two-arm, multi-center, open-label, dose escalation trial of LBH589 administered orally via different dosing schedules in adult patients with advanced hematological malignancies
B2108	An open-label, single center trial to determine the absorption, distribution, metabolism, and excretion (ADME) of LBH589 after a single oral administration of 20 mg [14C]-LBH589 in advanced cancer patients
B2109	A phase IB, open-label, multicenter trial to investigate the effect of oral PAN on dextromethorphan, a CYP2D6 substrate, and to assess the efficacy and safety of oral PAN in patients with advanced solid tumors
B2110	A phase b trial to investigate the effect of ketoconazole, a CYP3A4 inhibitor, on oral LBH589 and to assess the efficacy and safety of oral LBH589 in patients with advanced solid tumors
B2111	A phase Ib open-label, multicenter, cross-over trial to investigate the effect of food on the rate and extent of oral LBH589 absorption in patients with advanced solid tumors
B2201	A phase II trial of oral LBH589 in adult patients with refractory cutaneous T-Cell lymphoma
B2202	A phase II, multicenter trial of oral LBH589 in patients with chronic phase chronic myeloid leukemia with resistant disease following treatment with at least two BCR-ABL tyrosine kinase inhibitors
B2203	A phase II trial of oral LBH589 in adult patients with MM who have received at least two prior lines of therapy and whose disease is refractory to the most recent line of therapy
B2206	A phase Ib, multi-center, open-label, dose-escalation trial of oral PAN when administered in combination with oral lenalidomide and DEX in adult patients with MM
B2207	A phase Ib, multi-center, open-label, dose-escalation trial of oral LBH589 and iv BTZ in adult patients with MM
B2211	A phase II, multicentre trial of oral LBH589 in patients with accelerated phase or blast phase (blast crisis) chronic myeloid leukemia with resistant disease following treatment with at least two BCR-ABL tyrosine kinase inhibitors
D2308	A multicenter, randomized, double-blind, placebo-controlled phase III trial of PAN in combination with BTZ and DEX in patients with relapsed MM
DUS71	A phase II, multi-center, single arm, open label trial of PAN in combination with BTZ and DEX in patients with relapsed and BTZ-refractory MM
E2214	A phase II trial of oral PAN in adult patients with relapsed/refractory classical Hodgkin's lymphoma after high-dose chemotherapy with autologous stem cell transplant
X2101	A phase I, open-label, multicenter trial to evaluate the pharmacokinetics and safety of oral PAN in patients with advanced solid tumors and various degrees of hepatic function
X2105	A phase I, open-label, multi-center trial to evaluate the pharmacokinetics and safety of oral PAN in patients with advanced solid tumors and varying degrees of renal function

Source: Reviewer generated from the clinical pharmacology summary report and tabular listing of all clinical studies

The safety and efficacy of FARYDAK is based primarily on a multicenter, randomized, double-blind, placebo-controlled phase 3 trial of PAN in combination with BTZ and DEX in patients with relapsed MM. A total of 768 patients with relapsed or relapsed and refractory MM were enrolled in Trial D2308, and randomized to receive either PAN+BTZ+DEX (n=387 patients) or PBO+BTZ+DEX (n=381 patients). The primary endpoint of this trial was progression-free survival (PFS). Pharmacokinetic sampling was only collected in a small subgroup of Japanese patients.

Progression-free survival (PFS), using modified European Bone Marrow Transplant Group (EBMT) criteria, was assessed by the investigators as the primary endpoint. PFS was statistically significantly different between the treatment arms. At the time of final PFS analysis, 69% of Overall Survival (OS) events had occurred and 416 patients were being

followed for survival. Efficacy results are summarized in Table 3. The most common[1] non-hematologic adverse reactions were diarrhea, fatigue, nausea, peripheral edema, decreased appetite, hypokalemia, pyrexia, vomiting, asthenia and cough. The most common hematologic toxicities included thrombocytopenia, and neutropenia. Pneumonia (15%), diarrhea (11%) and thrombocytopenia (7%) were the most common treatment emergent SAEs that occurred in ≥5% of patients treated with FARYDAK. Deaths occurred in 8% of PAN+BTZ+DEX treated patients versus 5% of PBO+BTZ+DEX treated patients. The most frequent causes of death included infections and hemorrhage.

Table 3: Efficacy Results from the Multiple Myeloma Trial D2308

	FARYDAK, bortezomib and dexamethasone N=387	Placebo, bortezomib and dexamethasone N=381
Progression-free Survival		
Median, months [95% CI]	12.0 [10.3, 12.9]	8.1 [7.6, 9.2]
Hazard ratio [95% CI][1]	0.63 [0.52, 0.76]	
p-value[2]	<0.0001	
Overall Survival		
Median, months [95% CI]	38.2 [34.6, 45.4]	35.4 [29.4, 39.9]
Hazard ratio [95% CI][1]	0.87 [0.70, 1.07]	
p-value[2]	0.2586	

NE = not evaluable
[1] Hazard ratio is obtained from stratified Cox model
[2] 2-sided p-value is obtained from the stratified log-rank test
Source: Applicant's proposed labeling document

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

In PK trials the primary pharmacodynamic biomarker was the level of histone acetylation in a surrogate tissue (i.e., peripheral blood mononuclear cells [PBMC]). PBMC was used because the applicant found collecting serial biopsies from patients for PD assessments challenging compared to the preclinical studies in animal models. Unfortunately, a robust pharmacokinetic/pharmacodynamic (PK/PD) analysis could not be performed due to limitations in the sample matrix (i.e., quality PBMC isolation), and that lack of a well characterized and qualitative assay. Consequently, the investigation of the PD of PAN relies mainly upon the clinical safety and efficacy endpoints in this application.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess PK parameters and exposure response relationships?

Yes. See Section 2.6

2.2.4 Exposure-response

### 2.2.4.1 What is the dose selection rationale for the phase 3 trial?

The dose and schedule of PAN (20 mg PAN, 2 weeks on/ 1 week off) used in phase 3 Study D2308 was selected mainly based on a phase 1b dose-finding Study B2207, in

---

[1] Occurred in >20% of patients treated with FARYDAK/bortezomib/dexamethasone at a >10% greater frequency than the control arm

patients with relapsed multiple myeloma who had received at least one prior line of therapies.

Five difference dose levels were tested in the dose escalation phase (three times every week, in six dose-cohorts). The MTD of PAN in combination with BTZ was determined to be PAN 20 mg + BTZ 1.3 mg/m^2 based on Bayesian logistic regression model integrated with information from clinical assessment. This dose level was carried forward to the dose expansion phase (cohort 7) with introduction of 1 week of treatment holiday, as well as the addition of DEX. The 1-week rest period was introduced in order to manage thrombocytopenia and allow for accelerated platelet recovery. DEX was added because preclinical and established clinical data indicated that the triple combination of PAN, BTZ, and DEX yielded synergistically greater anti-myeloma activity and there was a clinical benefit of DEX when added to BTZ in patients with relapsed/refractory MM. Efficacy (best overall response) and safety profiles (AEs rates) at each doses level are displayed in Figure 1. The best overall response rates increased with higher doses of combination up to PAN 20 mg + BTZ 1.3 mg/m^2, and increased further with addition of DEX. However, it should be noted that the severe AE rates were high (>85%) across all cohorts and also increased with higher dose of PAN.

With 77% of patients requiring dose intervention and 50% discontinued treatment due to AEs, it is unclear why the 20 mg PAN + 1.3 mg/m^2 dosing regimen was taken further to the to be evaluated in phase 3 setting.
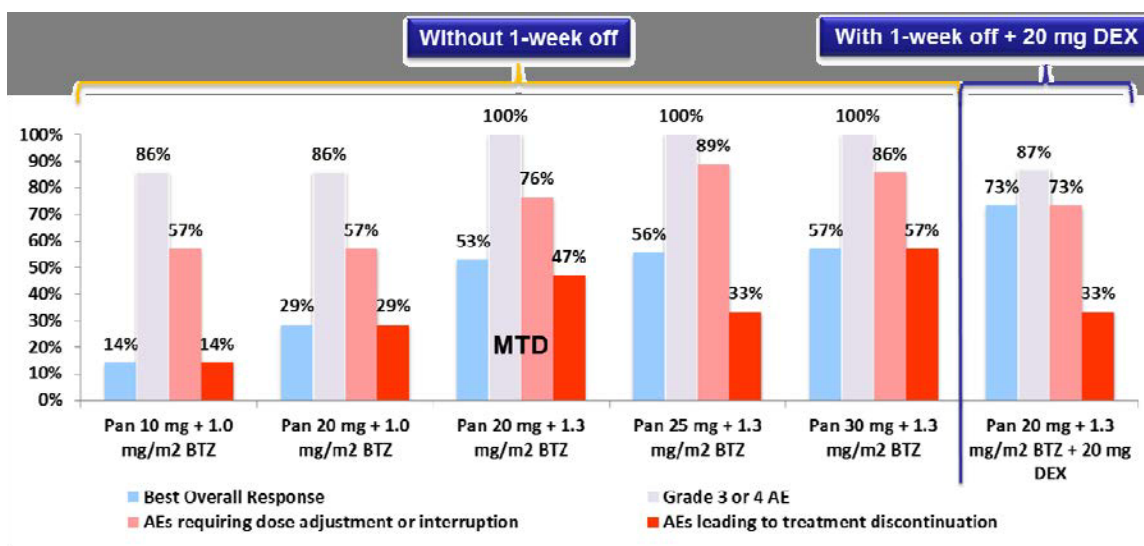
Source: Applicant's final trial report for trial B2207

Figure 1: Summary of best overall response and adverse event rates by cohort in dose escalation phase of Trial B2207

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Exposure-response relationship cannot be explored since no PK samples were collected from the phase 3 trial. Upon the information request by the Agency, sponsor conducted dose intensity (DI) – response analyses for PFS and overall response rate (ORR), using a range of metrics for DI. The analysis for efficacy results show a slight increase of hazards of PFS events and lowers ORR for higher DI, which may indicate a longer PFS for lower DI. However, due to the trial design, patients will generally have a higher PAN DI in the initial

cycles compared to those in the later cycles, where they had opportunity to dose-adjust, generally downwards. Thus patients who had events later had greater chances of dose reduction due to longer treatment and thus more likely to have lower DI. Therefore, the DI-response analyses for efficacy are confounded and cannot represent the exposure-response relationship for PAN. Refer to the Pharmacometric review in Section 4.2.1 for details.

The primary efficacy endpoint was progression-free survival (PFS), using modified European Bone Marrow Transplant Group (EBMT) criteria assessed by the investigators. The combination of PAN+BTZ+DEX showed superior PFS compared to PBO+BTZ+DEX with a hazard ratio (HR) of 0.63 (95% CI: 0.52, 0.76). Median PFS (95% CI) was prolonged by 3.9 months, from 8.1 months (7.56, 9.23) to 12.0 months (10.32, 12.94). As seen from Figure 2, the Kaplan-Meier curves for PFS separated at approximately month two of treatment, with a sustained separation over the course of the trial. PFS was also assessed by independent review committee (IRC) in a sensitivity analysis, from which the median PFS difference was 2.2 months: 9.9 months in the PAN arm versus 7.7 months in the control arm, with a hazard ratio of 0.69 (95% CI: 0.58, 0.83). The key secondary efficacy endpoint is overall survival (OS). As the cut-off date (18 Aug 2014), 86.5% of overall survival (OS) events had occurred and 342 patients were being followed for survival. Interim analysis showed that 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 38.2 months for patients in the PAN arm compared to 35.4 months for patients in the control arm.
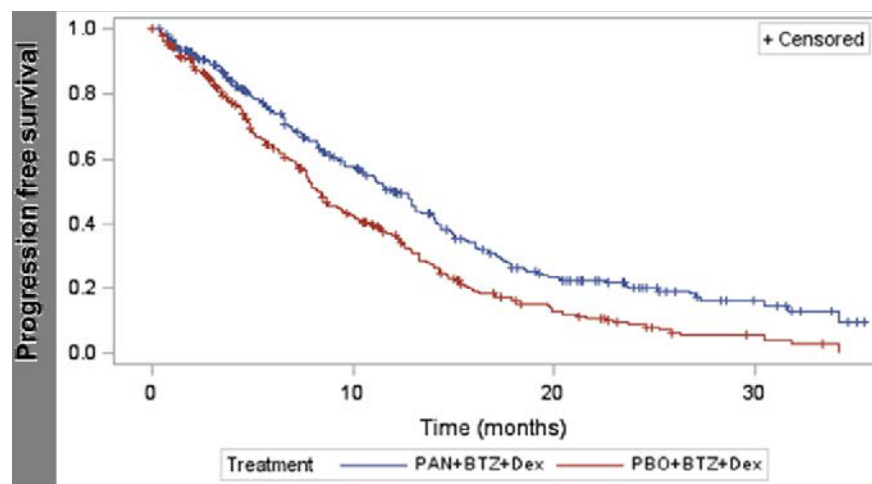
Source: Agency generated from Trial D2308 datasets

Figure 2. Kaplan-Meier Curve of Progression-Free Survival in Patients with Multiple Myeloma (Study D2308)

2.2.4.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The applicant did not provide an analysis of exposure safety for the proposed combination therapy PAN+BTZ+DEX. A visual analysis of the adverse event (AE) rates from trial B2207, where escalating doses of the PAN +BTZ were evaluated (see Section 2.2.5.1 for trial design details), suggests trend toward increased treatment related adverse events and serious adverse with increased dose (see Figure 1). Similarly the rate of AE related drug discontinuation increase with dose. In addition, a consistently high rate (~60%) of AE related hospitalization was also reported across the doses studied.

In the P3 trial D2308, high toxicity was observed in PAN+BTZ+DEX arm as compared to PBO+BTZ+DEX arm. The rate of adverse reactions leading to dose modification or interruption was 89% with PAN versus 76% with control respectively. The most common treatment emergent adverse reactions leading to dose modification or interruption in the PAN arm were thrombocytopenia (31%), diarrhea (26%) and fatigue (16%). Treatment discontinuation rates due to adverse events were 36% in patients treated with PAN compared to 20% in the control arm. Deaths rate was also higher in PAN treated patients (8% versus 5%). Kaplan-Meier Curves of time to adverse events also showed that the occurrences of severe event were earlier in PAN+BTZ+DEX group compared to the control group. Kaplan-Meier Curves of time thrombocytopenia are shown in Figure 3 as an example.

Source: Agency generated from Trial D2308 datasets

Figure 3: Kaplan-Meier Curve of Time to Thrombocytopenia (grades 3/4) by treatment group

Exposure-response relationship cannot be explored since no PK samples were collected from the phase 3 trial. Upon the information request by the Agency, sponsor conducted dose intensity (DI) – response analyses for most frequent treatment-emergent AEs (including thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia using a range of metrics for DI. Refer to the Pharmacometric review in Section 4.2.1 for details.

The time to AEs by DI-quartiles showed a trend across all safety endpoints suggesting possible association between AEs and higher PAN DI. An increasing risk of thrombocytopenia (all grades and grade 3/4) with increasing PAN DI was identified based on Cox proportional hazards model (Table 4). The association with change in DI of PAN for the other AEs was not statistically significant. As seen in Figure 4, thrombocytopenia occurred relatively early during treatment with a median onset time around 1 month for both mild and severe events. Age, race (Asian), baseline platelet count were identified as significant covariates to the risk of thrombocytopenia and were adjusted for in the cox-proportional hazard analysis.

Table 4: Hazard ratio of time to first thrombocytopenia with dose increase (covariate-adjusted)

DI metric	HR for 5-mg increase in PAN dose (95% CI)
Any grade	
Day 1 to onset	1.34 (1.10, 1.63)
last 3 weeks	1.39 (1.19, 1.63)
last 6 weeks	1.39 (1.16, 1.67)
last 9 weeks	1.36 (1.13, 1.65)
last 12 weeks	1.36 (1.12, 1.65)
Grade 3/4	
Day 1 to onset	1.52 (1.19, 1.94)
last 3 weeks	1.49 (1.24, 1.80)
last 6 weeks	1.63 (1.29, 2.07)
last 9 weeks	1.55 (1.22, 1.97)
last 12 weeks	1.53 (1.20, 1.94)

Source: Sponsor's Response to FDA Request (IR11), page 10

All Grades
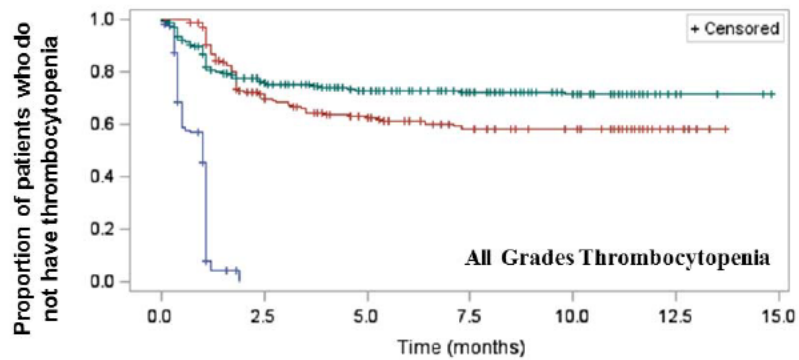
Grades 3/4
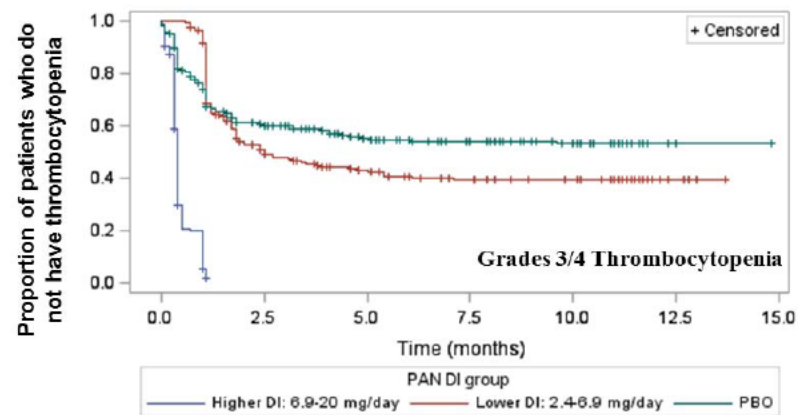
Source: Agency generated from Trial D2308 datasets

Figure 4: Kaplan-Meier Curve of Time to Thrombocytopenia (all grades and grades 3/4) by dose intensity groups

A semi-mechanistic indirect PK-PD model was used to describe the population platelet dynamics with effects resulting from panobinostat concentrations of an effect

compartment following the treatment of single-agent panobinostat in 441 patients. Individual panobinostat concentrations were simulated based on the PK parameter estimates obtained from a prior population PK model. Model analysis showed a dose and schedule dependent relationship between panobinostat exposure and TCP (see Figure 5). The platelet dynamics also exhibited a strong dependence on baseline platelet count, as well as tumor type (hematological vs. solid). For example, solid-tumor patients with higher platelet counts at baseline have a lower probability to get a thrombocytopenia event.
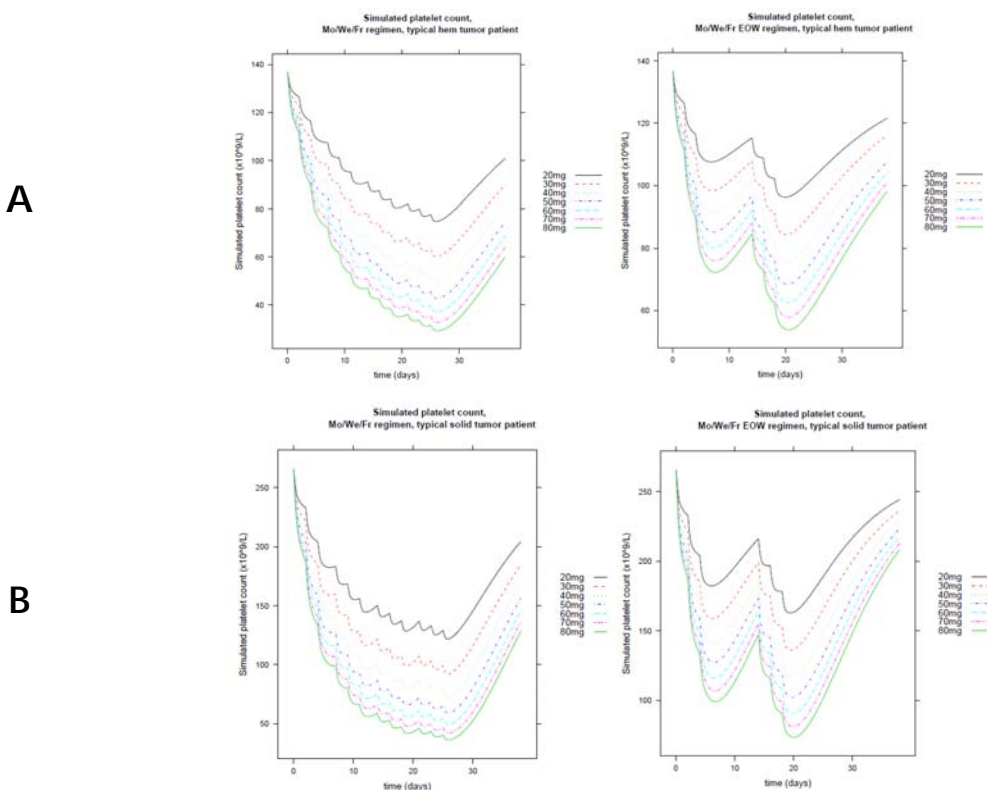
Source: Applicant's Modeling Report- PKPD-Platelets Pools CLBH589

Figure 5: Simulations of typical hematological (A) and solid tumor (B) patient platelet profile

2.2.4.4   Does this drug prolong the QT or QTc interval?

Yes. During development, administration of PAN by intravenous and oral routes causes a dose-related increase in the QT interval. There was one case of TdP with the 20 mg/m² consecutive intravenous dosing regimen which has been discontinued. This property is probably a class effect of HDAC inhibitors. The effect of PAN on QT appears to occur hours after T_{max} of the parent drug. The mechanism for this delayed effect is unknown. It is possible that this delayed effect occurs due to metabolites, delayed myocardial distribution or due to human ether-à-go-go related gene (hERG) trafficking. The division formerly named DDOP determined that further non-clinical studies to elucidate the mechanism for this delayed effect were not required. The sponsor has conducted a hERG trafficking study for the parent drug which was negative (reviewed by DCRP pharmacologist Dr. James Willard under IND 69862). In response to this finding intensive ECG monitoring and other procedures for risk minimization where PAN is being administered as monotherapy or combination chemotherapy has been incorporated in

various protocols by the sponsor in consultation with the review division. This issue was evaluated by the FDA Interdisciplinary Review Team (QT-IRT) for QT Studies on several occasions.[2]

In the current NDA submission, the incidence of grade 3 QTc prolongation (QTcF > 500 ms) with intermittent dosing is about 1% with the highest frequency of <5% seen in patients treated with the 60-mg oral dose. The relationship between plasma PAN concentration and heart-rate corrected QTc prolongation was explored using a linear mixed-effect model with the time-matched (within 60 minutes) conc-QT data in 499 patients from 12 pooled single-agent studies with oral doses between 10 and 80 mg. Contribution of BJB432 and its BJB432 metabolites, whose IC_{50} was 1.6 µM in the hERG channel assay towards QTcF prolongation, was also investigated in 140 patients from two studies. The QT-IRT reviewer found that the applicant's exposure-QTc analysis is not reliable because the QT prolongation is dose but not concentration dependent; however, the labeling language related to the QT risk appeared to be adequate in mitigating risk after FARYDAK is approved to be marketed with minor edits. The QT-IRT recommendations are also acceptable from a clinical pharmacology perspective. We defer to the clinical safety reviewer regarding whether or not information regard TdP should be communicated in the labeling.

2.2.4.5 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

No. The totality of evidence of efficacy and safety information available from the phase 1b and phase 3 trial does not support the proposed combination dosing regimen. There was no exposure data available from the phase 3 trial and therefore the exposure-response relationship cannot be explored.

The proposed dose is based on the MTD (20 mg PAN TIW and 1.3 mg/m^{2} BTZ). The dosing schedule (2 weeks on/ 1 week off) was introduced to manage thrombocytopenia and to allow for accelerated platelet recovery. Twenty milligrams of DEX was chosen based on literature evidence showing that the addition of 20 mg of DEX was associated with improved responses for patients who had worsening disease/suboptimal response while receiving bortezomib alone.

The OCP review team has determined that the proposed dosing regimen for FARYDAK is not acceptable despite the reported efficacy findings because 77% of the patients treated at the recommended dose in the dose escalation trial B2207 required a dose modification or interruption. This is further complicated by the excessive rate of TRAE, serous TRAE, AE related drug discontinuation, and AE related hospitalization. The OCP review team attempted a DI analysis (see Section 2.2.4.3) which was inconclusive. Consequently was not able to recommend to an optimized dosing regimen based on the information provided by the applicant. Therefore the OCP team finds that this is a substantial approvability issue from a clinical pharmacology perspective.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

---

[2] *IND 69862:* (2/11/2008, 3/19/2008, 9/23/2008, 9/28/2009 and 8/9/2010); (b) (4) and *IND 67091:* (5/16/2008).

2.2.5.1 What are the single dose and multiple dose PK parameters?

<u>Single Agent in Advanced Cancer:</u>

The single dose and multiple dose PK of single-agent PAN was evaluated in fourteen phase 1 and 2 trials that enrolled approximately 600 patients following intravenous (2 trials) or oral (12 trials) PAN administration. Dense PK sampling (8-12 samples per profile) was collected in all trials over a 48 hour period with the exception of trials X2101 and X2105, where sampling was over 96 hours, and the phase 2 trials B2201, B2202, B2203, and B221 where a limited sampling strategy was used (≤ 6 samples per profile). Pharmacokinetic parameters were derived from both noncompartmental analyses and a pooled pop-PK approach.

The dose escalation trials B2101 and B2102 evaluated single agent PAN following single and multiple oral dosing (i.e., MWF of every week [q.w.]) in adult patients with various solid or hematologic malignancies, respectively. The derived PK parameters from the noncompartment analysis are reported in Table 5 and Table 6 below. Based on this information and a visual inspection of the time concentration profiles (See Appendix Section 4.1, Figure 18) PAN PK appears to follow a linear process, although limited data are available at doses at or above 45 mg.

Since the noncompartmental approach used to assesses the PK of PAN was limited by the ≤ 48 hour sampling period and unlikely to have captured the complete terminal elimination phase, information from trials B2101 and B2102 should only be used to assess absorption (i.e., maximum concentration [C_{max}] and Time to C_{max} [T_{max}]) and dose proportionality rather than draw conclusions regarding half-life ($T_{1/2}$), area under the curve (AUC) to infinity, oral clearance (CL/F), and oral volume of distribution (Vz/F).

Table 5: Arithmetic mean (CV%) of PAN PK parameters following a single oral dose on Day 1 using all schedules in trials B2101 and B2102

PK Parameter	Trial	Dose						
		15 mg	20 mg	30 mg	40 mg	45 mg	60 mg	80 mg
N	2101	3	36	31	NA	17	4	NA
	2102	NA	9	18	24	15	53	18
C_{max} (ng/mL)	2101	12.2 (65%)	23.6 (57%)	34.0 (56%)	NA	48.6 (79%)	55.4 (40%)	NA
	2102	NA	19.5 (61%)	39.8 (69%)	58 (59%)	54 (53%)	66.9 (70%)	63.5 (58%)
^T_{max} (hr)	2101	1 (0.5-2)	1 (0.5-4.5)	1 (0.5-8)		1 (0.5-4)	2 (1-3)	NA
	2102	NA	2.1 (0.5-3.1)	1 (0.5-28)	0.8 (0.5-3.1)	1 (0.5-1.1)	1 (0.5-45.7)	1 (0.5-6)
AUC_{0-inf} (ng*h/mL)	2101	NA	209.2 (57%)	264.4 (57%)	NA	372.4 (33%)	454.0 (35%)	NA
	2102	NA	145 (59%)	272 (52%)	329 (77%)	290 (41%)	356 (64%)	397 (49%)
AUC_{0-48h} (ng*h/mL)	2101	NA	198.1 (48%)	261.5 (49%)	NA	362.7 (39%)	390.3 (28%)	NA
	2102	NA	131 (58%)	310 (117%)	299 (76%)	249 (44%)	330 (62%)	342 (54%)
CL/F (L/h)	2101	NA	133.5 (60%)	135.8 (44%)	NA	130.9 (28%)	142.0 (30%)	NA
	2102	NA	180 (49%)	158 (72%)	201 (77%)	179 (38%)	240 (58%)	246 (50%)
$T_{1/2}$ (h)	2101	NA	12.4 (36%)	13.4 (36%)	NA	15.2 (18%)	16.8 (13%)	NA
	2102	NA	14 (48%)	18 (30%)	14 (24%)	20 (59%)	15 (27%)	15 (18%)
V_z/F (L)	2101	NA	2160 (52%)	2581 (54%)	NA	2880 (34%)	3342 (19%)	NA
	2102	NA	3109 (37%)	3324 (61%)	3604 (58%)	4272 (53%)	5062 (53%)	5402 (63%)

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
<u>Source: Applicant's final trial reports for trials B2101 and B2102</u>

Table 6: Arithmetic mean (CV%) of PAN PK parameters following multiple oral doses (MWF q.w.) on Day 15 in in trials B2101 and B2102

PK Parameters	Trail	PAN Dose MWF q.w.					
		15 mg	20 mg	30 mg	40 mg	60 mg	80 mg
N	B2101	3	18	4	NA	NA	NA
	B2102	NA	8	12	22	17	4
C_{max} (ng/mL)	B2101	13.2 (58%)	28.8 (62%)	17.3 (61%)	NA	NA	NA
	B2102	NA	33.6 (49%)	38.4 (61%)	41.6 (88%)	51.8 (56%)	69.6 (39%)
^T_{max} (h)	B2101	1 (1 – 2)	1 (0.5 – 3)	2.1 (1 – 4)	NA	NA	NA
	B2102	NA	1 (0.5-2.1)	2 (0.7-4.0)	1.1 (0.5-4.0)	1.1 (0.5-6.0)	1.5 (0.7-2.0)
AUC_{0-inf} (ng*h/mL)	B2101	285.0 (n/a)	280.0 (51%)	328.0 (23%)	NA	NA	NA
	B2102	NA	193 (50%)	333 (69%)	373 (50%)	349 (49%)	365 (65%)
AUC_{0-48h} (ng*h/mL)	B2101	148.7 (48%)	263.8 (56%)	235.0 (62%)	NA	NA	NA
	B2102	NA	245 (87%)	280 (59%)	271 (59%)	306 (50%)	369 (52%)
CL/F (L/h)	B2101	53 (n/a)	86.4 (46%)	94.7 (23%)	NA	NA	NA
	B2102	NA	124 (41%)	148 (86%)	150 (76%)	213 (45%)	331 (83%)
$T_{1/2}$ (h)	B2101	23.4 (n/a)	15.5 (26%)	13.2 (4.6%)	NA	NA	NA
	B2102	NA	20 (35%)	20 (31%)	21 (41%)	18 (26%)	18 (50%)
V_z/F (L)	B2101	1779 (n/a)	1789 (30%)	1807 (26%)	NA	NA	NA
	B2102	NA	3230 (52%)	3098 (73%)	3303 (55%)	5283 (47%)	6087 (20%)

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
Source: Applicant's final trial reports for trials B2101 and B2102

To evaluate half-life ($T_{1/2}$), area under the curve (AUC) to infinity, oral clearance (CL/F), and oral volume of distribution (Vz/F), information from the normal groups of the hepatic (B2101) and renal (B2105) impairment trials was used since PK sampling was conducted over 96 hours following a single oral 30 mg PAN dose administered in patients with advanced solid tumors. Plasma samples for PAN and its metabolite BJB432 were collected under the dense sampling scheme described above. The derived PK exposure parameters for PAN and its metabolite BJB432 from the noncompartment analysis of these trial data are reported in Table 7 below. BJB432 is a reductive metabolite of PAN that, as described in Section 2.2.4.4, inhibits hERG potassium channel activity, but is not pharmacologically active vis-a-vis HDAC inhibition.

Table 7: Summary of arithmetic mean (CV%) PAN and BJB432 plasma PK parameters following a single oral 30 mg PAN dose administered in patients with advanced solid tumors in trials X2101 and X2105

PK Parameter	PAN		BJB432	
	X2101	X2105	X2101	X2105
n	10	11	10	11
T_{max} (h)^	2.0 (0.5-7.0)	1.02 (0.5; 4.0)	24.0 (2.0; 48.0)	4.08 (1.0; 48.0)
C_{max} (ng/mL)	23.2 (74.2)	41.0 (69.0)	4.0 (132.2)	2.60 (50.1)
AUC_{0-48} (ng*h/mL)	146.2 (53.1)	225.2 (45.6)	NR	86.5 (64.3)
AUC_{0-96} (ng*h/mL)	165.7 (53.0)	253.9 (46.5)	NR	140.7 (71.9)
AUC_{last} (ng*h/mL)	165.5 (53.3)	253.4 (46.9)	218.0 (138.2)	140.6 (72.1)
AUC_{0-inf} (ng*h/mL)	176.5 (53.0)	275.2 (47.6)	291.3 (136.0)	208.9 (85.2)
CL/F (L/h)	247.0 (80.1)	210.0 (144.1)	211 (61.0)	317.7 (109.4)
V_z/F (L)	9318.2 (50.3)	6092.8 (43.3)	13404 (80.1)	16234.4 (71.9)
$T_{1/2}$ (h)	29.6 (20.9)	32.4 (39.6)	46.0 (62.6)	46.9 (35.0)

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
Source: Applicant's final trial reports for trials X2101 and X2105

Single Agent in MM:

The PK of PAN and its metabolite BJB432 was assessed as a single agent in the treatment of MM in trials B2203 and B2207. Trial B2203 was a phase 2, open-label trial where oral PAN was administered at 20 mg TIW, every week in adult patients with MM who had received at least two prior lines of therapy (including BTZ or lenalidomide) and whose disease was refractory to the most recent line of therapy. Plasma samples for PAN and its metabolite BJB432 were collected under the limited sampling scheme described above

on Days 1 and 8 during the first treatment cycle. The derived PK exposure parameters for PAN and its metabolite BJB432 from the noncompartment analysis are reported in Table 8 below. Since the last available sampling time, around 24 hours post-dose, these findings are not sufficient to adequately characterize the terminal phase PK parameters (i.e., $T_{1/2}$, AUC to infinity, CL/F, Vz/F) and were not reported.

Table 8: Arithmetic mean (CV%) of PAN and BJB432 PK exposure parameters on Days 1 and 8 following oral administration of PAN 20 mg three times weekly (TIW), every week in adult patients with MM (trial B2203)

Substance	Day	T_{max} (hr)^	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/ml)
PAN	1	1.7 [0.2, 5.2] n=27	7.6 (72.6) n=27	72.0 (50.1) n=27
	8	1.2 [0.2; 23.7] n=22	9.7 (67.2) n=22	81.6 (46) n=21
BJB432	1	24 [1.7; 47.5] n=27	0.9 (57.9) n=27	15.2 (55.2) n=27
	8	22.2 [0.8; 26.2] n=21	1.8 (52.4) n=21	32.5 (54.4) n=13

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
*Source:* Applicant's final trial reports for trials B2203

Trial B2207 was a phase Ib trial which evaluated several dosing regimens of orally administered PAN alone and in combination with intravenous BTZ, with and without oral DEX in 62 adult patients with MM whose disease had relapsed, as well as patients with relapsed-and refractory MM, following at least one prior line of therapy, and who were suitable for treatment (or re-treatment) with BTZ. In the dose escalation phase FARYDAK was administered at escalating doses for three days per week every week (i.e., Days 1, 3, 5, 8, 10, 12, 15, 17, 19 in a 21 day cycle) and BTZ was administered at escalating doses twice weekly for two weeks (i.e., Days 1, 4, 8 and 11) followed by a 10-day treatment holiday (Days 12-21). Plasma samples for PAN were collected under the dense sampling scheme described above on Cycle 1 Days 8, 9, 10 and Cycle 1 Days 15, 16, 17. The derived PAN PK parameters for PAN from the noncompartmental analysis are reported in Table 9 below. Additional exposure information for other PAN doses studied in trial B2207 can be found in Appendix Section 4.1, Table 32.

Table 9: Arithmetic mean (CV%) of PAN PK parameters on day 15 following oral administration of PAN 20 mg three times weekly (TIW), every week in adult patients with MM (trial B2207)

Parameter	PAN 20 mg + BTZ 1.0 mg/m^2	PAN 20 mg + BTZ 1.3 mg/m^2
n	4	14
$AUC_{(0-48)}$ (ng.h/mL)	82.6 (61.4)	91.9 (91.9)
C_{max} (ng/mL)	7.6 (50.6)	12.2 (103.3)
T_{max} (h)^	2.0 [1.0;3.9]	1.8 [0.5;3.0]
$T_{1/2}$ (h)	14.4 (56.7)	14.1 (62.3)
CL/F (L/h)	191.9 (74.5)	193.3 (103.7)
V_z/F (L)	3989.3 (105.9)	3930.0 (56.6)

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
Source: Applicant's final trial reports for trials B2207

A final determination regarding a possible disease effect could not be definitively made from the noncompartmental analysis because the sampling differences and the high variability did not permit a direct comparison between trials B2102, B2203, and B2207. However, a visual comparison of the exposure data does appear to show some overlap (Figure 6).
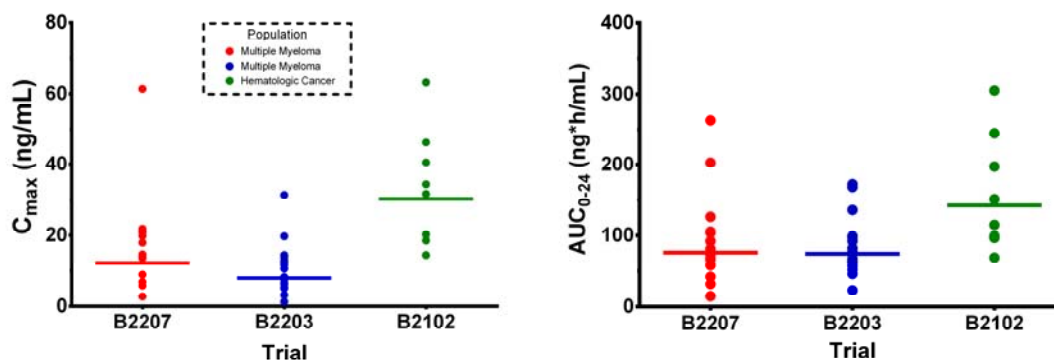
Figure 6: Comparison of Geometric Mean (range) PAN exposure following multiple dosing in patients with hematologic malignancies (B2102) or multiple melanoma (B2203 and B2207)

To address the limitations of the noncompartmental approach to assessing the single agent PK of PAN in the submitted phase 1 and 2 trials that were limited by the ≤ 48 hour sampling period the applicant also conducted a pop-PK analysis with data from a combined analysis of eight phase 1 trials (B1101, B2102, A2101, A2102, B2101, B2109, B2110 and B2111) and six phase 2 trials (B2201, B2202, B2203, B2211, B1201 and E2214). It is unclear why the PK information from the "normal" groups from trials B2101 and B2105 and the "PAN alone" sampling from the dose escalation phase of trial B2207 were not included in the model. The pop-PK model was based on 7834 observations in 581 patients receiving either intravenous (1.2 to 20 mg/m^2) or oral doses of single-agent PAN (10 to 80 mg TIW) with either solid or hematological tumors from 14 phase 1 or 2 clinical studies.

Using this model the PK of PAN was characterized with a 3-compartment model that suggested that PAN is linear in the dose range tested. The absolute bioavailability for the FMI oral formulation was estimated to be 21%. Terminal elimination half-life was approximately 37 hours, and average effective half-life based on rate of accumulation was 16 hours. Systemic clearance (CL) was 33 L/hour and CL/F was approximately 160 L/hour, with a large inter-subject variability on clearance of 65%. The central volume of distribution was 24.8 liters. The estimates for clearance and half-life are similar to that reported for PAN PK sampling collected over 96 hours and analyzed using noncompartmental methods (see Table 7). A disease effect was also not noted in the pop-PK analysis which is consistent with the visual analysis of the noncompartmental findings (see Figure 6). Because of the limitations with the noncompartmental analysis described above, the pop-PK estimates for PK parameters for PAN should be used in labeling.

Combination Agent in MM:

Under the proposed indication, FARYDAK therapy is to be combined with both BTZ and DEX (see Section 2.1.3). The PK of this combination was described in the expansion phase of trial 2207 that is described above. In the expansion phase patients received 20 mg FARYDAK TIW with a 2 weeks on/1 week off schedule, with 1.3 mg/m^2 BTZ on D1, D4, D8 and D11 + 20 mg DEX on each day of and day after BTZ dosing in a 3 week cycle allowing a treatment holiday of 1 week for all drugs for 8 cycles of BTZ/DEX, and PAN continued thereafter until progression. PAN PK samples were collected on Cycle 1 Day 8

21 | P a g e

and Cycle 2 Day 8 using a 28 hour dense sampling schedule. The derived PAN PK parameters for the full combination (i.e., cycle 2) are described in Table 10 below. Additional exposure information for other PAN+BTZ doses studied in trial B2207 can be found in Appendix Section 4.1, Table 32. Since the last available PK sampling time, around 28 hours post-dose, is not sufficient to adequately characterize the terminal phase, additional PAN PK parameters (i.e., $T_{1/2}$, AUC to infinity, CL/F, Vz/F) from this trial analysis are not considered reliable and should not be reported in labeling.

Table 10: Arithmetic mean (CV%) of PAN PK parameters following a PAN + BTZ + DEX combination regimen on cycle 2 day 8 in trial 2207

PK Parameter (unit)	PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m^2 + DEX 20 mg
n	12
$AUC_{(0-24)}$ (ng.h/mL)	47.5 (76.8)
C_{max} (ng/mL)	8.1 (90.3)
T_{max} (h)^	1.0 [0.5;6.3]
$T_{1/2}$ (h)	15.9 (29.2)
CL/F (L/h)	285.2 (79.4)
V_z/F (L)	6539.0 (81.0)

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
Source: Applicant's final trial reports for trials B2207

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

PAN has not been evaluated in healthy volunteer subjects because of the observed genotoxicity in preclinical mutagenicity and COMET (a single cell gel electrophoresis assay to detect DNA damage) assays.

2.2.5.3 What are the characteristics of drug absorption?

The mass balance (ADME) trial B2108 reports that the extent of PAN absorption following oral administration of [^{14}C]-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.

The absolute bioavailability of the clinical service formulation (CSF) and final market image (FMI) of PAN, defined as the geometric mean ratio (GMR) between intravenous (2 trials) and oral (8 trials) AUC$_{inf}$ values, was estimated to be approximately 28% by a cross trial assessment of the GMR from a noncompartmental assessment of dense PK sampling and approximately 21% based on a pop-PK approach which included the dense PK sampling as well as additional trough samples. Since it is unlikely that the 48 hour dense sampling period captured the complete terminal elimination phase, the pop-PK estimate should be used in labeling.

PAN is a P-gp substrate (Km >100 µM), but not subject to MRP mediated efflux. The P$_{eff}$ under LY335979 inhibition at a concentration of either 5.0 µM or 23 µM was measured to be ~35 ×10^{-5} cm·min^{-1} which suggests that PAN is a highly permeable compound. Due to the high permeability of PAN and likely saturation of transporters at commonly administered oral doses of PAN, it is not expected that P-gp would affect absorption of PAN from the intestinal tract. This hypothesis is strengthened by the findings of a patient with a hepatico-jejunostomy in the ADME trial B2108 where PAN absorption, based on exposure, did not appear altered substantially. This procedure can result in a reduction

in the functional length of the gastrointestinal tract which could affect any P-gp mediated absorption of PAN.

The solubility determination of PAN (also known as LBH589) was assessed in 250 mL of aqueous media across a pH range of 1.2 to 7.6 and the results are presented in Table 11. These results suggest that PAN has non-linear solubility with strong dependence pH. Particularly, the solubility in 250 ml of pH 7.6 phosphate buffer is less (~16 mg) than the highest dose strength of 20 mg. In order to determine whether pH modifying agents could influence the absorption of PAN, the applicant provided PBPK simulations suggesting that elevating stomach pH does not influence oral absorption of Pan (See Appendix Section 4.2.2), also see Figure 7. This model also appears to qualitatively describe the effect of food on T_{max} and C_{max} of PAN observed in a dedicated clinical trial (see Section 2.5.3).

Table 11: Solubility of LBH589 (PAN) lactate, anhydrous drug substance at 37.0°C (+/- 0.5°C), batch 0724011

Solution / buffer	Approximate solubility in mg/mL of solution at 37°C (±0.5°C)	Corresponding maximum amount of drug soluble in 250 ml of solution (in mg)
Water	4.775	1194
pH 1.2 (HCl)	1.017	254
pH 2.0 (HCl)	1.256	314
pH 4.5 (acetate)	4.771	1193
pH 6.0 (phosphate)	3.845	961
pH 6.8 (phosphate, simulated intestinal fluid)	0.261	65
pH 7.6 (phosphate)	0.064	16

Source: Applicant's CMC Drug Substance General properties reports
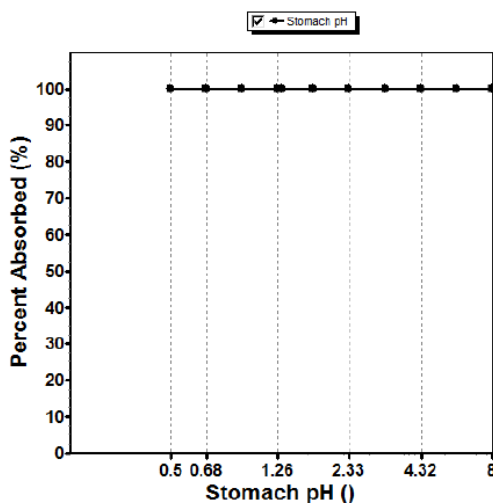
Source: Applicant's final reports "ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans"

Figure 7: Projected absorption of 20 mg PAN vs. stomach pH in humans

2.2.5.4 What are the characteristics of drug distribution?

In vitro, PAN is 89.6% bound to plasma proteins (88.2% in human serum). In study R0200414, the mean percent bound of PAN to human plasma proteins was 90.7%, 89.7%, 92.5%, 89.5%, and 86.8% at 0.1, 0.5, 1, 10, and 100 μg/mL, respectively. Therefore, PAN protein binding is independent of concentration over the 0.1 to 100 μg/mL range

studied. These findings are acceptable and the potential risk of a drug-protein interaction does not warrant additional in vivo trials. The fraction of PAN in the erythrocyte is 0.60 in vitro and is also independent of concentrations over the range assessed (0.1 to 100 µg/mL).

Plasma protein binding of PAN was also assessed in patients with normal and impaired hepatic and renal function in studies X2101 and X2105, respectively. The mean percent bound of PAN to human serum proteins averaged 84.1%, 83.9%, and 76.5% in patients with normal, mild, and moderate hepatic impairment, respectively (see Section 2.3.2.7). Similarly, the renal impairment trial reports the mean percent bound of PAN to human serum proteins averaged 87.7%, 83.3%, 84.9%, and 86.4% in patients with normal, mild, moderate, and severe renal impairment, respectively (see Section 2.3.2.6).

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 (see Section 2.2.5.3) 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.

2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The ADME of single agent PAN was assessed in a phase I, open-label trial using a single oral 20 mg dose of [^{14}C]-PAN (50 µCi) in four advanced cancer patients. Plasma, urine, and fecal samples were collected over 168 hours for PAN and metabolic profiling. The disposition of PAN was described by a relatively fast absorption followed by a biphasic elimination phase. Mass balance was achieved in this trial with ≥ 87% of the administered radioactivity being recovered in the excreta of all four patients after 7 days (see Table 12). Multiple metabolites contributed to the circulating drug-related material in plasma at levels comparable to or greater than unchanged PAN. The plasma exposure of BJB432, based on a comparison of AUC$_{0-last}$, ranged from 25 to 97% of the exposure to PAN.

Overall a median (range) of 48% (44 – 77%) of the dose was recovered in the feces and 41% (29 – 51%) of the dose was recovered in the urine (see Table 12). The metabolite BJB432 represented 1.47 to 22.5% and 0.24 to 1.24% of the PAN dose in feces and urine, respectively. 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. The disposition of a single 20 mg dose of [^{14}C]-PAN in patients was found to be variable, in particular with regard to the routes of elimination.

Table 12: Excretion of radioactivity in urine and feces (% of dose) in ADME Trial B2108

Patient #	1	2	3	4	Mean ± SD (ALL)	Mean ± SD (pt:2-4)
Age/Sex/ Race	63/F/Ca	53/F/Ca	61/M/Ca	59/M/Ca		
Urine (0-168 h)	28.6	51.2	44.9	37.6	40.6 ± 9.73	**41.25±5.16**
Feces[a]	77.4	44.4	46.1	49.4	54.3 ± 15.5	**47.75±2.54**
Dose recovery (%)	106	95.6	91.0	87.0	94.9 ± 8.19	**89±4.30**

a=The last fecal sample was collected at 154 hours for patient 1, 168 hours for patient 2, 147 hours for patient 3, and 148 hours for patient 4.
Ca=Caucasian

For three of the four patients (2, 3 and 4) the contributions of the urinary and fecal route of elimination were comparable, while in the remaining patient 1 the fecal elimination route was major. The cause of this discrepancy remains unclear, but an Agency review of the case report form showed that this patient had a history of a hepatico-jejunostomy several years prior to enrollment in the trial. The possibility that this procedure could have affected PAN absorption and any potential enteroheterohepatic recirculation of metabolites cannot be ruled out following a visual analysis of the fecal and urinary metabolite elimination by patient. Removing this patient from the analysis of radioactive elimination in trial B2108 did not appear to affect the conclusion to a large extent. The applicant should consider evaluating this issue further if it intends to develop PAN for use in populations where this procedure is common (e.g., pancreatic cancer).

2.2.5.6 What are the characteristics of drug 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 (See Figure 8 and Appendix, Section 4.1 Figure 19). In the four patients studied in the ADME trial (B2108) PAN was metabolized into at least 77 distinct metabolites, of which approximately 40 were observed circulating in plasma. A primary metabolic pathway involved modifications of the hydroxamic acid side chain to form the amide BJB432 via reduction. BJB432 has a hERG IC_{50} (1.6 µM) [PAN (3.5 µM)], but it appears to be pharmacologically inactive for HDAC inhibition activity.

Recombinant enzyme preparations of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, and CYP4A11 were used to identify the P450 enzymes involved in PAN's metabolism. 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. The CYP3A4 inhibitors ketoconazole, terfenadine, DEX, troleandomycin, and azamulin resulted in maximal inhibitions ranging from 70-98%. Inhibitors of CYP2D6, CYP2C19, CYP1A2, CYP2C8, and CYP2C9 resulted in maximal inhibitions of PAN metabolism ranging from 8-58%, with the applicant proposing that the higher inhibition observed for some inhibitors was due to non-specific CYP3A4 inhibition. From these in vitro findings, the reviewer agrees with the applicant's position that CYP3A4 is likely the predominant CYP isozyme responsible for the metabolism of PAN.

These in vitro findings are consistent with that reported in the ADME trial B2108. In this trial the percent of CYP mediated oxidative metabolism is estimated to be within the range of 30 to 47% of the dose, based on the identification and amount of metabolites excreted. Using both the in vitro estimates above and the AUCi/AUC ratio from the

ketoconazole drug interaction trial (B2110), the fraction metabolized through CYP P450 3A accounts for approximately 40% of PAN elimination with additional minor contributions from CYP2D6 and 2C19 also reported in vitro. In vitro, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, and UGT2B4 contribute to the glucuronidation of PAN. The relative contribution of each UGT enzyme was not explored.
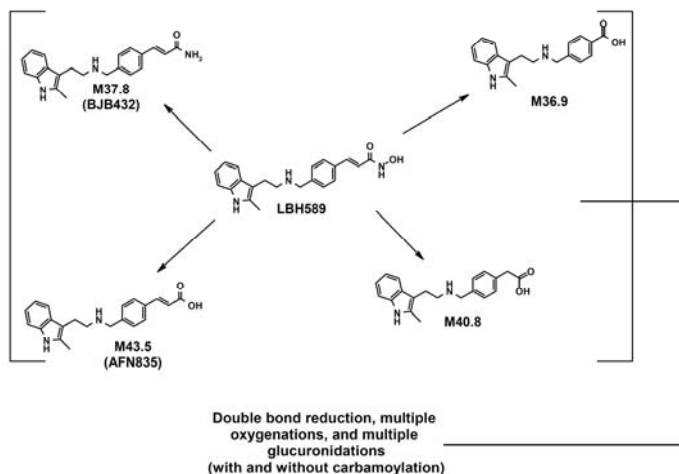
Figure 8: Primary PAN metabolic scheme

2.2.5.7 What are the characteristics of drug excretion?

As described in detail on Section 2.2.5.5, approximately 44-77% and 29-51% of an oral PAN dose was recovered in the feces and urine from four patients studied in the ADME trial B2108, respectively. In the normal group of the special population trials X2101 and X2105, where PK sampling was collected over 96 hours the mean (%CV) oral plasma clearance (CL/F) of single agent PAN from the noncompartmental analysis was 247.0 (80.1) and 210.0 (144.1) L/hr, respectively (see Table 7). Despite the high variability, this finding was consistent with the median (range) CL/F estimate of 209 (114; 248) L/hr from patients studied in trial B2108. The pop-PK model reported a PAN systemic clearance (CL) of 33 L/hour and CL/F of approximately 160 L/hr, with a large inter-subject variability on clearance of 65%. The mean (%CV) renal clearance of single agent PAN is estimated to be 1.39 (13.0) mL/hr in patients with normal renal function from the dedicated renal impairment trial X2105.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

A cross trial visual inspection of dose normalized PAN C_{max} and AUC_{0-48} following single dose and multiple dose single agent oral PAN administration in trials B2101 and B2102 implies dose proportionality across the dosage range tested (Figure 9). A similar finding was observed from a visual inspection of the respective time versus concentration plots (See Appendix Section 4.1, Figure 18).
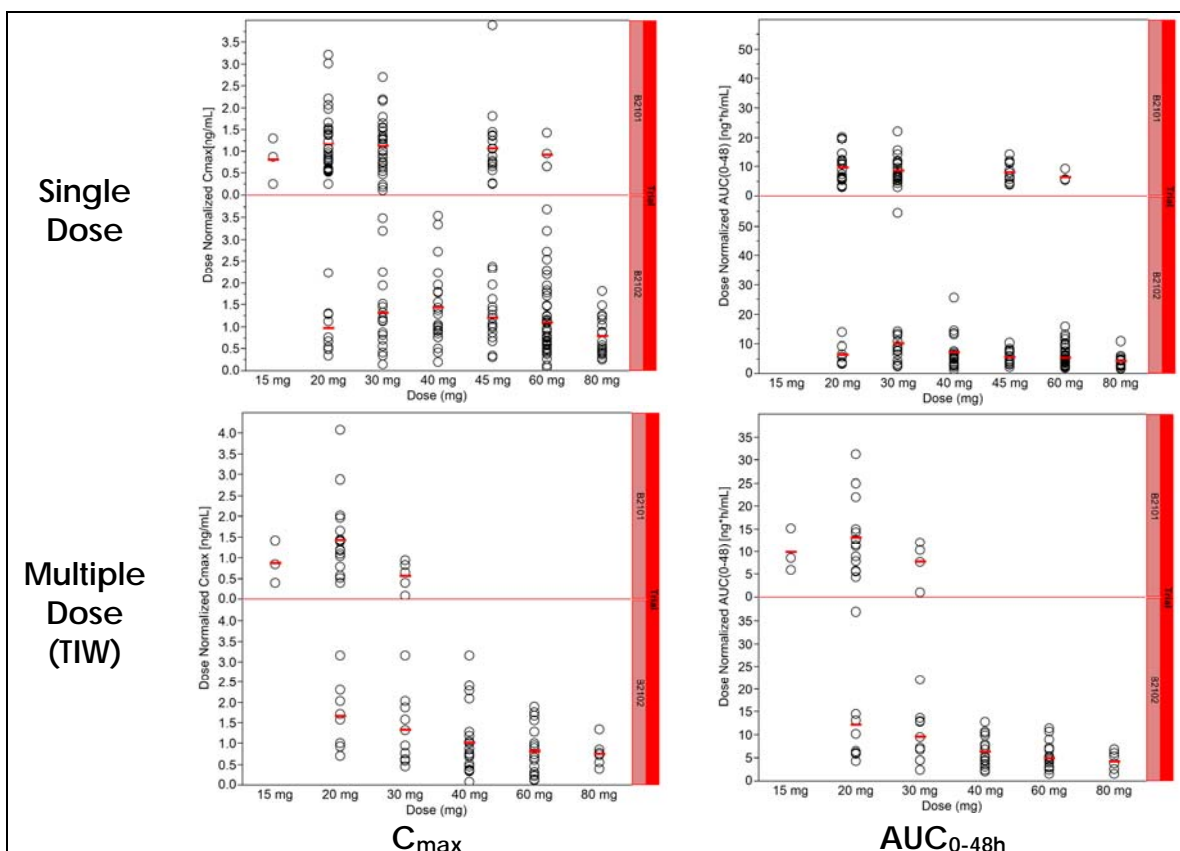
Figure 9: Comparison of dose normalized exposure in the oral PAN single agent dose escalation trials B2101 and B2102

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Accumulation ratio following multiple FARYDAK dosing (MWF q.w.) from the single agent dose escalation trials B2101 (solid tumor) and B2102 (hematological malignancies), expressed as GMR of AUC_{0-48} between Day 15/17 and Day 1, is 0.93 to 1.41 and 0.98 to 2.16 across the dose range, respectively. The median accumulation is approximately 1.12 across these trials. In addition, an AUC_{0-24} accumulation ratio (i.e., day 8 to 1) of 1.1 for PAN and 2.1 for its metabolite BJB432 was reported from the phase 2 trial in MM (trial B2203); however, these estimates are limited by the short sampling time as discussed previously. 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.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

A large inter-subject variability of 65% on systemic clearance was reported from the pop-PK analysis. Similarly, the inter-patient variability on apparent PAN oral clearance and exposure from a pooled analysis of patients with advanced cancer was high (Table 13). This pooled analysis also reported an intra-patient variability on PAN C_{max} and AUC_{0-inf} was 52% and 38% in patients who received oral PAN on a three times weekly schedule, respectively (Table 13). The major cause of variability is likely due to differences in

absorption, given the relatively low intra-patient variability when PAN was administered intravenously (Table 13), and the multiple comorbidities in this cancer population.

Table 13: Reported inter- and inter-patient variability from the applicants pooled analysis of single agent PAN dose trials

Route	PK Parameter	Variability	
		Inter-patient[a]	Intra-patient[b]
Intravenous	C_{max}	NR	34%
	AUC_{0-inf}	39%	17%
Oral	C_{max}	80%	52%
	AUC_{0-inf}	66%	38%

a=pooled trials B1101, B2101, B2102, B2109, B2110, B2111 X2101, X2105
b=pooled trials B1101, B2101, B2102
NR= not reported
Source: Derived from applicant's clinical pharmacology summary appendix 1

2.3   Intrinsic Factors

2.3.1   What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

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 (see Section 2.3.2.7). A semi-mechanistic indirect PK-PD 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.

2.3.2   Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

Given the ADME profile of single agent PAN combined with the less than optimal exposure results from trial X2101due to high variability (see Section 2.3.2.7) 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.

2.3.2.1   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.

2.3.2.2 Pediatric patients

The expected exposure and PK in pediatrics is not known. Given this is an orphan drug it is excluded from PREA requirements.

2.3.2.3 Gender

The pop-PK analysis of single agent PAN showed no effect by gender on PAN clearance.

2.3.2.4 Body Weight and BSA

In the BSA range studied, approximately 95% of patients had BSA between 1.5 m2 and 2.5 m2. The pop-PK model predicts that a patient with a BSA of 1.5 m2 would have a 21% lower clearance and a 27% lower central volume compared to that of a typical patient (BSA of 1.9 m2), and a patient with a BSA of 2.5 m2 would have a 32% higher clearance and a 45% higher central volume compared to that of a typical patient. However, due to magnitude of these effects as compared to the unexplained inter-patient variation of clearance (65%) and volume (58%), the BSA effect on systemic exposure is unlikely to require a dose modification or a weight based dosing scheme.

2.3.2.5 Race

PAN PK has been characterized mainly in Caucasians, with limited data from Japanese patients following PAN administration as a single agent (i.e., Trial B1101) and combination therapy (i.e., trial D2308). Following multiple dosing of single agent PAN 20 mg TIW every week in six Japanese patients with advanced solid tumors or cutaneous T-cell lymphoma (CTCL), a trend suggesting a lower exposure in these patients compared to Caucasian patients receiving the same dose was apparent (see Figure 10). However, the small sample size and high inter-individual variability not allow for a robust comparison.
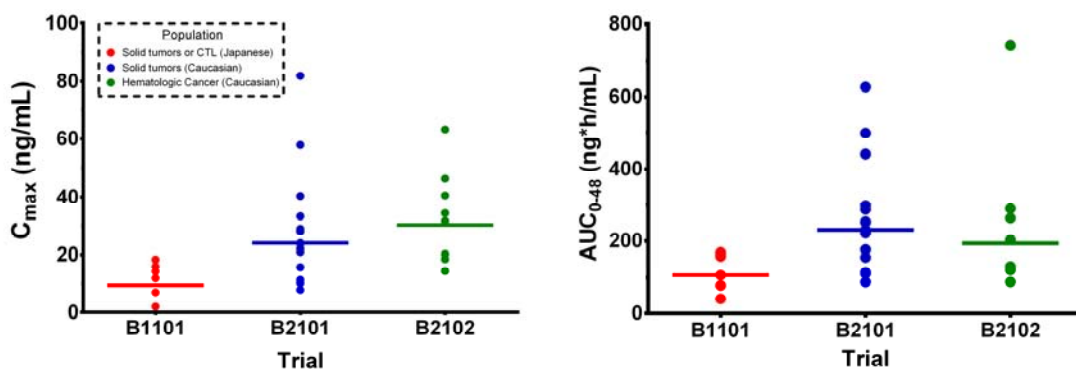
PK sampling was collected on day 15
Source: Applicant's final trial reports and PKPARM datasets for trials B1101, B2201 and B2102

Figure 10: Comparison of Geometric Mean (range) PAN exposure following multiple dosing in Japanese (B1101) or Caucasian (B2101 and B2102) patients with solid or hematologic malignancies

The pop-PK analysis reported a statistically significant covariate effect of race on clearance and central volume of distribution. An Asian patient with a BSA of 1.90 m2 would have a 17% higher clearance and a 37% higher central volume compare to that of a typical Caucasian patient. However, for a typical Asian patient with a BSA of 1.7 m2, this translates into an increase of only 4.7% and 17.7%, respectively. Again the magnitude of effect is small as compared to the unexplained inter-patient variation of clearance. Therefore the race effect on systemic exposure not considered clinically relevant.

In trial D2308 (treatment phase 1), patients received 20 mg FARYDAK or PBO TIW with a 2 weeks on/1 week off schedule, and 1.3 mg/m² BTZ on Days 1, 4, 8 and 11, and 20 mg DEX on each day of and after BTZ dosing in a 21 day cycle. Serial dense blood samples to characterize the PK of PAN (Day 1 and Day 8 of Cycle 1) and BTZ (Day 8 of Cycle 1) were collected in a subset of 13 Japanese patients. A Geometric Mean (CV%) AUC_{0-48h} of 76.01 (45.6%) and 118.9 (29.5%) ng*hr/mL and C_{max} of 9.16 (74.8%) and 15.33 (39%) ng/mL was reported on Cycle 1 days 1 and 8, respectively. Unlike the trend observed for single agent use, the PAN exposure in Japanese patients with MM following combination therapy was higher than Caucasian patients with MM receiving the same regimen (see Figure 11).

PK sampling was collected on days 8 (D2308 and B2207) or Day 15 (B1101)
SA= single agent; Combo = combination therapy
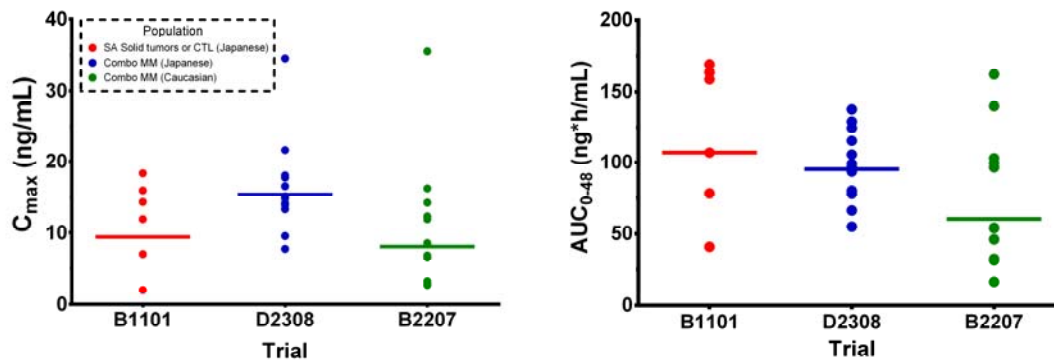*Source:* Applicant's final trial reports and PKPARM datasets for trials B1101, B2201 and B2102

Figure 11: Comparison of Geometric Mean (range) PAN exposure following multiple dosing of Single agent or combination PAN therapy in Japanese or Caucasian patients with solid or hematologic malignancies

A difference in efficacy parameters between Caucasian and Japanese patients in trial D2308 was not apparent; however; there appears to be a general tendency for a higher frequency of AEs for Asian than Caucasian in the PAN+BTZ+DEX arm of trial D2308 (i.e., thrombocytopenia (Caucasian vs. Asian: 60.7% vs. 70.1%), diarrhea (66.4% vs. 71.7%), fatigue (48.4% vs. 26.8%), hypokalemia (18.4% vs. 44.9%), decreased appetite (20.9% vs. 43.3%), pneumonia (12.7% vs. 26.0%), hypoesthesia (3.7% vs. 15.0%), hepatic function abnormal (0.0% vs. 3.9%), gastroenteritis (2.5% vs. 4.7%), and herpes zoster (2.9% vs. 8.7%)). This difference was not apparent when comparing only the Japanese patients with exposure information in trial D2308 to Caucasian patients with exposure information receiving the same dose in trial 2207 (See Appendix Section 4.1, Table 31).

Given the discrepancy in relative exposure in Japanese compared to Caucasian patients following single agent or combination FARYDAK therapy and the highly variable overlapping data in these trials, combined with the safety results in the Japanese population with exposure information, the effect of Japanese race on PAN exposure is considered indeterminate. We defer to the clinical safety reviewer regarding whether the increased frequency of AEs in Asian patients should be communicated in labeling.

2.3.2.6   Renal impairment

As described in Section 2.2.5.5, the ADME trial B2108 reports that the renal elimination of PAN is approximately half of the total elimination with less than 2.5% eliminated as PAN and less than 1.5% of the dose as the metabolite BJB432. To confirm this the applicant conducted a phase I trial (X2105) of 30 mg FARYDAK orally administered as a single

agent in patients with advanced solid tumors and varying degrees of renal function. Serial dense blood samples and urine samples were collected to characterize PAN and its metabolite B2108 PK during the core phase in all participating patients. The plasma protein binding of PAN was also assessed.

Thirty-seven patients received oral FARYDAK (11 patients with normal renal function, 10 patients with mild renal impairment, 10 patients with moderate renal impairment and 6 patients with severe renal impairment) in this trial. The PK parameters for the normal and renal impairment groups studied are reported in Table 14. The PAN geometric mean AUC_{0-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. The geometric mean exposures from the normal renal function group in this trial were higher than those from the normal hepatic function group in trial X2101, but were consistent with exposures obtained from other phase I single agent trails (see Section 2.2.5.1). While the average demographics where similar across groups, differences in patient characteristics such as age and weight were substantial and may have contributed to the high variability noted in the PK parameters. The extensive cancer related comorbidities in this population was also a likely factor. The applicant attempted to adjust the exposure parameters for weight and age (see Table 15) but this did not impact the interpretation of these data significantly.

The average protein binding for patients with normal kidney function, and with mild, moderate and severe renal impairment was 87.7%, 83.3%, 84.9% and 86.4%, respectively. Given the observed variability, it is unlikely that there is a difference in the PAN binding to plasma proteins among the subjects of different degrees of renal impairment that would impact systemic exposure enough to require a dose modification.

Table 14: Summary of single agent mean (%CV) PAN plasma PK parameters from trial X2105, by renal function group, following a single 30 mg oral dose of FARYDAK

PK Parameter (unit)	Normal (N=11)	Mild (N=10)	Moderate (N=10)	Severe (N=6)
T_{max} (h)	1.02 (0.5-4.0)	1.0 (0.5-4.3)	1.0 (0.5-2.0)	0.75 (0.5-4.0)
C_{max} (ng/mL)	31.0 (116.7)	18.2 (68.6)	29.6 (92.5)	14.0 (82.2)
AUC_{0-48} (ng*h/mL)	188.7 (87.5)	117.7 (66.8)	177.3 (77.3)	111.2 (49.1)
AUC_{0-inf} (ng*h/mL)	224.5 (98.6)	144.3 (62.1)	223.1 (76.7)	131.7 (49.5)
CL/F (L/h)	133.7 (98.6)	207.9 (62.1)	134.5 (76.7)	227.8 (49.5)
CLr (mL/h)	1.39 (13.0)	1.24 (7.29)	1.32 (5.1)	1.28 (8.55)
V_z/F (L)	5646 (41.7)	9922 (82.9)	6404 (76.9)	9039 (31.7)
$T_{1/2}$ (h)	29.3 (56.9)	33.1(26.0)	33.0 (21.5)	27.5 (23.8)

Source: Applicant's final trial report for trial X2105

Table 15: Adjusted Geometric mean ratios for exposure parameters in trial X2105

PK Parameter (unit)	Normal (N=11)	Mild (N=10)		Moderate (N=10)		Severe	(N=6)
	Adj GM	Adj GM	GMR	Adj GM	GMR	Adj GM	GMR
T_{max} (h)	1.02	1	-0.01 [-0.97; 0.50]	1	-0.02 [-.97; 0.50]	0.75	-0.01 [-1.18; 0.50]
C_{max} (ng/mL)	29.59	18.34	0.62 [0.33;1.16]	32.79	1.11 [0.56; 2.19]	14.18	0.48 [0.23 0.1]
$AUC_{0\text{-}inf}$ (ng*h/mL)	217.85	145.14	0.666 [0.39; 1.15]	227.95	1.05 [0.58; 1.89]	133.61	0.61 [0.33 1.16]

Adj GM= Geometric mean adjusted for baseline age and BSA in a linear mixed model analysis
GMR = Adjusted Geometric mean ratio [90% confidence interval]
Source: Applicant's final trial report for trial X2105

BJB432 plasma exposure (geometric mean $AUC_{0\text{-}inf}$) values were 144.6, 117.4, 251.0 and 158.0 ng·hr/mL in the normal renal function and in the mild, moderate and severe renal impairment groups, respectively with large variability (%CV geo-mean 69-138). Geometric mean ratio of $AUC_{0\text{-}inf}$ of BJB432 over the parent compound (PAN) was 0.64 in patients with normal renal function and 0.81, 1.13 and 1.20 in patients with mild, moderate and severe renal dysfunction, respectively. There were no cases of QTcF prolongation (absolute QTcF >480 ms, relative QTcF >60 ms).

2.3.2.7 Hepatic impairment

As described in Section 2.2.5.5, the ADME trial B2108 reports that the hepatic elimination of PAN is approximately half of the total elimination. Metabolism is the primary route of hepatic elimination leading to a biliary/fecal elimination of 0 to 3.3% as parent compound and 1.5 to 22.5% of the dose as the metabolite BJB432. To confirm this, the applicant conducted a phase I trial where 30 mg FARYDAK was orally administered in patients with advanced solid tumors and varying degrees of hepatic function. Serial dense blood samples were collected characterize PAN and its metabolite B2108 PK during the core phase in all participating patients. The plasma protein binding of PAN was also assessed.

Twenty-five patients received oral FARYDAK (10 patients with normal hepatic function, 8 patients with mild hepatic dysfunction, 6 patients with moderate hepatic dysfunction, and 1 patient with severe hepatic dysfunction based upon National Cancer Institute, Cancer Therapy Evaluation Program (NCI-CTEP) criteria) in this trial. The PK parameters for the normal and hepatic impairment groups studied are reported in Table 16. Pharmacokinetic information from the severe hepatic impairment group is considered indeterminate given the small sample size. The geometric mean $AUC_{0\text{-}inf}$ of PAN was increased by 43%, 105%, and 81%, respectively, in patients with mild, moderate, and severe hepatic impairment.. The geometric mean values of C_{max} followed similar pattern. Using Child-Pugh criteria, patients with mild (n=9) or moderate (n=5) hepatic impairment had a $AUC_{0\text{-}inf}$ GMR 66% and 78% greater and C_{max} GMR 92% and 40% greater than patients with normal hepatic function (n=10), respectively. While the average demographics where similar across groups the intra-patient variability with regard to the significant covariates age and weight were substantial and may have contributed to the high variability noted in the PK parameters. The extensive cancer related comorbidities in this population was also a likely factor. The applicant attempted to adjust the exposure parameters for weight and age (see Table 17) but this did not impact the interpretation of these data significantly.

The average protein binding for patients with normal hepatic function, and with mild and moderate hepatic impairment was 84.1%, 83.9% and 76.5%, respectively. Given the

observed variability, it is unlikely that there is a difference in the PAN binding to plasma proteins among the subjects with these different degrees of hepatic impairment that would impact systemic exposure enough to require a dose modification. The impact of severe hepatic impairment is not known.

Table 16: Summary of single agent FARYDAK plasma PK parameters from trial X2101, by hepatic function group[a], following a single 30 mg oral dose of FARYDAK

PK Parameter (unit)	Normal (N=10)	Mild (N=7)	Moderate (N=6)	Severe (N=1)
T_{max} (h)	2.0 (0.5-7.0)	2.0 (0.5-4.0)	2.0 (1.0-4.0)	2.0 (2.0-2.0)
C_{max} (ng/mL)	18.5 (81.18)	29.1 (57.3)	33.9 (50.9)	31.2 (NE)
AUC_{0-48} (ng*h/mL)	125.0 (70.3)	183.9 (54.2)	249.9 (43.2)	235.4 (NE)
AUC_{0-inf} (ng*h/mL)	150.3 (72.3)	214.8 (56.3)	308.0 (44.2)	272.3 (NE)
CL/F (L/h)	199.6 (72.3)	139.7 (56.3)	97.4 (44.2)	110.2 (NE)
V_z/F (L)	8295(54.7)	5297 (48.1)	4864 (35.1)	3157 (NE)
$T_{1/2}$ (h)	28.8 (27.3)	26.3 (27.6)	34.6 (31.5)	19.9 (NE)

a= NCI-CTEP criteria
Source: Applicant's final trial report for trial X2101

Table 17: Adjusted geometric mean ratios for exposure parameters in trial X2101

PK Parameter (unit)	Normal (N=10)	Mild (N=7)		Moderate (N=6)		Severe	(N=1)
	Adj GM	Adj GM	GMR	Adj GM	GMR	Adj GM	GMR
T_{max} (h)	2	2	0 [-1.03; 1.03]	2	0 [-.1.00; 1.50]	2	0 [-5.00; 1.50]
C_{max} (ng/mL)	16.29	32.35	1.99 [1.12;1.16]	42.20	2.59 [1.32; 5.07]	29.91	1.84 [0.61; 5.49]
AUC_{0-inf} (ng*h/mL)	151.63	214.58	1.42 [0.80; 2.51]	291.79	1.92 [0.98; 3.76]	272.12	1.79 [0.60 5.37]

Adj GM= Geometric mean adjusted for baseline age and BSA in a linear mixed model analysis
GMR = Adjusted Geometric mean ratio [90% confidence interval]
Source: Applicant's final trial report for trial X2101

BJB432 plasma exposure (geometric mean AUC_{0-inf}) values were 183.9, 132.9 and 308.3 ng·hr/mL in the normal, mild and moderate liver dysfunction groups, respectively with large variability (%CV 30-100), and 190.2 ng·hr/mL in the single patient with severe liver impairment. The GMR of AUC_{0-inf} of BJB432 over the parent compound (PAN) was 1.2 in patients with normal liver function and 0.62 and 1.0 in patients with mild and moderate liver dysfunction, respectively. There were no cases of QTcF prolongation (absolute QTcF >480 ms, relative QTcF >60 ms).

Given the ADME profile of single agent PAN combined with the less than optimal exposure results from trial X2101 and the 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. 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 is insufficient PK data for patients with severe hepatic impairment in order to make reliable exposure assessment.

2.3.2.8 Genetics

The applicant's assessment of the impact of pharmacogenomics on the exposure of PAN was minimal in this application. CYP3A4 is expected to be the main contributor to the oxidative metabolism of PAN. Genetic variants that affect CYP3A4 activity are rare. The CYP3A4*1B polymorphism is common but does not consistently affect CYP3A substrate metabolism. CYP3A5 dysfunction resulting from the *3 and *6 alleles is common in non-black and non-Asians; whites are not typically homozygous for functional CYP3A5.

Genetic polymorphism status in CYP3A4 and CYP3A5 genes were explored at baseline in trial B2110. No subjects carried the variant CYP3A4*1B allele. CYP3A5*3 was present in all subjects (3 CYP3A5*1/*3, 11 CYP3A5*3/*3). No apparent differences in PAN Cmax or AUC values were found between subjects with CYP3A5*1/*3 and CYP3A5*3/*3 genotypes. While these data do not rule out a pharmacogenetic effect on exposure, a substantive impact of genotyping status of CYP3A genes on PAN disposition is unlikely.

2.3.2.9 What pregnancy and lactation use information is there in the application?
Pregnancy and lactation was not evaluated in humans.

2.3.2.10 Other human factors that are important to understanding the drug's efficacy and safety
None

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
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 PK-PD 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. In the dose escalation phase of trial B2207, FARYDAK doses of 10 to 30 mg TIW weekly were combined with 1.0 -1.3 mg/m2 BTZ on Days 1, 4, 8 and 11. Best overall response generally increased with increase in PAN plasma exposure. Therefore a reduction in PAN exposure could potentially affect efficacy.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.
Based on the principle of exposure matching, patients receiving FARYDAK concurrently with a strong inhibitor of CYP3A4 should receive a starting dose of 15 mg with frequent monitoring (see Section 2.4.2.2). In addition, the use of 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 (see Section 2.4.2.2).

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Based on in vitro studies, PAN is metabolized by multiple liver enzymes including CYP3A4, CYP2D6 and CYP2C19. In addition, in vitro incubation of PAN in the presence and absence of selective CYP inhibitors suggests the potential for an interaction with the strong CYP3A4 inhibitors. See section 2.2.5.6 for additional details regarding these in vitro studies.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, PAN is primarily metabolized by CYP2C19, CYP2D6, and CYP3A4. The fraction metabolized through CYP P450 3A accounts for approximately 40% of PAN elimination, based on the results of the ADME trial, with additional minor contributions from CYP2D6 and 2C19 also reported in vitro (see section 2.2.5.6). The influence of genetic polymorphisms in these CYP enzymes was not addressed in vitro.

The applicant conducted a phase Ib, open-label trial to investigate the effect of ketoconazole, a strong CYP3A4 inhibitor on single agent oral PAN exposure in patients (N=14) with advanced solid tumors. Oral FARYDAK was administered at 20 mg on Day 1 and single-agent ketoconazole at 400 mg daily on Days 5 to 9. On Day 9 FARYDAK 20 mg was administered 1 hour after ketoconazole. Blood samples for the PAN PK evaluation were collected following 20 mg FARYDAK dose at pre-dose and serial time-points post-dose up to 48 hours on Days 1 (single agent FARYDAK) and 8 (combination of ketoconazole and FARYDAK). Genotyping analysis of CYP3A4*1B, CYP3A5*2, *3, *6 and *7 was performed and available in all 14 patients.

The PK parameters following an oral dose of 20 mg FARYDAK (Day 1) and in combination with 400 mg of ketoconazole (Day 8) are reported in Table 18. The interpretation of half-life is limited by the short 48 hour sampling time.. The applicant attempted to adjust the exposure parameters for weight and age (see Table 19) but this did not impact the interpretation of these data significantly. The PAN geometric mean ($CI_{90\%}$) C_{max} and AUC_{0-48} following concurrent therapy of FARYDAK and ketoconazole were 62% (21%; 117%) and 73% (44%; 107%) higher compared to treatment with FARYDAK alone, respectively. Ketoconazole concentrations were maintained fairly consistently when the drug was given either alone or with FARYDAK. No increases in QT/QTcB/QTcF intervals exceeding 60 ms and no new absolute QTcF intervals exceeding 480 ms were observed during the Core (DDI) Phase.

Table 18: Geometric mean (CV%) of PAN PK parameters following an oral dose of 20 mg FARYDAK (Day 1) and in combination with 400 mg of ketoconazole (Day 8) in 14 patients with advanced solid tumors

Parameter	Day 1 PAN alone	Day 8 PAN + Keto	Ratio D8/D1
T_{max} (hr)[a]	1 [0.5-4]	1 [0.5-6]	1
C_{max} (ng/mL)	18.52 (42.6)	29.98 (93.3%)	1.62
AUC_{0-24} (ng*hr/mL)	105.4 (34%)	164 (59.8%)	1.56
AUC_{0-inf} (ng*hr/mL)	133 (39.9%)[b]	220.7 (54.6%)[c]	1.66
$T_{1/2}$(h)	11.3 (39.7%)[b]	12.23 (34.1%)[b]	NA

a= median [range]; b= n=13; c= n=12
NA= Not applicable; PAN=panobinostat; Keto=ketoconazole
Source: Applicant's final trial report for trial B2110

Table 19: Statistical analysis of primary PK parameters of PAN in trial B2110

PK Parameter	Treatment	n	Adj GM	Comp.	GMR	90% CI	
						Lower	Upper
C_{max} (ng/mL)	Pano alone	14	18.5	Test:Ref	1.62	1.211	2.166
	Pano + Keto	14	30.0				
AUC_{0-48} (ng.h/mL)	Pano alone	11	120.0	Test:Ref	1.73	1.444	2.065
	Pano + Keto	13	207.2				
AUC_{0-inf} (ng.h/mL)	Pano alone	11	126.0	Test:Ref	1.78	1.451	2.177
	Pano + Keto	12	224.0				
T_{max} (h)	Pano alone	14	1.00	Test-Ref	0.00	-2.50	3.00
	Pano + Keto	14	1.00				

Adj GM= Geometric mean adjusted for baseline age and BSA in a linear mixed model analysis; GMR = Adjusted Geometric mean ratio [90% confidence interval]; Comp.=comparison
Source: Applicant's final trial report for trial B2110

Fourteen patients had homozygous wild-type CYP3A4*1A genotype, 11 had homozygous CYP3A5*3, and three had heterozygous CYP3A5*1/*3 genotype. There is no apparent difference in PAN C_{max} or AUC values between patients carrying CYP3A5*1/*3 and CYP3A5*3/*3 alleles (Figure 12); however the CYP3A5*1/*3 genotype population was too small to draw any definitive conclusions.
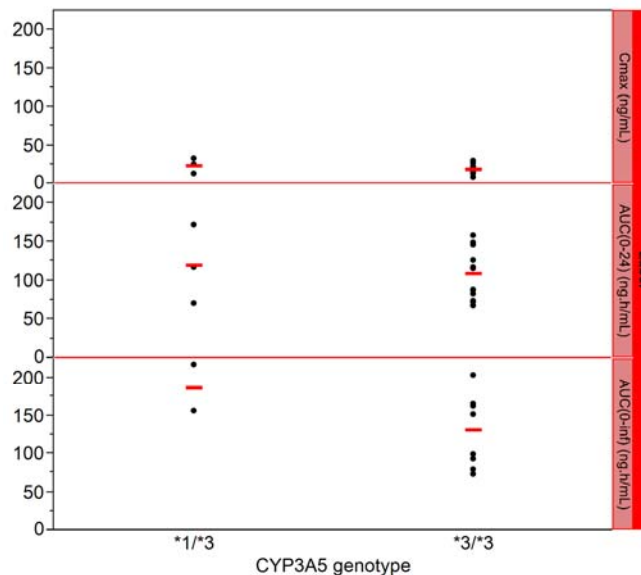
Source: Applicant's final trial report and dataset for trial B2110

Figure 12: Panobinostat Day 1 exposure in patients with homozygous G/G CYP3A5*3/*3 and heterozygous A/G CYP3A5*1/*3 alleles (red marker at arithmetic mean)

Based on the in vitro findings and the reported exposure changes noted in the above DDI trial, a dose modification is required for exposure matching. 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.;

The applicant developed a PBPK model as part this NDA submission to evaluate the effect of the strong CYP3A inducer rifampin on PAN exposure and to determine the need for additional in vivo trials. The applicant believes that, based on its analysis, the simulations using the updated PAN model are acceptable for describing the majority of the observed PAN single agent PK and that it can be applied PAN PBPK model to predict the effect of a strong CYP3A inducer rifampin on PAN PK. The Agency reviewed this PBPK model and relevant simulations (see Section 4.2.2) and finds that the strong CYP3A

inducer rifampin will likely result in a decrease in PAN AUC that is greater than 65% based upon the simulations (Table 20). The simulation results suggest there is no practical FARYDAK dose that will provide exposure matching when given concomitantly with strong CYP3A4 inducers. It is unlikely that a dedicated clinical trial will change this conclusion and is not recommended at this time.

Table 20: PBPK simulated PAN PK parameters in the presence or absence of rifampin

Group	N	Mean AUC_{0-24}	Mean AUC_{0-inf}	GM AUC_{0-inf}	Mean C_{max}	GM C_{max}
PAN alone	100	104 (103%)	256 (47%)	231	19.4 (146%)	9.67
PAN + rifampin (Day 7)	100	42.9 (109%)	97.4 (63%)	80.1	8.34 (149%)	4.34
GM ratio (90% CI)				0.35 (0.32-0.38) (65% decrease)		0.45 (0.41-0.49) (55% decrease)

GM =Geometric mean
Source: Applicant's final report for trial 1400354

2.4.2.3   Is the drug an inhibitor and/or an inducer of CYP enzymes?

Yes. Based on in vitro drug-drug interaction studies, PAN was shown to strongly inhibit CYP2D6 and weakly inhibit CYP3A4/5 (time dependent) and CYP2C19. PAN was not shown to be an inducer of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP3A5.

2.4.2.3.1   PAN Related CYP Enzyme Inhibition

In vitro CYP Enzyme Inhibition

The potential of PAN to inhibit CYP enzyme activities was examined in vitro in pooled human liver microsomes in study DMPK R0201469 for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 using standard probe substrates. These findings suggest that it is unlikely that PAN exhibits a high risk of CYP1A2, CYP2C8, CYP2E1 or CYP2C9 inhibition (IC_{50} >100 μM). Moderate risk of inhibition was observed for CYP3A4/5 and CYP2C19 (IC_{50} 15-75 μM) and moderate to high risk of competitive inhibition was observed for CYP2D6 (IC_{50} ~2 μM). Based on these IC_{50} values, the applicant did not determine Ki values for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5 which is acceptable. With a mean C_{max} at the highest proposed therapeutic dose for FARYDAK (20 mg) of 0.062 μM (21.6 ng/mL) and an apparent Ki of 0.167 μM for CYP2D6, the reviewer calculated R value (1+[I]/Ki) is 1.37. This suggests a possibility for PAN to cause clinical drug interactions via inhibition of these CYPs and the need for an additional in vivo trial which was conducted as described below.

The potential of time-dependent inhibition of PAN on CYP enzyme activities was examined in vitro in pooled human liver microsomes in study DMPK R0700973 for CYP1A1, CYP2C9, CYP2D6, and CYP3A4/5 using standard probe substrates. Time-dependent inhibition of CYP1A1, CYP2C9, and CYP2D6 was not observed. However, time- and concentration-dependent inhibition was observed for CYP3A4/5, with a reviewer calculated R2 = 1.4 [R2 = (K_{Obs} + K_{deg})/ K_{deg}, with K_{deg} = 0.000321 min-1 and K_{Obs} = 0.000117] and was NADPH-dependent. Thus, PAN may be a time-dependent inhibitor of CYP3A4/5.

Inhibition of CYP2D6 by PAN

PAN is an inhibitor of CYP2D6 in vitro. The applicant conducted a phase Ib, open-label trial to investigate the effect of oral PAN on dextromethorphan (DM), a CYP2D6 substrate in patients with advanced or metastatic incurable solid tumor that had already progressed on standard therapies or who were following standard therapies and agreed to stop the therapies. During the core (i.e., DDI assessment) phase (first 10 days of Cycle

1) oral FARYDAK 20 mg was administered once per day, on Days 3, 5, and 8. Oral DM at 60 mg was administered on the mornings of Day 1 and Day 8 of Cycle 1 only. On Day 8, the DM dose was administered 1 hour after FARYDAK dose. Dense PK sampling was drawn for PAN on days 3 and 8, DM on days 1 and 8, dextrorphan (DX) on days 1 and 8 and the CYP3A-mediated metabolites 3-methoxymorphinan (3-MEM) on days 1 and 8. Prior to drug administration, CYP2D6 genotyping status was obtained from all patients.

Seventeen patients (10 male; 7 female) were enrolled in this trial and all completed the Core Phase. The PK parameters for DM and its metabolites following an oral dose of DM at 60 mg (Day 1) and in combination with FARYDAK (Day 3, 5, and 8) in the fourteen enrolled extensive metabolizers are reported in Table 21. These DM data were extremely variable (CV% >150%) and limited by several patients having DM concentrations >5% of the C_{max} on day 8. The DM alone exposure and intra-subject variability is consistent with reports in the literature.[3][4] The reason for this variability in DM exposure is indeterminate, but may in part be related to DM absorption given the lower variability in DM half-life reported. PAN exposure on day three (i.e., without DM) did not appear to explain this extreme variability in the change in DM exposure on Day 8 (i.e., PAN+DM) as described in Appendix, Section 4.1 Figure 20.

Table 21: Geometric Mean (CV%) of Dextromethorphan and its metabolites PK parameters by treatment in extensive metabolizers

Parameter	Dextromethorphan (DM)		Dextrorphan (DX)		3-methoxymorphinan (3-MAM)	
	DM	DM+PAN	DM	DM+PAN	DM	DM+PAN
n	14	14	14	14	10	10
C_{max} (ng/mL)	5.1 (272)	9.4 (158)	476 (46)	498.8 (62)	0.52 (124)	0.53 (118)
AUC_{0-24} (ng.h/mL)	50.1 (279)	70.7 (210)	4712.8 (24)	5461.7 (39)	14.8 (176)	18.3 (111)
AUC_{0-48} (ng.h/mL)	61.4 (302)	85.6 (245)	5537.6 (25)	6647.7 (42)	NA	NA
AUC_{0-inf} (ng.h/mL)	59.7 (340)	73.6 (194)	5647 (26)	7010.7 (43)	NA	NA
*T_{max}(h)	2.5 (1-4)	1.8 (0.5-3)	2.5 (1.5-10.1)	3 (1.5-7.0)	1.75 (1.1-4)	3 (0-23)
$T_{1/2}$ (h)	11.4 (39)	11 (55)	8.3 (52)	8.8 (52)	22.0 (105)	19.1 (100)
*MR	0.012 (0.001-0.164)	0.008 (0.002-0.226)	NA	NA	NA	NA

NA= not applicable; MR= metabolic ratio (DM/DX); PAN =panobinostat

Given this variability, the GMR of exposure parameters and their relative 90% confidence intervals were considered unreliable for assessing the impact of PAN on DM exposure. Instead nonparametric descriptive variables for the ratio of PAN+DM to PAN for the DM exposure parameters were evaluated visually (Figure 13). The reported median (range) for the ratio of PAN+DM to PAN for DM Cmax and AUC_{0-inf} is 1.6 (1.2; 3.1) and 1.4(1.2; 2.3), respectively. Removing the apparent outlier changes these values to 1.4 (1.1; 3.2) and 1.4(1.1; 2.9), respectively. In view of the unexplained variability and the nonparametric descriptive assessment, that suggested a change in exposure as high as 200% was possible in 50% of the population, the use of sensitive 2D6 substrates or 2D6 substrates with a narrow therapeutic index should be avoided.

---

[3] Manap RA, Wright CE, Gregory A, et al. The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol* 1999; 48: 382-7.
[4] Pope LE, Khalil MH, Berg JE, et al. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol 2004*; 44, 1132-42.
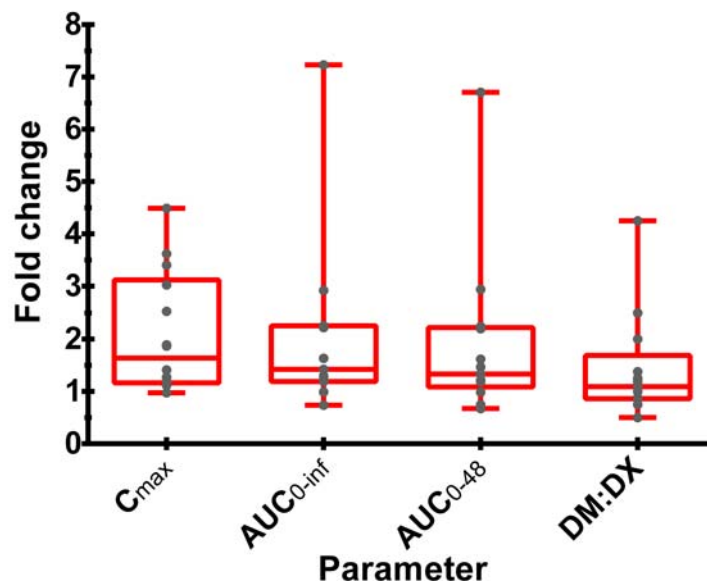
Figure 13: Box whisker plots with data superimposed (grey) for the ratio (DM + PAN/DM) of exposure parameters from trial B2109

The DM+PAN/DM ratio of geometric mean (90% CI) for DX C_{max} and AUC_{0-24} was 1.05 (0.9; 1.29) and 1.3 (1.1; 1.5), respectively. Surprisingly, the DX exposure was greater for DM+PAN compared to DM even though the DM:DX conversion is expected to be reduced. The reason for this is unclear, but hypothetically it could suggest inhibition of DX phase 2 metabolism. The potential for PAN to inhibit UGT is not known; however these are likely involved in its metabolism.

The DM+PAN/DM GMR (90% CI) for DX C_{max} and AUC_{0-24} was 1.02 (0.85; 1.22) and 0.96 (0.74; 1.25), respectively. This analysis is limited because of inadequate detection beyond 8 hours and only 3 patients having AUC_{0-24} for the DM+PAN and DM sampling. In addition, 3-MEM exposure changes related to PAN's inhibition of CYP3A4 was not expected due to the time dependent nature of this effect combined with the single dose FARYDAK treatment in the core phase of this trial. While there is a trend in this trial suggesting that 3-MEM exposure was not influenced by PAN, this analysis is considered inconclusive due to the above limitations.

Summary PK parameters of PAN following a single oral dose of FARYDAK administered alone (Day 3) and in combination with DM (Day 8) are summarized in Table 22. The change in PAN exposure between the first (PAN) and third (DM+PAN) dose appears consistent with previous and expected accumulation following multiple dosing (see Section 2.2.5.1). Therefore the potential for DM affecting PAN exposure is unlikely.

Table 22: Geometric Mean (CV%) of PAN PK parameters by treatment

Parameters (unit)	PAN (1st dose) (N=15)	DM+ PAN (3rd dose) (N=15)
C_{max} (ng/mL)	9.9 (106)	14.2 (192)
AUC_{0-48} (ng.h/mL)	135.9 (74)	216.4 (76)
AUC_{0-inf} (ng.h/mL)	145.5 (90)	258.3 (68)
T_{max}(h)a	2.5 (0.5-4.2)	2 (0-49)
$T_{1/2}$ (h)	9.1 (37)	12.6 (55)

a= Values were median (range) for Tmax

In the core phase of this trial, 3 patients reported a new QTcF reading of > 450 msec; no patient had a new QTcF reading > 480 msec. There were no deaths, clinically significant AEs, or discontinuations from the trial due to an AE during this phase.

Inhibition of CYP3A4 by PAN

The applicant developed a PBPK model as part this NDA submission to evaluate the effect of PAN on CYP3A probe substrate midazolam and to determine the need for additional in vivo trials. The applicant believes that, based on its analysis of the model prediction and sensitivity, PAN will not significantly increase midazolam exposure (midazolam AUC ratio <1.25). The Agency reviewed this PBPK model, relevant simulations, and conducted additional sensitivity analyses (see Section 4.2.2) and finds that the potential for the concurrent use of FARYDAK with sensitive CYP3A4 substrates to result in a change in the CYP3A substrate exposure that requires intervention is unlikely, but not conclusive (Table 23).   (b) (4)

labeling should communicate that PBPK simulations suggested that the effect of PAN on the sensitive CYP3A substrate midazolam is minimal (e.g. exposure increase less than (b) (4).   (b) (4)

Table 23: Prediction of the drug interaction of LBH589 (20 mg MWF weekly) and midazolam (5 mg single dose on day 15)

Group	N	Mean AUC_{0-inf}	GM AUC_{0-inf}	Mean C_{max}	GM C_{max}
Midazolam alone	100	70.0 (64%)	56.2	17.1 (57%)	14.5
Midazolam + PAN	100	73.2 (64%)	58.7	17.8 (56%)	15.1
GM ratio (90% CI)			1.04 (1.04-1.05)		1.04 (1.03-1.04)

GM =Geometric mean

2.4.2.3.2   PAN Related CYP Enzyme Inhibition

In vitro CYP Enzyme Induction

The potential for PAN to induce CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 mRNA and activity was examined in vitro using primary human hepatocyctes from three individual donors in study DMPK R0500725. For all CYP isozymes tested, mRNA induction was within 2-fold of the vehicle control and/or less than 40% of the positive control. Therefore the reviewer agrees with the applicant's position that PAN is an unlikely inducer of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 enzymes.

2.4.2.4   Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

In study DMPK R0500488, PAN exhibited a high apparent permeability in Caco-2 cell monolayers, with a Papp ratio (B-A/A-B) of ~15. MK571 and LY353979 inhibitors were used

to explore the role of MRP and P-gp on PAN transport, respectively. MK571 did not appreciably affect the A-B or B-A rates, suggesting that PAN is not an inhibitor of MRP. In the presence of LY335979, PAN transport was altered such that an increased A-B flux was observed, which resulted in a permeability ratio of 1. Although this suggests that PAN is a substrate of P-gp, PAN is a BCS class 2 drug suggesting that intestinal absorption is not a rate-limiting step. In flow cytometry studies DMPK R0500600-01, PAN did not inhibit the efflux of the fluorescent probe Rhodamine123 by P-gp. Therefore, it is unlikely that PAN will inhibit the P-gp mediated transport of concomitant drugs that are P-gp substrates.

2.4.2.5   Are there other metabolic/transporter pathways that may be important?

Hepatocellular uptake of PAN by transporters OCT1, OAT2, OATPs was not altered in the presence of transporter specific inhibitors in study DMPK R1200557. In studies of PAN as an inhibitor (DMPK R1200558, DMPK R1200559, and DMPK R1200560), PAN did not inhibit OAT1 but was found to be an inhibitor of OATP1B1, OATP1B3, OAT3, OCT1, and OCT2. The reviewer calculated R for both OATP1B1 and OATP1B3 was 1.0, and the reviewer calculated Cmax/IC50 for OAT3, OCT1 and OCT2 were < 0.1 (0.003, 0.01, and .0001, respectively). The reviewer agrees with the applicant that these results suggest that clinical DDIs with respect to OATP1B1, OATP1B3, OAT3, OCT1, and OCT2 inhibition are unlikely.

In flow cytometry study DMPK R1300018, PAN did not inhibit the efflux of the fluorescent probe Bodipy FL prazosin by BCRP. Therefore, it is unlikely that PAN will inhibit the BCRP mediated transport of concomitant drugs that are BCRP substrates.

Study DMPK R0500725 examined the potential for PAN to induce UGT1A1, ABCB1 (P-gp), and ABCC2 (MRP2) in vitro in primary human hepatocyctes. For all three, mRNA induction was within 2-fold of the vehicle control and/or less than 40% of the positive control, suggesting that it is unlikely that PAN is an inducer of UGT1A1, ABCB1 (P-gp), and ABCC2 (MRP2).

2.4.2.6   Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes. Under the proposed indication FARYDAK is combined with BTZ and DEX. The interaction potential between these drugs was not evaluated in vitro. The potential effect of BTZ and DEX on PAN and vice versa was assessed descriptively as part of the phase Ib trial B2207 which evaluated several dosing regimens of orally administered FARYDAK in combination with intravenous BTZ, with and without oral DEX in 62 patients with MM. A description of the trial design can be found in Section 2.2.5.1.

Summary PK parameters of PAN in combination with BTZ (Cycle 1 Day 8) and PAN alone (Cycle 1 Day 15) are summarized in Appendix, Section 4.1 Table 32. Although the geometric mean exposure of PAN alone appears to be low as compared to historical PAN single-agent exposure (see Section 2.2.5.1), it is likely due to the small number of subjects and high variability in PAN exposure. These shortcomings also limit the usefulness of parametric summary statistics to evaluate the effect of BTZ on PAN exposure. Therefore, the data was evaluated visually for obvious signals of increased PAN exposure with concurrent BTZ therapy (Figure 14). While a DDI cannot be definitively ruled out by this analysis, the exposure of PAN in combination with BTZ appears to be consistent with the PAN alone exposure in each cohort given the high variability and no obvious signals suggesting DDI were noted.

PAN or P= panobinostat; B+P= bortezomib + panobinostat;
Source: Applicant's final trial report and dataset for trial B2207

Figure 14: Box whisker plot with superimposed data points (red) of PAN exposure parameters following treatment with PAN alone or in combination with BTZ in adult patients with MM (trial B2207)

The potential effect of PAN on BTZ exposure was limited because treatment with BTZ alone was not assessed. Therefore, this potential DDI was assessed by a visual evaluation of the data itself for obvious signals of increased BTZ exposure with increasing doses of concurrent FARYDAK therapy (Figure 15). While a DDI cannot be definitively ruled out by this analysis, the exposure of BTZ overlaps across cohorts regardless of FARYDAK or BTZ doses and no obvious signals suggesting DDI were noted.

P= panobinostat; B+P= bortezomib + panobinostat; BTZ= bortezomib
Source: Applicant's final trial report and dataset for trial B2207
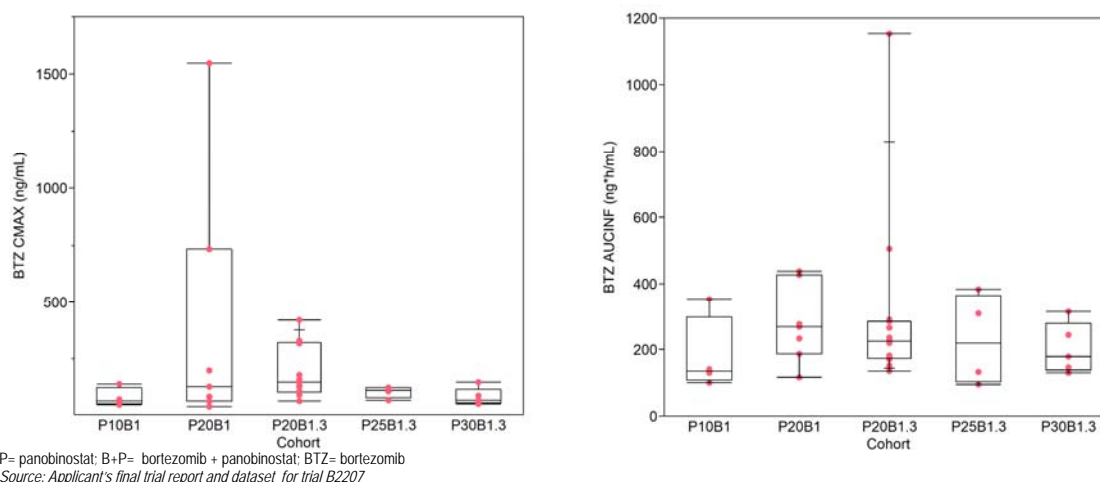
Figure 15: Box whisker plot with superimposed data points (red) of BTZ exposure parameters following treatment with FARYDAK alone or in combination with BTZ in adult patients with MM (trial B2207)

To assess the impact of DEX on PAN exposure, DEX 20 mg was administered intermittently in combination with BTZ and FARYDAK from Cycle 2 on (i.e., D1, D2, D4, D5, D8, D9, D11 and D12 during a 21-day cycle) of the dose expansion phase of trial 2207and compared to PAN+BTZ treatment in cycle 1. The applicant reports that based on an anecdotal assessment of summary statistics PAN exposure on Cycle 2 Day 8 (in combination with DEX) is approximately 20% lower than those from Cycle 1 Day 8 and suggests that this is related to the enzyme induction potential of CYP3A4 by DEX. While the potential for CYP3A4 induction by DEX could not be ruled out by a visual comparative analysis (Figure

16) of these data, the FDA reviewer finds that the small sample size and high intra-individual variability made any conclusions or quantification of an exposure reduction following the inclusion of DEX into the treatment regimen for the proposed indication unreliable. (b) (4)

PAN= panobinostat; P+B= panobinostat + bortezomib ; P+B+D= panobinostat + bortezomib + dexamethasone
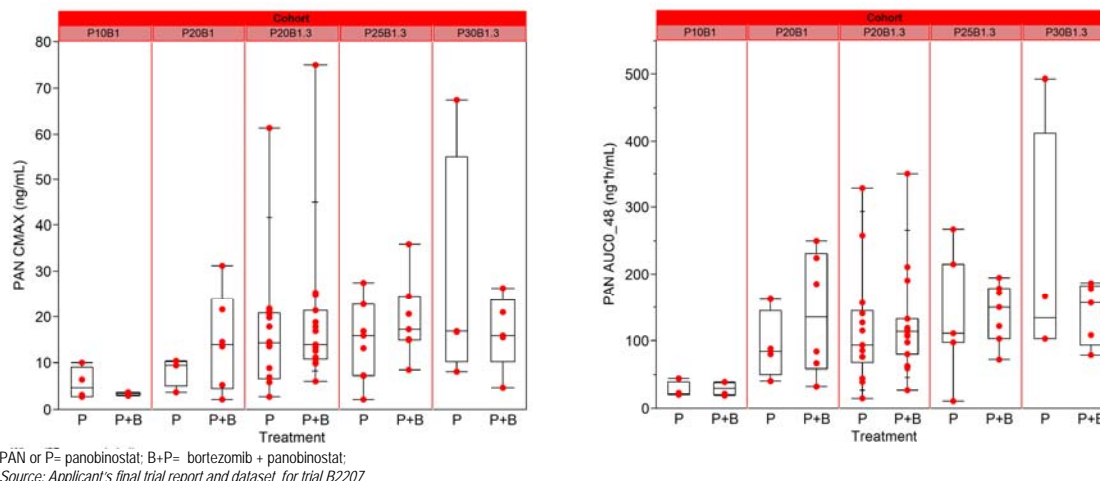*Source: Applicant's final trial report and dataset for trial B2207*
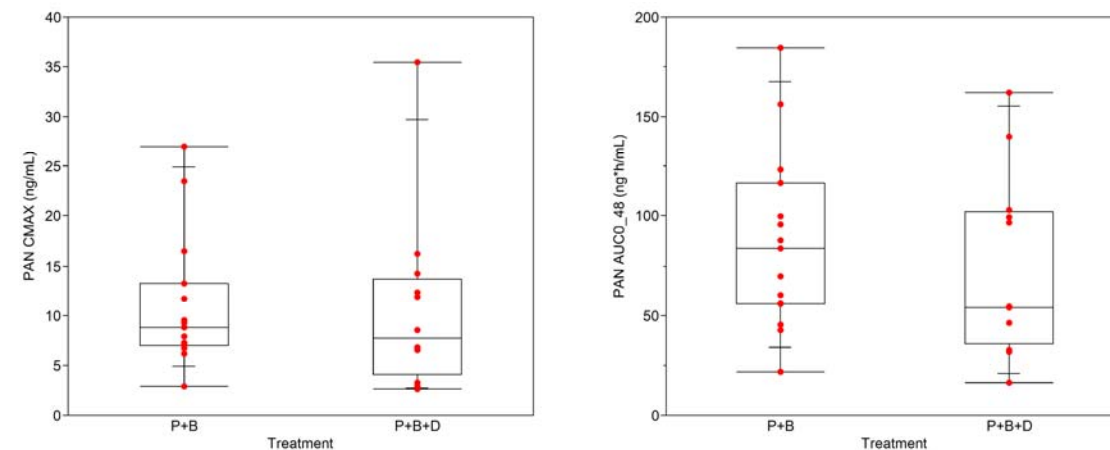
Figure 16: Box whisker plot with superimposed data points (red) of PAN exposure parameters following treatment with FARYDAK in combination with either BTZ alone or BTZ+DEX in adult patients with MM (trial B2207)

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

This is an agent designed to be used in severely ill cancer patients with multiple comorbidities. There are no specific medicines that would likely be administered in the target population outside of the proposed combination regimen. Patients will likely be on diverse treatments.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. See Sections 2.4.2.2 and 2.4.2.6 above.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes. Given PAN has been reported to increase the QTc interval (see Section 2.2.4.4), concomitant use of drugs that are known to prolong the QT interval should be avoided.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Additional investigation into the potential for PAN to inhibit the UGT metabolic pathway should be suggested to the applicant, but this is not required at this time.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

See Section 2.2.4.5.

2.5 General Biopharmaceutics

For the studies where oral administration of PAN was used, either the pilot clinical service formulation (CSF) or the final market image (FMI) was used. The pilot CSF was used in several early phase I oral studies (B1101, B2101 and B2102); it was a   (b) (4) formulation. This pilot formulation was subsequently modified to improve the manufacturing process by using   (b) (4) an anhydrous salt formulation (FMI). Subsequently, four phase II studies (B2201, B2202, B2203, and B2211) and five clinical pharmacology (CP) studies (B2109, B2110, B2111, X2101 and X2105) were conducted using the FMI formulation, which was also used for the pivotal phase 3 Trial D2308 and is intended for commercialization.

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

PAN (LBH589) lactate, anhydrous has high permeability and pH dependent solubility with low solubility at pH 7.6 (see Section 2.2.5.3), and therefore is a likely Biopharmaceutics Classification System (BCS) II compound. However, we defer to the Office of New Drug Quality Assessment (ONDQA) regarding the final determination of BCS Classification per a memorandum of understanding with OCP.

2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal trial formulation in terms of comparative exposure?

The proposed commercial formulation (supplied as (b) (4) 15 mg, or 20 mg capsules) was used in the pivotal phase 3 trial. The absolute bioavailability of the clinical service formulation (CSF) and final market image (FMI) of PAN, defined as the geometric mean ratio (GMR) between intravenous (2 trials) and oral (8 trials) AUC_{0-inf} values, was estimated to be approximately 21% based on a pop-PK approach which included the dense PK sampling as well as additional trough samples (see Section 2.2.5.3).

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

The applicant is seeking a waiver from conducting in-vivo bioavailability studies for the 10 mg and 15 mg hard gelatin capsule strengths due to the establishment of bioequivalence with the highest strength (20 mg) based upon composition, manufacturing process, in vitro dissolution, and apparent linear PK. We defer to the ONDQA regarding whether the requested waiver should be granted per a memorandum of understanding with OCP.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

A semi-mechanistic indirect PK-PD 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. In the dose escalation phase of trial B2207, FARYDAK doses of 10 to 30 mg TIW weekly were combined with 1.0 -1.3 mg/m^2 BTZ on Days 1, 4, 8 and 11. Best overall response generally increased with increase in PAN plasma exposure. Therefore an

increase in PAN exposure could increase the risk of thrombocytopenia and a reduction in exposure may affect efficacy.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

The proposed commercial formulation (supplied as ^{(b) (4)} 15 mg, or 20 mg capsules) was used in the pivotal phase 3 trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food effect was evaluated in a randomized 3-way crossover formal food effect trial in patients with advanced solid tumors that were randomized to receive 20 mg FARYDAK on days 1, 8, and 15 as part of a 21-day cycle after either an overnight fast, 30-minutes after a high-fat breakfast (i.e., 1000 calories with approximately 50% of the calories from fat), or 1-hour after a "normal" breakfast (i.e., 500 calories with approximately 35% of the calories from fat). Single agent PAN PK was evaluated using dense sampling over 48 hours after each patient had received three of the above prandial conditions on Days 1, 8, and 15.

A total of 36 patients were evaluated, of which 33 patients had evaluable PK. There were 8 PK profiles that had non-zero pre-dose concentrations suggesting some potential carryover. However, the pre-dose concentrations exceeded 5% of C_{max} values in two occasions and these were excluded from the PK analysis. Given that the inter-patient variability in the systemic exposure of PAN was high (i.e., 59%) with or without food in this trial, box whisker plots, with superimposed raw data, were created and used to describe the C_{max} and AUC_{0-48} of PAN (Figure 17). Based on this information, food (high fat or normal meal) appears to decrease the C_{max} of PAN by approximately 50%, but only marginally decreases AUC_{0-48}. The median T_{max} was delayed by 1 and 2.5 hours in the presence of normal and high fat meal, respectively. This delayed absorption may explain the greater effect of food on PAN C_{max} rather than $AUC_{0-48.}$ Similarly, an analysis of fed/fasting geometric mean ratio (Table 24) for the high fat meal cohort reported that PAN C_{max} and AUC_{0-48} was lowered by an average of 44% and 15%, respectively. This difference is consistent with findings in Figure 17. In addition, the effect of food on T_{max} and C_{max} of PAN observed in this trial was qualitatively described using a PBPK model submitted by the applicant (See Appendix Section 4.2.2).

A food effect cannot be ruled out based on these results because the 90% confidence intervals for the fed/fasting geometric mean ratio for the high fat meal are outside of the 0.8 to 1.25 equivalence criteria. Despite this, the potential impact of a high fat meal on PAN exposure during chronic administration in patients is not expected to have substantial clinical consequences that would necessitate food to be restricted around FARYDAK administration. Further, FARYDAK was administered without regard to food in the pivotal trial D2308. The product labeling should communicate the observed differences in exposure and T_{max} for the high fat meal cohort and that FARYDAK can be administered without regard to food.
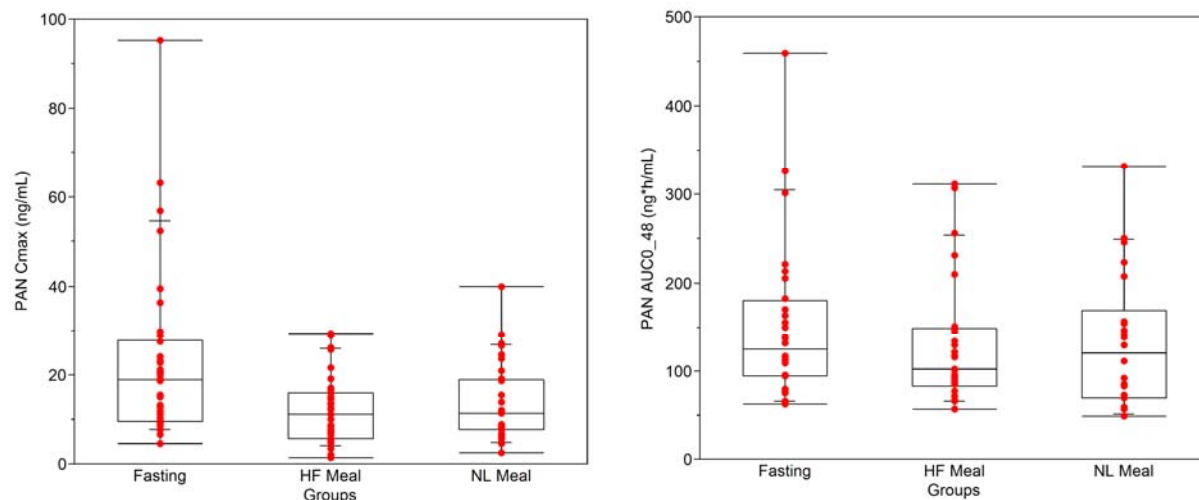
PAN= panobinostat; HF Meal = High fat breakfast; NL meal = "normal" breakfast
Source: Applicant's final trial report and dataset for trial B2111

Figure 17: Box whisker plot with superimposed data points (red) of PAN exposure parameters following treatment with FARYDAK after either an overnight fast, 30-minutes after a high-fat (HF) breakfast after a "normal" (NL) breakfast in adult patients with advanced solid tumors (trial B2111)

Table 24: Summary of statistical analysis of PAN primary PK parameters

PK parameter	Treatment	n	Adjusted Geo-mean*	Comparison	Treatment comparison		
					Geo-mean Ratio	90% CI	
						Lower	Upper
C_{max} (ng/mL)	Fasting	33	17.5				
	High Fat	34	9.8	H : F	0.56	0.446	0.704
	Normal Meal	31	11.2	N : F	0.64	0.504	0.811
$AUC_{(0-48)}$ (h.ng/mL)	Fasting	27	127.9				
	High Fat	29	108.2	H : F	0.85	0.745	0.962
	Normal Meal	21	112.8	N : F	0.88	0.763	1.020
T_{max} (h)**	Fasting	33	1.50				
	High Fat	34	4.00	H : F	2.48	-2.000	7.020
	Normal Meal	31	2.50	N : F	1.45	-2.500	2.017

Fasting (F), High (H) and Normal (N): panobinostat taken under fasting, 30 min after starting a high fat meal or 60 min after starting a normal meal.
*Geo-mean = geometric mean. Geo-mean, Geo-mean ratio and 90% CI are determined from a mixed effect model for log-PK parameters with fixed effects (sequence, period, and treatment) and a random effect (patient nested with sequence)
** For Tmax, median is presented under "Geo-mean", median difference under "Geo-mean ratio", minimum and maximum difference under "Lower" and "Upper"
Source: Applicant's final trial report and dataset for trial B2111

2.5.4 When would a fed BE trial be appropriate and was one conducted?

Not applicable.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

We defer to the ONDQA regarding this issue per a memorandum of understanding with OCP.

2.5.6   If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

The proposed commercial formulation (supplied as ⬛ (b) (4), 15 mg, or 20 mg capsules) was used in the pivotal phase 3 trial.

2.5.7   If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8   If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9   What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

No.

2.6   Analytical Section

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies are outlined in Table 25.

Table 25: Bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

Panobinostat	
Plasma (A-01)	A semi-automated protein precipitation extraction of human plasma samples followed by analysis via reversed-phase high performance liquid chromatography (HPLC) [report DMPK R0101758A-01] on: • ChromegaBond PSC C8/C18 column (3 µm particle size, 50×2.1 mm) with a gradient elution using (1) 10 mM ammonium formate (containing 0.2% formic acid, mobile phase A), and acetonitrile (mobile phase B); or (2) 10% acetonitrile in water (containing 0.1% formic acid and 0.1% acetic acid, mobile phase A) and 90% acetonitrile in water (containing 0.25% formic acid and 0.25% acetic acid, mobile phase B). • Xbridge C8 column (2.5 µm particle size, 50 × 2.1 mm) was used with gradient elution using 10% acetonitrile in water (containing 0.1% formic acid and 0.1% acetic acid, mobile phase A) and 90% acetonitrile in water (containing 0.25% formic acid and 0.25% acetic acid, mobile phase B). [M+6]LBH589 was used as the internal standard.
Urine (D-01)	A semi-automated method was employed for human urine sample preparation followed by LC-MS/MS analysis [report DMPK R0101758D-01]. After transfer and evaporation of the sample extracts to dryness, the sample residues were reconstituted using 10% aqueous acetonitrile and 0.2% formic acid, followed by analysis via reversed-phase HPLC on an Xbridge C18 (3.5 µm particle size, 4.6 ×

Table 25: Bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

	150 mm) column with gradient elution using 10% acetonitrile in water (containing 0.1% formic acid and 0.1% acetic acid, mobile phase A) and 90% acetonitrile in water (containing 0.25% formic acid and 0.25% acetic acid, mobile phase B). [M+6]LBH589 was used as the internal standard.
Panobinostat and BJB432	
Plasma (01)	A semi-automated protein precipitation extraction of human plasma samples was employed to separate the analytes (PAN and BJB432) from the bulk matrix and protein. After transfer and evaporation of the extracts to dryness, the sample residues were reconstituted using 10% aqueous acetonitrile and 0.2% formic acid, followed by analysis via reversed-phase HPLC [DMPK R0600958-01] on an Xbridge C18 (3.5 μm particle size, 4.6 × 150 mm) column with gradient elution using 10% acetonitrile in water (containing 0.1% formic acid and 0.1% acetic acid, mobile phase A) and 90% acetonitrile in water (containing 0.25% formic acid and 0.25% acetic acid, mobile phase B). [M+6]BJB432 and [M+6]LBH589 were used as internal standards.

Source: Applicant's reports DMPK R0101758A-01, DMPK R0600958-01 and DMPK R0101758D-01

2.6.2 Which metabolites have been selected for analysis and why?

BJB432 was also selected for analysis. BJB432, is a reductive metabolite of PAN, is one of the approximately 77 human biotransformation products of PAN circulating in plasma and accounts for <1.5% of the total drug related material in plasma. In vitro, BJB432 inhibits hERG potassium channel activity with an IC_{50} value of 1.6 μM in vitro, but is not pharmacologically active vis-a vis HDAC inhibition.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentrations were measured. Given the plasma protein binding of PAN is < 90% and does not appear to be effected by hepatic or renal impairment, this decision is acceptable.

2.6.4 What bioanalytical methods are used to assess concentrations?

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) as described in section 2.6.1.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of the standard curve and fitting methods for the bioassays submitted in this application are described in Table 26. This range combined with the validated dilution method as sufficient to meet the requirements of the submitted clinical trials.

Table 26: Standard curve and fitting methods for bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

Assay	Substance	Standard Curve Range[a,b]	Dilution (Bias & Precision ±15%)
A-01 (Plasma)	PAN	0.500 to 500 ng/mL	1:2, 1:4, 1:5, 1:20, 1:100, 1:200
D-01 (Urine)	PAN	0.500 to 500 ng/mL	1:20 & 1:200
01 (Plasma)	PAN	0.100 to 100 ng/mL	1:20 & 1:200
	BJB432	0.100 to 100 ng/mL	1:20 & 1:200

a=fitting :$y = ax^2 + bx + c$ (weighting factor = $1/x^2$) and b=($r^2 >0.99$)
Source: Applicant's reports DMPK R0101758A-01, DMPK R0600958-01 and DMPK R0101758D-01

2.6.6   What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ for the bioassays submitted in this application are described in Table 27. This is sufficient to meet the requirements of the submitted clinical trials.

Table 27: The LLOQ and ULOQ for bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

Assay	Substance	LLOQ	ULOQ
A-01 (Plasma)	PAN	0.500 ng/mL	500 ng/mL
D-01 (Urine)	PAN	0.500 ng/mL	500 ng/mL
01 (Plasma)	PAN	0.100 ng/mL	100 ng/mL
	BJB432	0.100 ng/mL	100 ng/mL

Source: Applicant's reports DMPK R0101758A-01, DMPK R0600958-01 and DMPK R0101758D-01

2.6.7   What are the accuracy, precision, and selectivity at these limits?

The accuracy, precision, and selectivity for the bioassays submitted in this application are described in Table 28. This is sufficient to meet the requirements of the submitted clinical trials.

Table 28: The accuracy, precision, selectivity and other relevant parameters for the bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

Parameter	A-01 (Plasma)	D-01 (Urine)	01 (Plasma)	
	PAN	PAN	PAN	BJB432
Intra-day accuracy within ±15% (±20% at LLOQ)[c]	Y	Y	Y	Y
Intra-day precision within ≤15% (≤20% at LLOQ)[c]	Y	Y	Y	Y
Inter-day accuracy within ±15% (±20% at LLOQ)[c]	Y	Y	Y	Y
Inter-day precision within ±15% (±20% at LLOQ)[c]	Y	Y	Y	Y
Mean Recovery (Bias ≤15%)[b]	87.6% (Y)	101% (Y)	101% (Y)	101% (Y)
ISR ±30% for at least 2/3 of samples analyzed	Y	Y[a]	Y	Y
Specificity: Interference ≤ 20 at the LLOQ (internal standard ≤5%)	Y	Y	Y	Y

a=±20%; b= 3 concentration levels; c= at a minimum of 6 different levels
Y=yes; ISR = incurred sample reanalysis; PAN=panobinostat; LLOQ= lower limits of quantification
Source: Applicant's reports DMPK R0101758A-01, DMPK R0600958-01 and DMPK R0101758D-01

2.6.8   What is the sample stability under the conditions used in the trial?

The accuracy, precision, and selectivity for the bioassays submitted in this application are described in Table 29. This is sufficient to meet the requirements of the submitted clinical trials.

Table 29: The Sample stability for the bioassay systems used to identify and measure active moieties in plasma and urine in the clinical pharmacology and biopharmaceutics studies

Parameter	A-01 (Plasma)	D-01 (Urine)	01 (Plasma)	
	PAN	PAN	PAN	BJB432
Stock solutions (≤ -60°C) precision ≤15% and peak area difference ≤10% (days)	1293	2162	1293	685
Freeze-thaw stability (≤ -60°C) bias within ±15% (cycles)	4	3	4	3
Short term (room temperature) bias within ±15% (hours)	146	24	146	48
Long term (≤ -60°C) bias within ±15% (days)	1001	297	1001	579
Long term (≤ -15°C) bias within ±15% (days)	30	NA	31	31

2.6.9   What is the QC sample plan?

A run was defined as a set of C standards, QC samples and unknown clinical samples. QC samples were freshly prepared on each analysis day by spiking the respective working solutions into human plasma or urine. Six concentrations in the range of the standard curve were used. Acceptance criteria for QC samples in each run was bias within the range of ±15% for at least 2/3 of the individual values and a minimum of 3 QC levels with at least 50% of the results at each level fulfilling the acceptance criteria.

3   DETAILED LABELING RECOMMENDATIONS

- **HIGHLIGHTS:**
    - Revised DRUG INTERACTIONS section to include dose modification with concurrent strong CYP3A4 inhibitors, avoidance of foods that inhibit CYP3A4.
    - Revised DRUG INTERACTIONS section to include avoidance of concurrent use with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index.
    - Revised USE IN SPECIFIC POPULATIONS section to include dose modification for mild and moderate hepatic impairment and avoidance in severe impairment.
- **Section 2.1 Recommended Dosing:** Added cross reference to Section 12.3 (PK) to food recommendation.
- **Section 2.2 Dose Adjustments and Modifications:** Revised to Dose Adjustments and Modifications for Toxicity.
- **Added Section 2.3 Dose Modifications for use in Hepatic Impairment:** Dose modification for mild and moderate hepatic impairment and avoidance in severe impairment.
- **Added Section 2.4 Dose Modifications for Use With Strong CYP3A Inhibitors:** Added dose modification with concurrent strong CYP3A4 inhibitor use.
- **Section 5.6 Hepatotoxicity:** Revised "dose adjustments may be considered" to "dose modifications are recommended".
- **Section 7 DRUG INTERACTIONS:** Revised general statement regarding metabolic and transporter systems that effect and are affected by panobinostat.
- **Section 7.1 Agents that may Increase Panobinostat Blood Concentrations:** Revised to include the expected exposure change, dose modification with concurrent strong CYP3A4 inhibitor and CYP3A4 inhibitor examples consistent with the revised FDA DDI guidance. Non actionable information moved to section 12.
- **Section 7.2 Agents that may Decrease Panobinostat Plasma Concentrations:** Revised to include lack of clinical information, the expected exposure change from PBPK simulations, avoidance language with concurrent strong CYP3A4 inhibitor use, and CYP3A4 inducer examples consistent with the revised FDA DDI guidance. Non actionable information moved to section 12.
- **Section 7.3 Agents whose Plasma Concentrations may be Increased by FARYDAK:** Revised to include the range expected exposure change in CYP2D6 substrates, avoidance language for concurrent use with sensitive CYP2D6 substrates or CYP2D6 substrates that have with a narrow therapeutic index, and CYP2D6 inhibitor examples consistent with the revised FDA DDI guidance. Non actionable information moved to section 12.
- **Section 7.4 Agents for which anticipated interactions should be considered:** Caution was revised to "frequent ECG monitoring" in the sentence "Anti-emetic drugs with known QT prolonging risk, such as dolasetron, ondansetron, and tropisetron   (b) (4)
- **Section 8.6 Hepatic Impairment:** Non actionable information removed, dose modification for mild and moderate hepatic impairment and avoidance in severe impairment. Added more actionable monitoring recommendations.
- **Section 8.7 Renal Impairment:** Non actionable information removed and a sentence that the dialyzability of panobinostat is unknown was added.
- **Section 12.2 Pharmacodynamics:** Extraneous preclinical information was removed.
- **Section 12.3 Pharmacokinetics:**
    - Bioavailability, T_{max} and dose proportionality information was condensed and revised to create a more logical flow and extraneous information was removed.
    - Additional study context for the food effect trial added.

- o Additional context added for pH based solubility and DDI potential.
- o Distribution subsection condensed and additional information regarding P-pg substrate effects was added.
  - o Additional context regarding the metabolism of panobinostat? added.
- o Nonactionable information regarding [redacted] (b) (4) was removed. The contribution of UGT systems was added.
- o Nonactionable information regarding [redacted] (b) (4) was removed, caveat regarding a patient with hepatico-jejunostomy in the ADME trial was added and oral clearance, half-life, and variability information from the pop-PK analysis was added.
- o Additional information regarding accumulation added.
- o The special populations subsections was revised to include information regarding gender and age from the pop-PK analysis. Additional clinical trial context to support hepatic and renal impairment information in section 8 was added
- o In vitro DDI findings and additional clinical trial context to support information in section 7 added.
- FARYDAK was revised to panobinostat throughout the clinical pharmacology related sections where appropriate.

4 APPENDICES

4.1 Tables, figures and graphs referred to but not included in the text

Table 30: Clinical trials and PK sampling in support of dosing and other clinical pharmacology related claims in this application

Trial	Trial design & population	N (PK)	FARYDAK dose/regimen	PK sampling scheme	Sampling
Studies using oral route of administration					
Trial B1101	Dose escalation in Japanese adult patients with advance solid tumors or CTCL	13	10, 15, and 20 mg three times a week, q 28-day cycle	Dense; D1 & 15	48 hours
Trial B2101	Phase I dose escalation trial in patients with advanced solid tumors, NHL or CTCL	93	Arm 1, 4a and 6: 10, 15, 20 and 30 mg three times a week q 28-day cycle Arm 3: 30 or 45 mg three times a week every other week q 28-day cycle Arm 4b and 5: 30, 45, or 60 mg twice a week on Monday/Thursday weekly	Dense; Arm 1, 4a and 6: D1 & 15 Arm 3: D1 & 17 Arm 4b and 5: D1 and 15	48 hours
Trial B2102	Phase I dose escalation trial in patients with advanced hematologic malignances	140	Arm 1: 20, 30, 40, 60, or 80 mg three times a week, weekly q 28-day cycle Arm 2: 30, 45, 60, or 80 mg three times a week every other week q 28- day cycle	Dense; Arm 1: D1 & 15 Arm 2: D1 & 5	48 hours (Arm 2 D5 8 hours)
Trial B2201	Phase II trial in patients with CTCL	114	20 mg three times a week, weekly q 28- day cycle	Limited; D1& 8	48 hours
Trial B2202	Phase II trial in patients with chronic phase CML	19	20 mg three times a week, weekly q 28- day cycle	Limited; D1& 8	48 hours
Trial B2203	Phase II trial in patients with MM	30	20 mg three times a week, weekly q 21- day cycle	Limited; D1 & 8	48 hours
Trial B2211	Phase II trial in patients with accelerated phase or blast crisis CML	16	20 mg three times a week, weekly q 28- day cycle	Limited; D1& 8	48 hours
Trial B2109	Interaction with dextromethorphan in patients with advanced solid tumors	16	PAN 20 mg days 3, 5, 8 x 3 doses, dextromethorphan 60 mg x 1 oral dose on Days 1 and 8 (with PAN)	Dense; D3 & 8	48 hours
Trial B2110	Interaction with ketoconazole in patients with advanced solid tumors	14	PAN 20 mg x 1 dose on Day 1 and Day 8 Ketoconazole 400 mg daily x 5 oral doses (days 5-9)	Dense; D1 & 8	48 hours
Trial B2111	Interaction with food in patients with advanced solid tumors	33	PAN 20 mg Days 1 and 4 weekly taken with high fat, normal meal or at fasting	Dense; D1, 8, & 15	48 hours
Trial X2101	Phase I trial in patients with advanced solid tumors and various degrees of hepatic function	24	Core phase: 30 mg on Day 1. Extension phase: 30 mg three times a week, weekly q 28- day cycle	Dense; D1 to D5	96 hours
Trial X2105	Phase I trial in patients with advanced solid tumors and various degrees of renal function	37	Core phase: 30 mg on Day 1. Extension phase: 30 mg three times a week, weekly q 28- day cycle	Dense; D1 to D5	96 hours
Trial B2108	Open-label ADME trial in patients with advanced cancer patients	4	20 mg [^{14}C] PAN, 49.5 μCi capsule x1	Plasma, urine and Feces: Dense; D1	168 hours
Trial B2207	A phase Ib, multi-center, open-label, dose-escalation trial of oral LBH589 and iv BTZ in adult patients with MM	54	Escalation phase: Groups 1-5: PAN single dose on Days 1, 3, 5, 8, 10, 12, 15, 17, 19 (3 times weekly, 21 day cycle). BTZ bolus injection twice weekly, on Days 1, 4, 8 and 11, followed by a 10 day rest period. DEX 20 mg single daily dose 4 days a week for 2 weeks (Days 1, 2, 4, 5, 8, 9, 11 & 12) from Cycle 2 only at Investigators discretion. Dose: Group 1: PAN 10 mg + BTZ 1.0 mg/m²; Group 2: PAN 20 mg + BTZ 1.0 mg/m²; Group 3: PAN 20 mg + BTZ 1.3 mg/m²; Group 4: PAN 30 mg + BTZ 1.3 mg/m²; Group 5: PAN 25 mg + BTZ 1.3 mg/m². **Expansion phase:** Group 6: PAN 20 mg single dose on Days 1, 3, 5 & 8, 10, 12 (3 times weekly, 2 weeks on, one week off) BTZ 1.3 mg/m² 3 to 5 second bolus injection twice weekly, on Days 1, 4, 8 and 11, followed by a 10 day rest period. DEX 20 mg single daily dose 4 days a week for 2 weeks	**Escalation phase:** BTZ: Dense; Cycle 1 Days 8, 9, 10 PAN: Dense; Cycle 1 Days 8, 9, 10, 15, 16, 17 **Expansion phase:** BTZ and PAN: Dense; Cycle 1 (without DEX) and Cycle 2 (with DEX) on days 8 and 9.	Escalation phase: 48 hrs Expansion phase: 28 hrs

Table 30: Clinical trials and PK sampling in support of dosing and other clinical pharmacology related claims in this application

Trial	Trial design & population	N (PK)	FARYDAK dose/regimen	PK sampling scheme	Sampling
			(Days 1, 2, 4, 5, 8, 9, 11 & 12) from Cycle 2.		
Trial D2308	A multicenter, randomized, double-blind, placebo-controlled phase III trial of PAN in combination with BTZ and DEX in patients with relapsed MM [Japanese PK subset analysis]	13	Total planned duration of treatment was 48 weeks, divided into two phases: **Treatment phase 1 (TP1):** 24 weeks of combined treatment with PAN or placebo + BTZ/DEX (8 cycles of 21 days duration each) **Treatment phase 2 (TP2):** 24 weeks of combined treatment with PAN or placebo + BTZ/DEX (4 cycles of 42 days duration each) **Doses:** **Treatment phase 1:** PAN 20 mg or Placebo single dose on Days 1, 3, 5 & 8, 10, 12 (3 times weekly, 2 weeks on and 1 week off, 21 day cycle). BTZ 1.3 mg/m2, 3 to 5 second bolus injection on Days 1, 4, 8 and 11, followed by a 10 day rest period. DEX 20mg single daily dose on days of and after BTZ administration, i.e., Days 1, 2, 4, 5, 8, 9, 11 and 12. **Treatment phase 2:** PAN 20 mg or Placebo single dose on Days 1, 3, 5, 8, 10, 12, 22, 24, 26, 29, 31, and 33. BTZ 1.3 mg/m2, 3 to 5 second bolus injection on Days 1, 8, 22 and 29. DEX 20 mg single daily dose on days of and after BTZ administration, i.e., Days 1, 2, 8, 9, 2, 23, 29 and 30.	BTZ and PAN: Dense; Cycle 1 Day 1 and Cycle 1 Day 8.	48 hours
Studies using intravenous route of administration					
Trial A2102	Phase Ia/II dose escalation trial in patients with advanced hematological malignancies	15	4.8, 7.2, 9, 11.5, 14 mg/m^2 D1-7 q 21- day cycle	Dense; D1, 5 & 7	24 hours
Trial A2101	Phase Ia dose escalation trial in patients with advanced solid tumors, NHL and CTCL	76	Arm 1: 1.2, 2.4, 4.8, 7.2, 9.0 mg/m^2 D1- 3 & D8-10 q 21-day Arm 2: 2.4, 4.8, 9.6, 15, 20 mg/m2 D1-3 & D15-17 q 28-day cycle Arm 3: 10, 15, 20 mg/m^2 D1, 8, and 15 q 28-day cycle	Dense; Arms 1 & 2: D1 & 3 Arm 3: D1 & 8	Arms 1 & 2: 24 hours Arm 3: 48hours

CML-AP: Chronic myelogenous leukemia, acute phase; CML-BC: Chronic myelogenous leukemia, blast crisis; CTCL: Cutaneous T cell lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma

Source: Reviewer generated from the clinical pharmacology summary report and tabular listing of all clinical studies
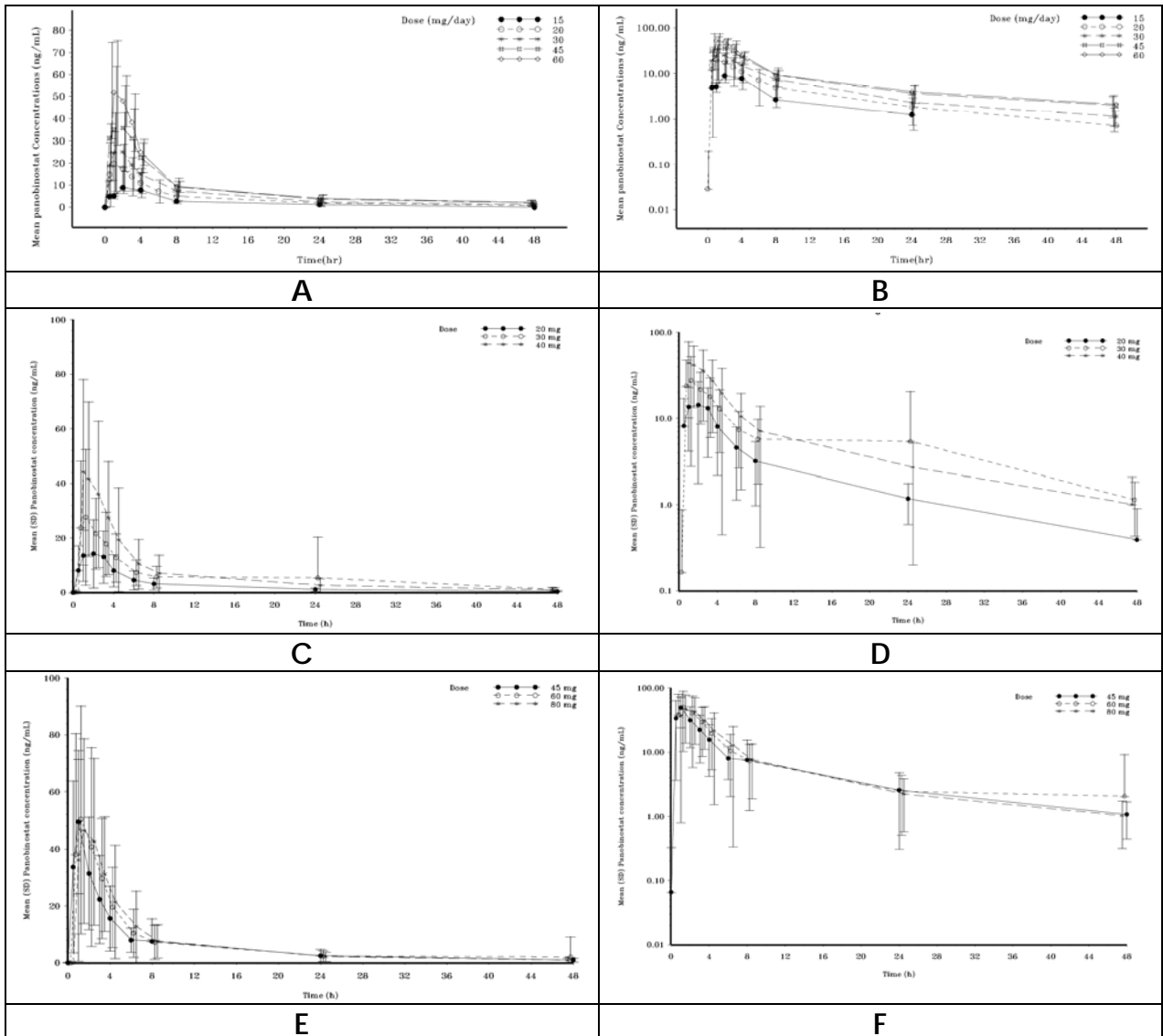
Figure 18: Arithmetic mean (SD) PAN linear (A, C & E) and semilog (B, D & F) plasma concentration-time plots following day 1 dose in all schedules in trials B2101 (A & B) and B2102 (C, D, E & F)

Source: Final trial report for trials B2101 and B2102
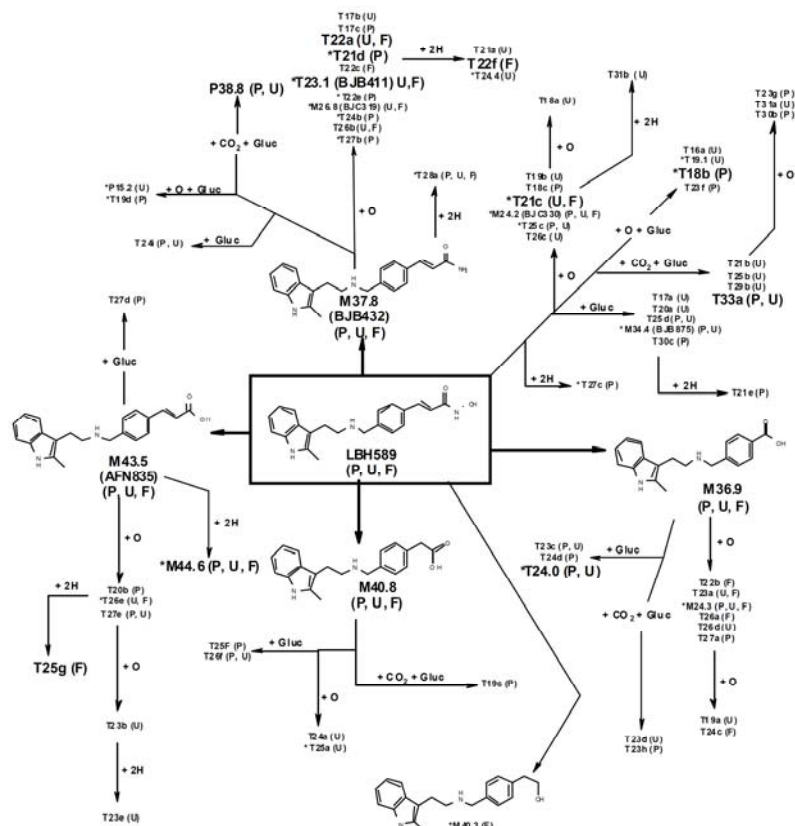
P=plasma, U = urine, F = Feces, Gluc = glucuronic acid
Source: Applicant's final trial report for trial B2108

Figure 19: Panobinostat metabolic scheme

Table 31: Selected AEs regardless of causality on patients with PK data from Trial B2207 vs D2308

Preferred term	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m² + DEX 20 mg (D2308 Japanese patients, N=18)		PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m² + DEX 20 mg (B2207 expansion phase, N=15)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Any preferred term	18 (100%)	17 (94.4%)	15 (100.0)	11 (73.3)
Thrombocytopenia	15(83.3)	14(77.8)	11 (73.3)	10 (66.7)
Neutropenia	9(50.0)	6(33.3)	9 (60.0)	7 (46.7)
Diarrhea	13(72.2)	4(22.2)	13 (86.7)	2 (13.3)
Nausea	11(61.1)	1(5.6)	9 (60.0)	0
Anaemia	8(44.4)	3(16.7)	5 (33.3)	1 (6.7)
Asthenia	0	0	7 (46.7)	2 (13.3)
Fatigue	8(44.4)	3(16.7)	10 (66.7)	3 (20.0)
Vomiting	8(44.4)	0(0.0)	5 (33.3)	0

Source: Applicant's final trial report for trials B2207 and D2308
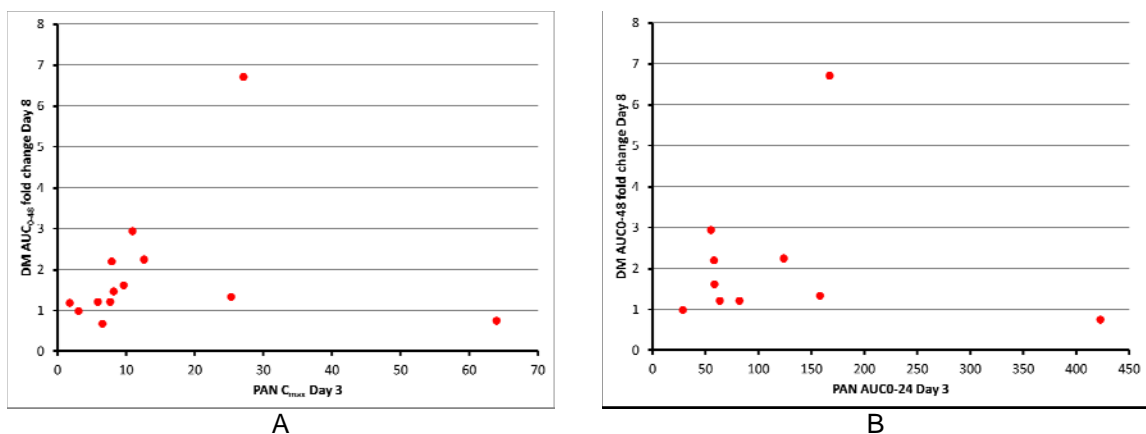
PAN= panobinostat and DM= dextromethorphan
Source: Reviewer created from the applicant's final trial report and dataset for trial B2109

Figure 20: Relationship between PAN Cmax and AUC_{0-24} on day 3 (i.e., PAN alone) and the change in DM exposure on day 8 (i.e., PAN +DM) in trial B2109

Table 32: Arithmetic mean (CV%) of PAN PK parameters following treatment with FARYDAK alone or in combination with BTZ in adult patients with MM (trial B2207)

Parameter	PAN 10 mg + BTZ 1.0 mg/m²		PAN 20 mg + BTZ 1.0 mg/m²		PAN 20 mg + BTZ 1.3 mg/m²		PAN 25 mg + BTZ 1.3 mg/m²		PAN 30 mg + BTZ 1.3 mg/m²	
	PAN	PAN+BTZ	PAN	PAN+BTZ	PAN	PAN+BTZ	PAN	PAN+BTZ	PAN	PAN+BTZ
n	4	4	4	6	14	15	7	7	4	5
$AUC_{(0-48)}$ (ng.h/mL)	25.5 (39.0)	27.8 (38.6)	82.6 (61.4)	111.4 (95.6)	91.9 (91.9)	107.8 (64.6)	95.1 (142.4)	134.7 (36.9)	171.3 (85.7)	134.6 (38.4)
Ratio (P+B/P)	1.1		1.3		1.2		1.4		0.8	
C_{max} (ng/mL)	4.8 (68.8)	3.5 (10.8)	7.6 (50.6)	10.8 (125.5)	12.2 (103.3)	15.8 (63.2)	12.0 (105.4)	18.0 (47.6)	19.8 (109.6)	14.5 (74.8)
Ratio (P+B/P)	0.73		1.4		1.3		1.5		0.7	
T_{max} (h)^	1.0 [0.5;2.8]	2.0 [1.0;2.0]	2.0 [1.0;3.9]	2.4 [1.0;3.0]	1.8 [0.5;3.0]	1.0 [0.1;6.0]	2.0 [0.9;6.0]	2.0 [0.5;3.0]	1.8 [0.5;3.5]	1.0 [1.0;3.0]
Ratio (P+B/P)	2		1.2		0.6		1		0.6	

^Values are median (range) for Tmax, and arithmetic mean (CV%) for all other parameters. NA: not available when CV% is determined < 3 patients
BTZ= bortezomib; PAN= panobinostat
Source: Applicant's final trial reports for trials B2207

4.2   Consult Reviews

4.2.1   Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the dose/exposure-response relationship for efficacy and safety support the proposed panobinostat combination dosing regimen (panobinostat 20 mg, with bortezomib 1.3 mg/m^2 injected intravenously with dexamethasone 20 mg taken orally once every other day for three doses per week of weeks 1 and 2 of each 21 day cycle) in the treatment of patients with multiple myeloma?

No. The proposed dosing regimen of panobinostat (PAN) in combination with bortezomib (BTZ) and dexamethasone (DEX) is not supported by dose/exposure - response relationship for efficacy and safety because of the following reasons:

- 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 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: 0.69, 1.10), and a median OS of 33.6 months for patients in the PAN arm compared to 30.4 months for patients in the control arm.

- There was no exposure data available from the phase 3 trial and therefore the assessment is based on the dose-intensity data from the phase 3 trial. 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 proposed dosing regimen of 20 mg every other day for three doses per week of weeks 1 and 2 of each 21 day cycle.

- 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.

- OS 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 multiple myeloma.

Dose selection rationale

The dose and schedule of PAN (20 mg PAN, 2 weeks on/ 1 week off) used in phase 3 Study D2308 was selected mainly based on a phase 1b dose-finding Study B2207, in patients with relapsed multiple myeloma who had received at least one prior line of therapies.

Five difference dose levels were tested in the dose escalation phase (three times every week, in six dose-cohorts). The MTD of PAN in combination with BTZ was determined to be PAN 20 mg + BTZ 1.3 mg/m^2 based on Bayesian logistic regression model integrated with information from clinical assessment. This dose level was carried forward to the dose expansion phase (cohort 7) with introduction of 1 week of treatment holiday, as well as the addition of DEX. The 1-week rest period was introduced in order to manage thrombocytopenia and allow for accelerated platelet recovery. DEX was added because preclinical and established clinical data indicated that the triple combination of PAN, BTZ, and DEX yielded synergistically greater anti-myeloma activity and there was a clinical benefit of DEX when added to BTZ in patients with relapsed/refractory MM. Efficacy (best overall response) and safety profiles (AEs rates) at each doses level are displayed in **Figure 1**. The best overall response rates increased with higher doses of combination up to PAN 20 mg + BTZ 1.3 mg/m^2, and increased further with addition of DEX. However, it should be noted that the severe AE rates were high (>85%) across all cohorts and also increased with higher dose of PAN. With 73% of patients requiring dose intervention and 33% discontinued treatment due to AEs, it is unclear why the 20 mg PAN + 1.3 mg/m^2 BTZ + 20 mg DEX dosing regimen was taken further to the to be evaluated in phase 3 setting.

Figure 1. Best Overall Response and AEs rates in dose escalation phase (Cohort 1-6) and dose expansion phase (Cohort 7) of Study B2207
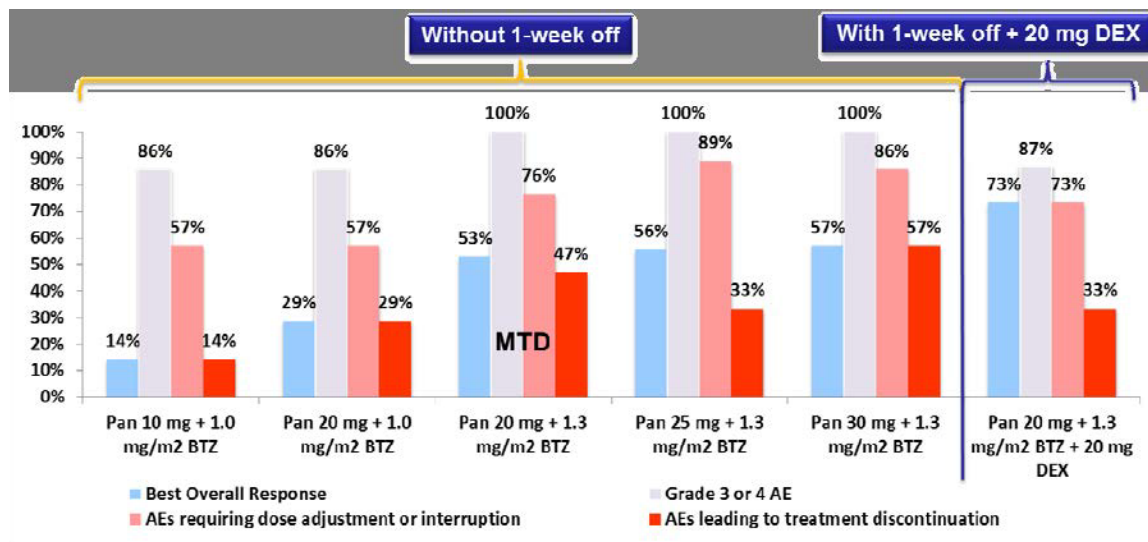
Efficacy considerations

The efficacy and safety of PAN was primarily based on data from the registration trial D2308, a multinational, randomized, double-blind, placebo-controlled, parallel group phase 3 study comparing PAN+BTZ+DEX to placebo (PBO)+BTZ+DEX in multiple myeloma patients with 1 to 3 previous lines of therapy whose disease has recurred or progressed and is not refractory to BTZ. Treatment was administered for a maximum of 16 cycles (48 weeks).

The primary efficacy endpoint was progression-free survival (PFS), using modified European Bone Marrow Transplant Group (EBMT) criteria assessed by the investigators. The combination of PAN+BTZ+DEX showed superior PFS compared to PBO+BTZ+DEX with a hazard ratio (HR) of 0.63 (95% CI: 0.52, 0.76). Median PFS (95% CI) was prolonged by 3.9 months, from 8.1 months (7.56, 9.23) to 12.0 months (10.32, 12.94). As seen from **Figure 2**, the Kaplan-Meier curves for PFS separated at approximately month two of treatment, with a sustained separation over the course of the trial. PFS was also assessed by independent review committee (IRC) in a sensitivity analysis. IRC-assessed median PFS difference was 2.2 months: 9.9 months in the PAN arm versus 7.7 months in the control arm, with a hazard ratio of 0.69 (95% CI: 0.58, 0.83). The key secondary efficacy endpoint is overall survival (OS). As the cut-off date (18-Aug-2014), 86.5% of overall survival (OS) events had occurred and 342 patients were being followed for survival. Interim analysis showed that 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 38.2 months for patients in the PAN arm compared to 35.4 months for patients in the control arm.

Figure 2. Kaplan-Meier Curve of Progression-Free Survival in Patients with Multiple Myeloma (Study D2308)
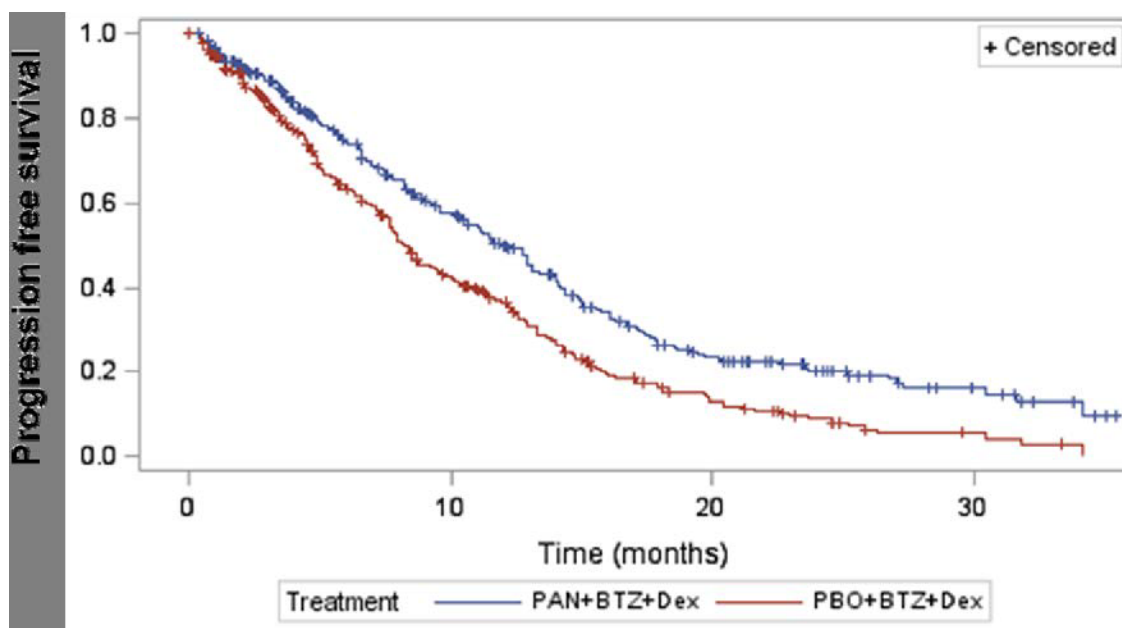
Safety considerations

In study D2308, high toxicity was observed in PAN+BTZ+DEX arm as compared to PBO+BTZ+DEX arm. The rate of adverse reactions leading to dose modification or interruption was 89% with PAN versus 76% with control respectively. The most common treatment emergent adverse reactions leading to dose modification or interruption in the PAN arm were thrombocytopenia (31%), diarrhea (26%) and fatigue (16%). Treatment discontinuation rates due to adverse events were 36% in patients treated with PAN compared to 20% in the control arm. Deaths rate was also higher in PAN treated patients (8% versus 5%). The most common adverse reactions that occurred in >20% of patients (all grades) treated with PAN at a >10% greater frequency than the control arm are summarized in **Table 1.** In addition, the Kaplan-Meier Curves of time to adverse events also showed that the occurrences of severe event were earlier in PAN+BTZ+DEX group compared to the control group**.** Kaplan-Meier Curves of time thrombocytopenia are shown in **Figure 3** as an example**.**

Table 1. Most common AEs >20% and >10% difference between arms

Preferred term	PAN+BTZ+DEX (n=386) N(%) All grades	PBO+BTZ+DEX (n=372) N(%) All grades	PAN+BTZ+DEX (n=386) N(%) Grade 3 to 4	PBO+BTZ+DEX (n=372) N(%) Grade 3 to 4
Diarrhea	264 (68)	153 (41)	98 (25)	29 (8)
Thrombocytopenia	249 (65)	153 (41)	219 (57)	92 (25)
Anemia	160 (41)	124 (33)	63 (16)	60 (16)
Fatigue	158 (41)	109 (29)	65 (17)	33 (9)
Nausea	139 (36)	77 (21)	21 (5)	2 (<1)
Neutropenia	114 (30)	40 (11)	92 (24)	30 (8)
Peripheral edema	111 (29)	70 (19)	8 (2)	1 (<1)
Decreased appetite	110 (29)	44 (12)	12 (3)	4 (1)
Hypokalemia	106 (27)	52 (14)	74 (19)	24 (6)
Pyrexia	99 (26)	54 (15)	5 (1)	7 (2)
Vomiting	99 (26)	48 (13)	28 (7)	5 (1)
Asthenia	85 (22)	54 (15)	37 (10)	14 (4)

Figure 3. Kaplan-Meier Curve of Time to Thrombocytopenia (grades 3/4) by treatment group
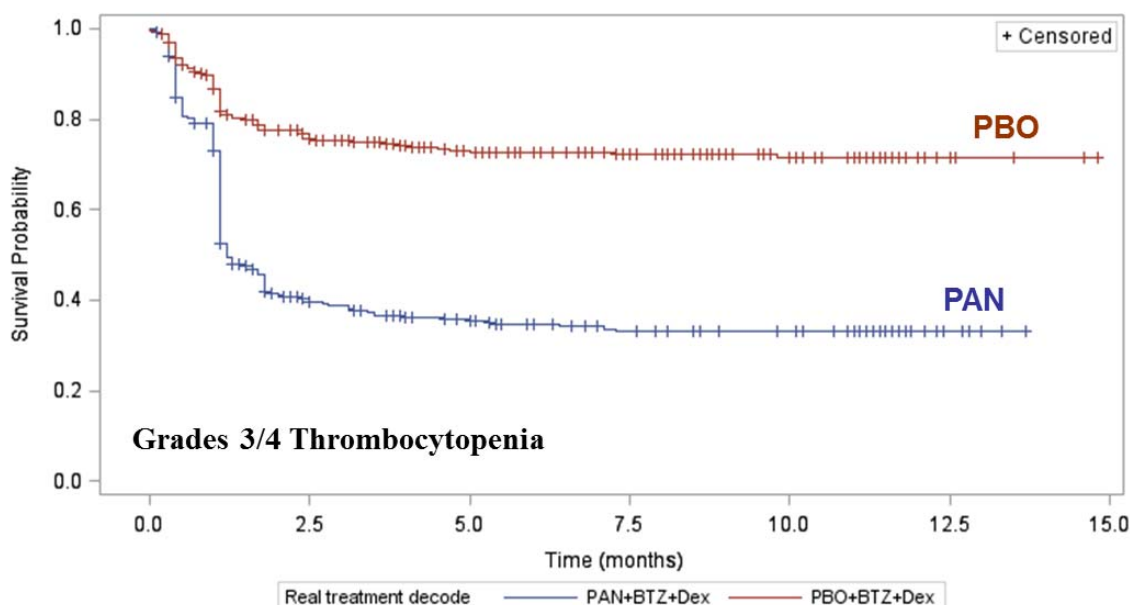
Assessment of Relationship of Dose Intensity with Efficacy and Safety

Exposure-Response relationship cannot be explored since no PK samples were collected from the phase 3 trial. Upon the information request by the Agency, sponsor conducted dose intensity (DI) – response analyses for both efficacy and safety endpoints, using a range of metrics for DI. Refer to Section 3 for details. The endpoints of interest were:

- Efficacy: Progression-free survival (PFS) and overall response rate (ORR)
- Safety: Most frequent treatment-emergent AEs including thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia

The analysis for efficacy results show a slight increase of hazards of PFS events and lowers ORR for higher DI, which may indicate a longer PFS for lower DI. However, this is due to the trial design, patients will generally have a higher PAN DI in the initial cycles compared to those in the later cycles, where they had opportunity to dose-adjust, generally downwards. Thus patients who had events later had greater chances of dose reduction due to longer treatment and thus more likely to have lower DI. Therefore, the DI-response analyses for efficacy are confounded and cannot represent exposure-response relationship for PAN.

Time to AEs by DI-quartiles showed a trend across all safety endpoints (thrombocytopenia, diarrhea, anemia, fatigue, neutropenia and hypokalemia) suggesting possible association between AEs and higher PAN DI. An increasing risk of thrombocytopenia (all grades and grade 3/4) with increasing PAN DI was identified

based on Cox proportional hazards model (**Table 2**).The association with change in DI of PAN for the other AEs was not statistically significant. As seen in **Figure 4**, thrombocytopenia occurred relatively early during treatment with a median onset time around 1 month for both mild and severe events. Age, race (Asian), baseline platelet count were identified as significant covariates to the risk of thrombocytopenia and were adjusted for in the cox-proportional hazard analysis.

Table 2. Hazard ratio of time to first thrombocytopenia with dose increase (covariate-adjusted)

DI metric	HR for 5-mg increase in PAN dose (95% Cl)
Any grade	
DI from Day 1 to onset	1.34 (1.10, 1.63)
DI within last 3 weeks	1.39 (1.19, 1.63)
DI within last 6 weeks	1.39 (1.16, 1.67)
DI within last 9 weeks	1.36 (1.13, 1.65)
DI within last 12 weeks	1.36 (1.12, 1.65)
Grade 3/4	
DI from Day 1 to onset	1.52 (1.19, 1.94)
DI within last 3 weeks	1.49 (1.24, 1.80)
DI within last 6 weeks	1.63 (1.29, 2.07)
DI within last 9 weeks	1.55 (1.22, 1.97)
DI within last 12 weeks	1.53 (1.20, 1.94)

Source: Sponsor's Response to FDA Request (IR11), page 10

Figure 4. Kaplan-Meier Curve of Time to Thrombocytopenia (all grades and grades 3/4) by dose intensity quartiles
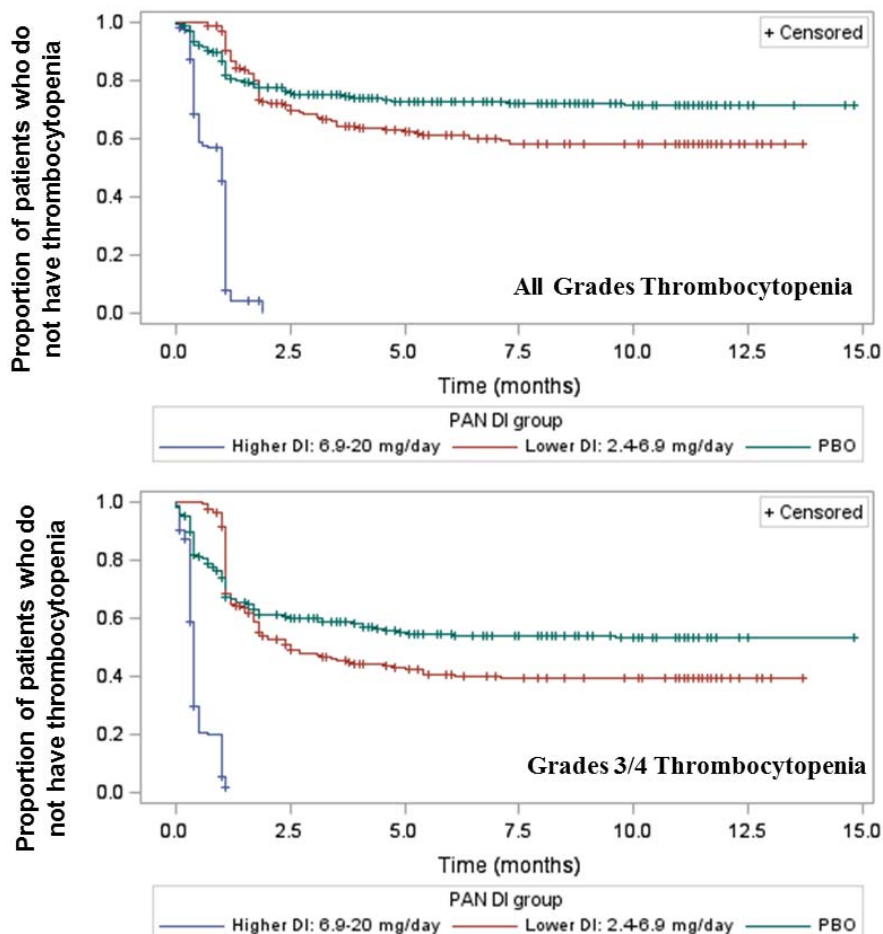
1.1.2 Is the baseline platelet count requirement (at least 100 x 10^9/L) a reasonable cutoff before initiating any treatment cycle?

Yes. The baseline platelet count cutoff is reasonable for prevention of severe thrombocytopenia. Analysis shows that patients who have lower baseline count have higher likelihood of experiencing thrombocytopenia and also thrombocytopenia occurs earlier in these patients (
Figure 5 and **Figure 6**). In patients with baseline platelet count lower than the cutoff 100 x 10^9/L, there was a high risk (~80% events rates) of severe thrombocytopenia observed, and most of these events occurred as early as within one month.

Figure 5. Time to Thrombocytopenia (grades 3/4) by baseline platelet count quartiles
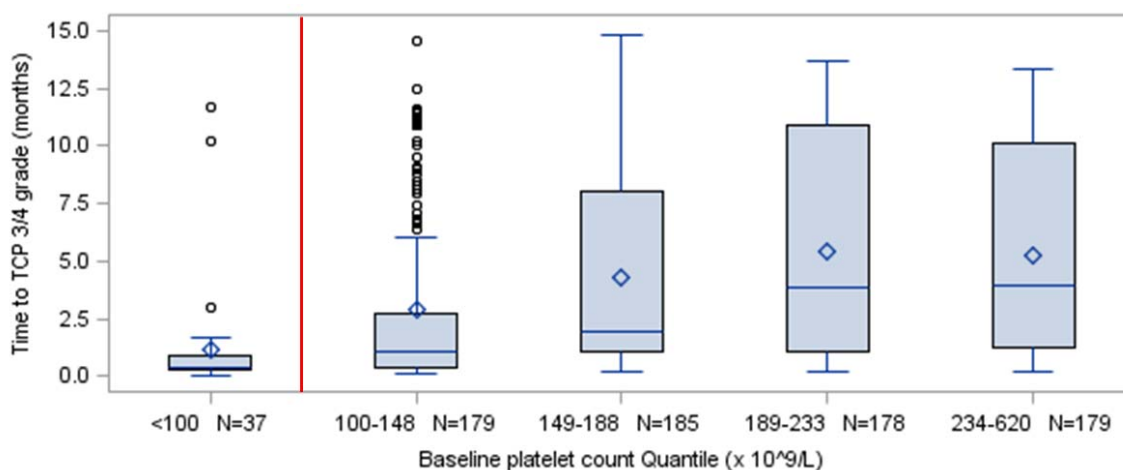
Figure 6. Event rates of thrombocytopenia (grades 3/4) by baseline platelet count quartiles
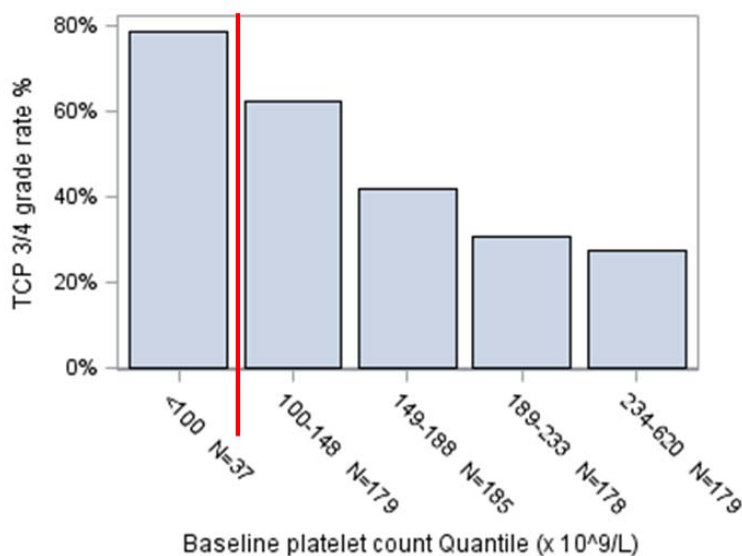
1.2 Recommendations

Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this NDA and has the following recommendations:

- The proposed dosing regimen for the combination of panabinostat+bortezomib+dexamethasone does not appear to offer a favorable benefit-risk profile for the treatment of patients with relapsed multiple myeloma.

- Given the data from the phase 1b and the phase 3 trials, it is not possible determine if a lower dose or a different combination of panobinostat and bortezomib doses will maintain efficacy and provide better safety thus offering a better benefit risk profile.
- The clinical benefit observed in terms of PFS [3.9 months based on investigator assessment (primary efficacy endpoint) and 2.2 months based on independent review assessment] in relapsed multiple myeloma patient population should be weighed against the safety findings from the phase 3 trial for determining whether this combination should be approved.
- The analysis of the overall survival when data is mature will be useful to better assess the benefit risk-profile of panabinostat+bortozemib+dexamethasone combination in the treatment of patients with relapsed multiple myeloma.

1.3 Label Statements

Please refer to clinical pharmacology QBR for detailed labeling recommendations.

2 PERTINENT REGULATORY BACKGROUND

Panobinostat is an orally active deacetylase (DAC) inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds. Panobinostat has shown *in vitro* inhibitory activity in the low nanomolar range against all class I, II and IV histone deacetylases. Deacetylase enzymes also target lysine groups on various non-histone proteins such as p53, α-tubulin, Hsp90, and HIF1-α; thus panobinostat is also referred to as a pan-DAC inhibitor. Panobinostat has been in clinical development as an investigational drug for solid and hematological malignancies since April 2003 as an intravenous formulation for injection (IND 67091) and since June 2004 as an oral capsule (IND 69862).

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Dose intensity assessment

Sponsor conducted multivariate logistic regression and time-to-event analysis to explore relationship between dose intensity (DI) and efficacy/ safety endpoints. Dose-intensities of BTZ and DEX were adjusted as continuous covariates. Potential factors (baseline characteristics) related to efficacy and safety was also identified and case-control analysis was performed. As sensitivity analysis, a range of DI metrics were tested:
DI time windows for safety:
- Start of study treatment component up to onset of AE or censor date
- weeks before the onset of AE up to onset of AE or censor date
- weeks before the onset of AE up to onset of AE or censor date
- 9 weeks before the onset of AE up to onset of AE or censor date

- 12 weeks before the onset of AE up to onset of AE or censor date

DI time windows for efficacy:

For PFS and ORR-responders:
- Start of study treatment component up to event date or censor date
- 6 weeks before the date of event up to event date or censor date
- 12 weeks before the date of event up to event date or censor date
- 18 weeks before the date of event up to event date or censor date
- 24 weeks before the date of event up to event date or censor date

For ORR- non-responders will be censored at the date of last adequate response assessment prior to the last dose of panobinostat.

The main findings of sponsor's analysis are listed below. For full details refer to Sponsor's Response to FDA Request (IR11, 15 and 16).
- A slight increase of hazards of PFS events was observed for higher DI, which may indicate a longer PFS for lower Dis. Though this may be mainly due to the fact that the majority of the events occurred post treatment and patients have had a longer time on study with dose adjustments, therefore resulting in lower panobinostat DI.
- There was a trend across all safety endpoints suggesting association of higher events rates of Grade 3-4 AE with higher DI. In addition, this trend was also observed for thrombocytopenia for all grades.
- An increased risk of thrombocytopenia due to change in PAN DI has been observed. No apparent association with change in DI of panobinostat was identified for the other AEs analyzed (i.e. diarrhea, fatigue, anemia, neutropenia, hypokalemia).
- After adjusting for baseline factors there appears to be a trend for higher risk in the high dose intensity case group for all grades and grade 3/4 thrombocytopenia, diarrhea, anemia and hypokalemia compared to the respective matched control group. In addition, there appears to be a trend for higher risk in the low DI PAN group for all grade and grade 3/4 for thrombocytopenia and diarrhea.

Reviewer's Comments: Due to numerous confounding factors, the interpretation of the association between both PFS and ORR with DI (that a lower DI of PAN may be associated with better outcomes) is challenging. Considering also the design of the study, no definitive conclusions can be made on the relationship between DI and efficacy outcomes. However, the DI-AEs analysis did provide some evidences that higher DI of PAN was associated with earlier occurrences of AEs.

3.2 Population pharmacokinetic model

Population PK analyses was conducted on combined data of 8 phase 1 trials and 6 phase 2 trials. A total of 581 patients were available: 87 from the i.v. formulation studies and 494 from the oral formulation studies. 106 patients received the Clinical Service Form (CSF), 388 patients the Final Market Image (FMI). A total of 7834 concentration values were available for analysis. The median age of the PK population was 61 years (range: 16

to 88 years), the median weight of the patients was 76.4 kg (range: 41 to 196.4 kg), the median height was 170cm (range: 143cm to 198cm), 362 patients were male and 219 female. Moreover, 496 patients were Caucasian, 34 Black, 27 Asian and the rest of 24 patients were classified as "Other".

The population PK models were fitted using NONMEM 6.2 with first order conditional estimation with interaction (METHOD = 1 INTERACTION) method. The PK of PAN was best characterized by a three-compartmental model with two peripheral compartments and with input of drug into the central compartment either directly (i.v. dosing) or via first order absorption from the gut (oral dosing), and first order elimination of drug from the central compartment. Covariate analysis was conducted to evaluate the effect of demographic parameters (body weight, body surface area, height, gender, race and age), as well as of creatinine clearance at baseline, liver function, tumor type and concomitant medications on both volume and clearance of PAN. The bioavailability and the absorption rate dependence on the oral formulation were also considered.

Key PK parameter estimates were provided in **Table 3**. Goodness-of-fit plots for the final model are shown in **Figure 7.** The population median of clearance (CL) was 33.1 L/h and the central volume of distribution (V2) was 24.8 L. The inter-patient variability in clearance was 65%, and inter-patient variability in the volume was 58%. The absolute bioavailability of oral PAN was 21%. Formulation had an effect on the rate but not on the extent of absorption of PAN. Simulation showed that the predicted difference in the absorption rate would result in an approximately 30% lower C_{max} for FMI formulation compared to CSF.

Table 3. Parameter estimates from the final three-compartment and the base model

Parameter	Final 3-compartment model		Base model (no covariates)	
	Estimate	(std. error)	Estimate	(std. error)
θ_1 CL (L/h)	33.1	(2.43)	32.9	(2.40)
θ_2 V2 (L) Central volume	24.8	(1.07)	25.4	(1.95)
θ_3 K23 (h^{-1})	1.81	(0.213)	1.82	(0.255)
θ_4 K32 (h^{-1})	0.507	(0.0542)	0.510	(0.0531)
θ_5 K24 (h^{-1})	1.42	(0.135)	1.42	(0.158)
θ_6 K42 (h^{-1})	0.04	(0.00193)	0.0398	(0.00187)
θ_7 KA for FMI formulation (h^{-1})	0.32	(0.0281)	0.321	(0.0301)
θ_8 KA for CSF formulation (h^{-1})	0.544	(0.0247)	0.545	(0.0257)
θ_9 F	0.214	(0.0161)	0.214	(0.0161)
θ_{10} CL exponent for BSA	1.00	(0.232)	NA	NA
θ_{11} V2 exponent for BSA	1.36	(0.2)	NA	NA
θ_{12} CL exponent for age	0.176	(0.0978)	NA	NA
θ_{13} V2 exponent for age	0.396	(0.0931)	NA	NA
θ_{14} CL factor for asian	1.17	(0.0997)	NA	NA
θ_{15} V2 factor for asian	1.37	(0.164)	NA	NA
θ_{16} CL factor for black	1.01	(0.128)	NA	NA
θ_{17} V2 factor for black	1.24	(0.190)	NA	NA
θ_{18} CL factor for others	0.719	(0.127)	NA	NA
θ_{19} V2 factor for others	1.13	(0.141)	NA	NA
Ω_{11} Intersubject variance for CL (CV in %)	0.439 (65.3%)	(0.0555)	0.465 (69.19%)	(0.0580)
Ω_{22} Intersubject variance for V2 (CV in %)	0.334 (57.8%)	(0.0288)	0.380 (61.64%)	(0.0295)
Ω_{12} Intersubject covariance for CL and V2	0.178	(0.0215)	0.205	(0.0235)
σ_1 Residual proportional random effect	0.242	(0.0107)	0.242	(0.0107)
σ_2 Residual additive random effect	0.0134	(0.00587)	0.0136	(0.00669)
NONMEM objective function	33757.951		33830.138	

Source: Sponsor's Population PK report, Table 5-2.

Figure 7. Observed plasma concentrations plotted against predicted (population and individual) concentrations for the final model
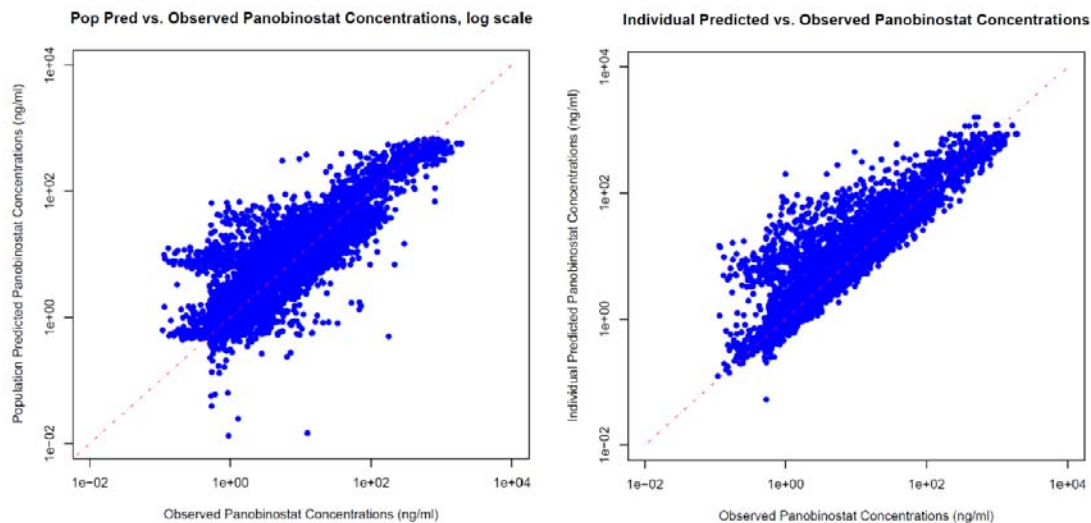
Source: Sponsor's Population PK report, Figure 5-1.

Among the covariates investigated, BSA, age and race, showed statistically significant effects on CL and central volume (V2). The effects of these covariates on CL and V2 of PAN are presented graphically by plotting individual posthoc predicted values of CL and V2 versus covariates in **Figure 8, Figure 9** and **Figure 10** below.

Figure 8. Individual posthoc predicted CL and V2 dependence on BSA
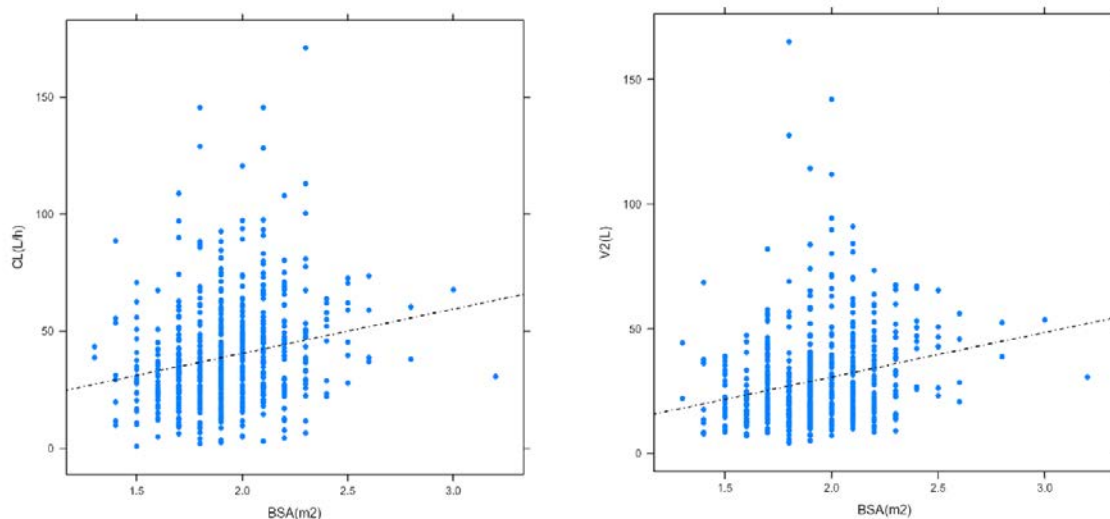
Figure 9. Individual posthoc predicted CL and V2 dependence on Age
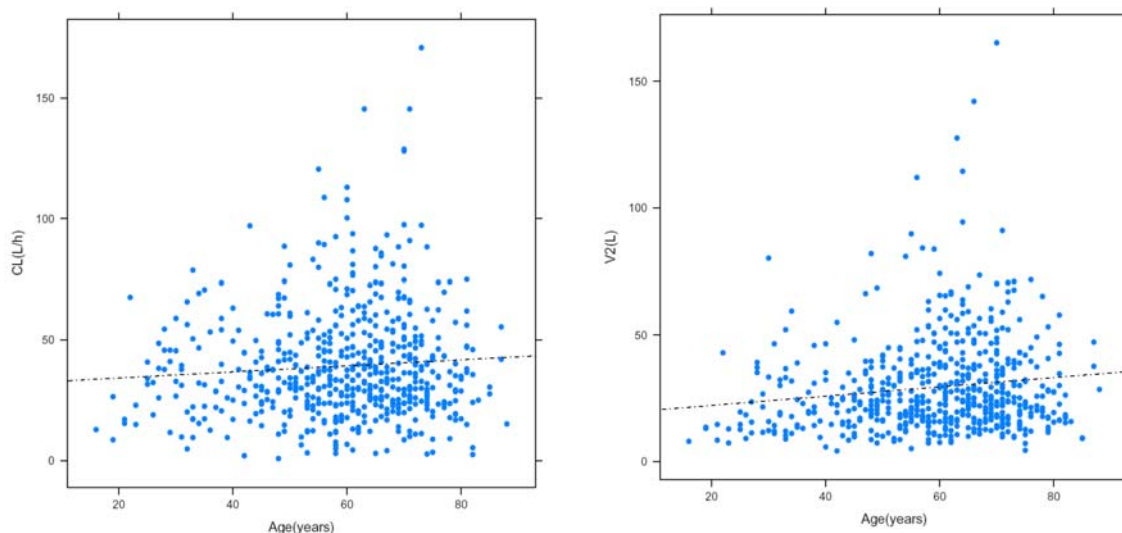
Figure 10. Boxplot of CL and V2 dependence on Race
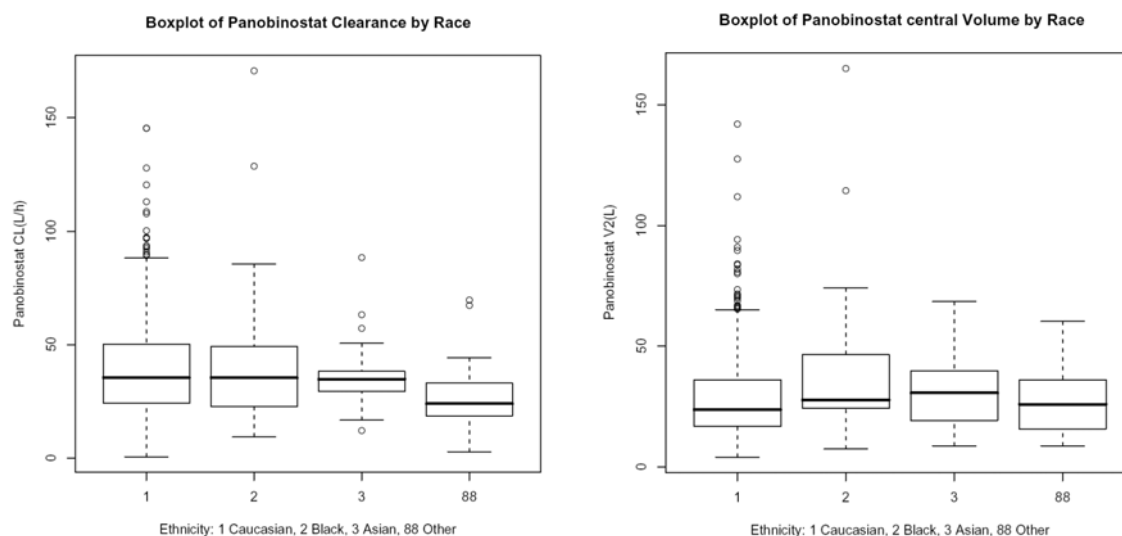
Source: Sponsor's Population PK report, Figure 5-4, Figure 5-5, Figure 5-6.

A patient with a BSA of 1.5 m^2 would have a 21% lower clearance and a 27% lower central volume compared to that of a typical patient (BSA of 1.90 m^2), and a patient with a BSA of 2.5 m^2 would have a 32% higher clearance and a 45% higher central volume compared to that of a typical patient. An Asian patient with a BSA of 1.90 m^2 would have a 17% higher clearance and a 37% higher central volume compare to that of a typical Caucasian patient. However, for a typical Asian patient with a BSA of 1.7 m^2, this translates into an increase of only 4.7% and 17.7%, respectively. A 30 year old patient would have respectively 12% and 25% lower clearance and volume in central compartment compared to a typical 61 year old patient.

However, due to the magnitude of these effects as compared to the unexplained interpatient variation of clearance (65%) and volume (58%), none of them is considered

to be clinically relevant. Among the other covariates investigated: gender, tumor type, creatinine clearance (Cockcroft-Gault) at baseline, indices of liver function, and concomitant medications, showed no statistically significant effect on PK of PAN.

Reviewer's Comments: The population PK model can describe adequately the observed data from intravenous and oral doses of PAN. Covariate analysis revealed relationship between PK of PAN and BSA at baseline, age and race. However, all of these effects were small compared to the unexplained interindividual variability and consequently should not have clinically significant impact on the PK of PAN. Thus no dose adjustment is recommended based on BSA, age or race.

4.2.2 PBPK review

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205494
Drug Name	Panobinostat
Proposed Indication	
Clinical Division	CDER/Oncology
PBPK Consult request	Joseph Grillo, Pharm.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Joseph Grillo, Pharm.D.
Sponsor	Novartis

PBPK Review 2 page 1

Physiological-based Pharmacokinetic Modeling Review 1

1. Objectives 3

2. Background 3

3. Methods 4

    a. Model building 4

    1.1.   Model verification 4

    1.2.   Model applications 5

4. Results 5

    a. Does the Panobinostat PBPK Model Suggest the Lack of the Effect of Elevating Gastric pH on Panobinostat Exposure? 5

5. Conclusion 7

6. Appendices 8

    a. Abbreviations 8

    b. Information requests 8

       Clinical Pharmacology July 22, 2014 (07222014IR) 8

    c. Appendix tables and figures 8

1. Objectives

The main objective of this review is to evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the effect of changing gastric pH on panobinostat PK.

To support its conclusions the sponsor provided the following PBPK modeling and simulation report:

- ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans [1].

2. Background

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) for the treatment of patients with multiple myeloma (MM) who received at least one prior therapy [2]. The proposed dosing regimen is oral administration of 20 mg three times a week (TIW), with a 2 weeks on/1 week off schedule in combination with bortezomib (BTZ) and dexamethasone (Dex). In advanced cancer patients, the extent of panobinostat after oral absorption was estimated to be more than 87% based on human mass balance study. After TIW (Monday/Wednesday/Friday) single agent dosing, steady state of panobinostat is reached on the 3rd dose with minimal accumulation. Panobinostat exposure appears to be dose-proportional over 10 to 30 mg after multiple dosing. Administration with Food does not have substantive effect on panobinostat exposure. The absolute bioavailability (F) for the oral anhydrous salt formulation (FMI) was estimated to be 21%, and the systemic clearance (CL) was estimated to be 33 L/hr based on population pharmacokinetic analysis. Panobinostat demonstrates extensive tissue distribution, with volume of distribution significantly exceeding blood volume. Panobinostat is metabolized by both non-CYP routes and CYP enzymes [2].

In a response to FDA's information request on definition of Biopharmaceutics Classification System (BCS) classification of panobinostat, sponsor stated that panobinostat lactate, anhydrous "has high permeability and pH dependent solubility with low solubility at pH 7.6, and therefore is considered to be in the Biopharmaceutics Classification System (BCS) II compound" [3]. In the presence of p-glycoprotein (P-gp) inhibition, panobinostat demonstrated good passive permeability in vitro, with an estimated passive permeability of 5.8×10^{-6} cm/s, or an effective passive permeability in human (P_{eff}) of 2.289×10^{-4} cm/s. The relatively high passive permeability is consistent with complete oral absorption that was observed in human mass-balance study (fraction absorbed F_a at least 87% [2]). The sponsor indicates that panobinostat has low solubility at neutral pH. As shown in **Table 1**, solubility of panobinostat is strongly dependent on pH, and the solubility in 250 mL at pH 7.6 (16 mg) is less than the dose strength of 20 mg.

Table 1. Solubility of panobinostat lactate, anhydrous drug substance at 37.0°C (+/- 0.5°C) (Table 3-1, Ref [1])

Solution / buffer	Approximate solubility in mg/ml of solution at 37°C (±0.5°C)	Corresponding maximum amount of drug soluble in 250 ml of solution (in mg)
Water	4.775	1194
pH 1.2 (HCl)	1.017	254
pH 2.0 (HCl)	1.256	314
pH 4.5 (acetate)	4.771	1193
pH 6.0 (phosphate)	3.845	961
pH 6.8 (phosphate, simulated intestinal fluid)	0.261	65
pH 7.6 (phosphate)	0.064	16

In response to FDA's information request on justifying the need to study the effect of pH-elevating agents on the absorption of panobinostat, sponsor stated that a dedicated clinical trial is not necessary, and provided PBPK simulations to support their position [1,3]. An information request was sent to the sponsor on July 22, 2014 requesting software model files be submitted for FDA review (07222014IR, **Appendix 5.2**). On July 25, 2014, sponsor provided required information.

The objective of this review is to assess the adequacy of sponsor's PBPK model in concluding a minimal effect of varying gastric pH on the absorption of panobinostat in humans.

3. Methods

GastroPlus® software (Simulations Plus Inc, Lancaster, CA [5-7]) was used by the sponsor to develop a PBPK model of panobinostat. Within GastroPlus, the advanced compartmental and transit model (ACAT) [5] describes transport of drug along the gastrointestinal (GI) tract and enterocytes, the release of the drug from formulation, drug dissolution, and permeation of the dissolved drug molecules. The ACAT model also accounts for pH dependent solubility and the effect of food on GI physiology. Sponsor connected ACAT model with a three compartmental PK model of panobinostat to evaluate the effect of elevated gastric pH on the PK of panobinostat. Drug-dependent parameters and their sources for panobinostat are summarized in **Appendix Tables 1** [1, 3]. Unless otherwise stated, simulations used one virtual healthy subject administered a single oral dose of panobinostat (20, 30 or 40 mg). Simulations lasted for 48 hours.

a. Model building

Physicochemical properties (experimentally measured or predicted in-silico), pH dependent solubility and permeability studies, and compartmental PK parameters were used to build the PBPK model of panobinostat [1]. Based on the model file provided by the sponsor [3], plasma protein binding (unbound fraction of 0.104) and blood to plasma ratio (1.4) measured in vitro were included in the model. In this model, the rate and extent of oral absorption from GI tract was mechanistically described by drug dissolution from an immediate release formulation, a pH dependent solubility, a precipitation process, and a passive permeation into cellular compartment of various types of intestinal cells across different regions of the GI tract. Post-absorption kinetics of panobinostat was described by PK parameters obtained from population PK analysis assuming a three compartmental distribution model [1] (**Appendix Table 2 and Appendix Figure 1**).

Because the estimated bioavailability (F) was only ~0.3 in patients, and the bioavailability in the liver (fraction that escapes hepatic metabolism F_h) can be estimated as ~0.7, the sponsor optimized panobinostat PBPK model by defining a first-pass metabolism in small intestine with a value of 0.6 (or a fraction that escapes intestinal metabolism F_g of 0.4). The rationale seems reasonable given a model predicted F_a of ~1.0 for panobinostat. However, sponsor did not specify which observed data have been used to fit the value of intestinal first pass metabolism (Appendix Table 1, footnote "g").

1.1. Model verification

There were no independent studies used by the sponsor to verify the panobinostat PBPK model. The FDA reviewer used the sponsor's model to simulate panobinostat absorption and PK under fasted and fed conditions. In GastroPlus, ACAT models of "Human-Physiology-fasted.cat" and "Human-Physiology-Fed.cat" contain predefined GI physiology under fast and fed conditions, respectively. These ACAT models include differences in liver blood flow, composition of luminal fluids in terms of their pH and bile

salt concentrations, and transit times between compartments.   Additional fed condition was tested by increasing gastric transit time from 1 hr to 3 hrs, partially mimicking the effect of meal with higher fat contents. These simulations were compared with the PK changes observed in the dedicated food effect study B2111 [2].

1.2. Model applications

Sponsor used panobinostat PBPK model to predict the effect of changing gastric pH on the PK of panobinostat.

4. Results

a. Does the Panobinostat PBPK Model Suggest the Lack of the Effect of Elevating Gastric pH on Panobinostat Exposure?

Yes. The sponsor's PBPK model integrates pH dependent solubility and cellular permeability information measured in vitro. Simulation using this model suggests the lack of effect of elevating gastric pH on panobinostat oral absorption and PK.

As shown in **Table 2**, sponsor's panobinostat PBPK model predicts a complete oral absorption (e.g., F_a ~1.0), which is consistent with that observed in human mass balance study [2]. In human mass balance study, F_a in patients taking 20 mg panobinostat orally was more than 0.87, suggesting near complete oral absorption of the drug [2]. It has to be noted that results from Study B2102 were part of the data for the development of panobinostat population PK model. Comparison of drug exposure (Cmax and AUC) between simulation and observation in Table 2 should not be considered as a verification process. In addition, the model tends to predict higher Cmax across all doses, which implies the need for further optimization of the model. Despite this limitation the model is acceptable to address this issue.

Table 2. PBPK model simulated PK parameters of panobinostat compared with the observed values (Table 6-1, ref [1])

Study	20 mg		30 mg		40 mg	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Fa, %	-	99.9		99.9	-	99.9
Tmax, h	2	1.28	1	1.28	1	1.28
Cmax, ng/mL	14.3	31	20.4	47.5	40.8	58.9
AUClast, ng*h/mL	133	151	193	231	231	280

Observed Cmax value referred to the Cmax of the geometric mean concentration-time profiles for panobinostat in study CLBH589B2102. Observed Tmax value referred to the Tmax of the geometric mean concentration-time profiles for panobinostat in study CLBH589B2102.

The ACAT models for fed and fasted conditions considered multiple physiological differences within the PBPK software. The prominent differences include stomach pH (fasted 1.3 vs fed 4.9), stomach volume (fasted 46 mL vs fed 919 mL), stomach transit time (fasted 0.25 hr vs fed 1 hr), and hepatic blood flow (fasted 1.5 mL/min vs fed 2 L/min for a 70 kg man). In order to evaluate sponsor's assumptions using ACAT model, the FDA reviewer used sponsor's model to simulate the effect of food on panobinostat PK in a human subject taking 20 mg oral dose as immediate release formulation (**Table 3**). In this simulation, two fed conditions were tested: (a) the use of default human fed physiology model (condition

2), and (b) a prolonged gastric transit time from 1 hr in the default fed physiology model to 3 hr (condition 3). As shown in **Table 3**, panobinostat PBPK model predicted a delay in Tmax and a decrease in Cmax as a result from food intake, and the effects were greater under condition 3. The prolonged gastric emptying time (3h compared to the default value of 1h) assumed in the PBPK simulations can be reasonably justified with the fact that food, especially high-fat meals, decelerate gastric emptying. These simulations show that food has no effect on panobinostat AUC. In a food effect study [2], normal breakfast and high fat breakfast delayed panobinostat Tmax by a median of 1.5 hours and 2.5 hours, decreased panobinostat Cmax by 36% (geometric mean ratio GMR of 0.64 (90% confidence interval CI: 0.50 – 0.81))and 44% (GMR of 0.56 (90% CI: 0.45 – 0.70)), respectively. However, food has marginal effect on panobinostat AUC [2]. Simulations using sponsor's PBPK model appear to qualitatively describe the moderate effect of food on Tmax and Cmax of panobinostat.

Table 3. FDA's simulations using sponsor's PBPK model to evaluate the effect of food on panobinostat PK and oral absorption (GMR: geometric mean ratio; data see Appendix Table 3)

Simulated compared to fasted condition (simulation Condition 1)		
	Default fed condition (gastric transit time 1 hr, Condition 2)	Modified fed condition (gastric transit time 3 hr, Condition 3)
Delayed T_{max} (hr)	0.5	1.3
% decrease in C_{max}	31%	62%
% change in AUC (0-48hr)	0%	0%
Observed compared to fasted condition		
	Normal Breakfast	High-fat Breakfast
Delayed median T_{max} (hr)	1.5	2.5
% decrease in GMR C_{max}	36%	44%
% change in GMR AUC_{0-inf}	-14%	-16%

In order to assess the effect of varying stomach pH on the absorption of 20 mg panobinostat in humans, the sponsor conducted sensitivity analysis on the stomach pH ranging from 0.5-8.0. The predicted F_a remained ~1.0 across this pH range (**Figure 1**).

Figure 1. Projected absorption of 20 mg panobinostat vs. stomach pH in humans (Figure 7-4 from reference [1])
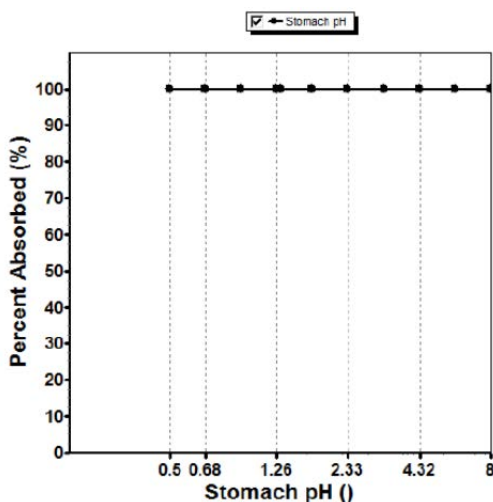
During the review of sponsor's prediction of drug-drug interaction potential using PBPK approach, the FDA reviewer conducted a similar evaluation of the effect of food and increase in gastric pH using another PBPK platform [8]. Preliminary simulations also show that panobinostat absorption and PK were not affected by elevation in gastric pH, and food delayed panobinostat Tmax and decreased Cmax without changing AUC.

5. Conclusion

Sponsor's PBPK model integrates pH dependent solubility and cellular permeability information measured in vitro. Model simulations suggested the lack of effect of elevating gastric pH on panobinostat oral absorption and PK.

6. Appendices

a. Abbreviations

ACAT, advanced compartmental absorption and transit model; ADME, absorption, distribution, metabolism, and excretion; BCS, Biopharmaceutics Classification System; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; AUC_{tau}, steady state AUC within a dosing interval; B/P, blood to plasma ratio; BTZ, bortezomib; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; C_{trough}, trough concentration; CL, clearance; CL_{int}, intrinsic clearance; DACi, deacetylase inhibitors; Dex, dexamethasone; DDI, drug-drug interaction; F, bioavailability; F_a, fraction absorbed; F_h, fraction that escapes hepatic metabolism; F_g, fraction that escapes intestinal metabolism; fp, fraction unbound in plasma; GI: gastrointestinal; IR, immediate release formulation; k_a, first order absorption rate constant; LogP, logarithm of the octanol-water partition coefficient; MM: multiple myeloma; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, effective passive permeability; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; TIW: three times a week; Tmax: time at maximal concentration in plasma; V_{ss}, volume of distribution at steady state.

b. Information requests

Clinical Pharmacology July 22, 2014 (07222014IR)

To facilitate our review of your PBPK simulation report: "Study 1400363 - ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans" submitted on May 5, 2014, you should submit executable GastroPlus model files being used to simulate final results in this study report. The model files should include, but are not limited to model compound file (mdb), solubility vs pH (.spd), particle size distribution(.psd), Tissue/Plasma Conc. vs. Time Data: Other Dosage Forms (.opd), and User-Defined ACAT Model (.cat).

c. Appendix tables and figures

Appendix Table 1. Summary of input parameters for panobinostat ACAT model in humans

Dose (mg)	20	30	40
Parameters			
Dosage form	(b) (4)		
LogP[b]			
Solubility (mg/mL)[c]			
pKa[b]			
Dose volume (mL)			
Particle density (g/mL)[b]			
Mean particle radius (µm)[d]			
Particle radius standard deviation[b]			
Particle radius bin[b]			
Precipitation time (sec)[b]			
Diffusion coefficient (cm^2/s $\times$ 105)[b]			
Permeability (cm/s$\times$10^4) e			
Simulation time (h)			

PBPK Review 2 page 8

Dose (mg)	20	30	40
Body weight (kg)[f]	(b) (4)	67.8	79.1
First pass elimination in small intestine, % [g]			
First pass elimination in liver, % [h]			
CL (L/h/kg)[i]			
Vc (L/kg)[i]			
K12 (1/h)[i]			
K21 (1/h)[i]			
K13 (1/h)[i]			
K31 (1/h)[i]			

[a] Dosage forms selected in GastroPlus™ for simulations
[b] Predicted by ADMET predictor or default values in GastroPlus™
[c] DSP5.2R5001203B
[d] Approximated estimation of mean particle size
[e] Estimated from Caco-2 permeability to human jejunum P_{eff} using Novartis internal worksheet   (b) (4)

)
 CLBH589B2102
[g] Estimated by fitting the observed plasma concentration profiles
[h] Estimated by GastroPlus™ based on CL/Qh ratio and Cb/Cp ratio
[i] LBH589 POPPK report

In addition, the sponsor provided model specifications for the following parameters [3]:

(b) (4)

Appendix Table 2. Panobinostat parameter estimates from the final three-compartment model in humans. (Table 3-2 of ref [1])

Parameters	Estimate
θ_1 CL (L/h)	(b) (4)
θ_2 V2 (L) Central volume	
θ_3 K23 (h^{-1})	
θ_4 K32 (h^{-1})	
θ_5 K24 (h^{-1})	
θ_6 K42 (h^{-1})	

Appendix Figure 1. Schematic representation of the three compartment model for panobinostat (Figure 3-1 of ref [1])
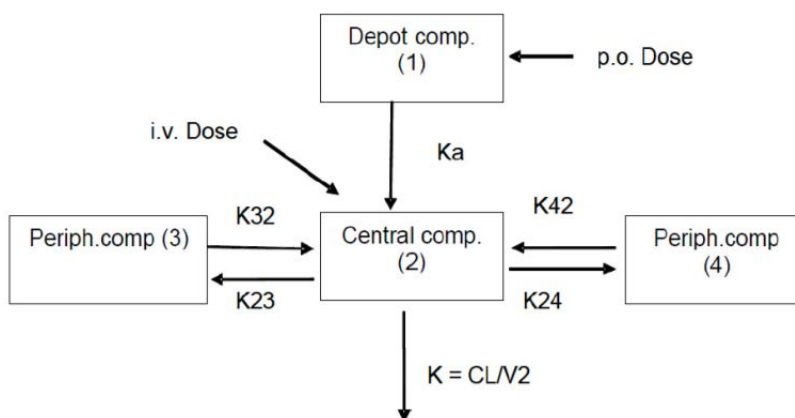
Appendix Table 3. Model simulated PK parameters of panobinostat under fasted and fed conditions

Parameters	Condition 1. Fasted (default gastric transit time of 0.25 hr)	Condition 2. Fed (default gastric transit time of 1 hr)	Condition 3. Fed (Gastric transit time of 3 hr)	Ratio condition 2/condition 1	Ratio condition 3/condition 1
C_{max} (ng/mL)	35.8	24.6	13.8	0.69	0.38
T_{max} (h)	1	1.5	2.3	1.5	2.3
AUC (ng/mL.h)	151.4	150.8	149.0	0.996	0.984
f_a	99.9	99.9	99.9	0.99	0.99
F_g	29.5	29.5	29.5	1.00	1.00

PBPK Review 2 page 10

References

1. Novartis. Study 1400363. ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans.

2. Novartis. Clinical Development Panobinostat (LBH589). CTD 2.7.2. Summary of Clinical Pharmacology.

3. Novartis. Response to FDA Information Request 21- Received July 25, 2014

4. Yu LX, Amidon GL. (1999) A compartmental absorption and transit model for estimating oral drug absorption. Int J Pharm.; 186(2):119–25.

5. Agoram B, Woltosz WS, Bolger MB (2001). Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv Drug Deliv Rev. 1;50 Suppl 1:S41-67.

6. Parrott N, Lukacova V, Fraczkiewicz G, Bolger MB (2009). Predicting pharmacokinetics of drugs using physiologically based modeling - application to food effects. AAPS J. 11(1):45-53

7. Lukacova V, Woltosz WS, Bolger MB. (2009) Prediction of modified release pharmacokinetics and pharmacodynamics from in vitro, immediate release, and intravenous data. AAPS J. 11(2):323-34

8. Office of Clinical Pharmacology, FDA: Physiologically based pharmacokinetics Review.

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205494
Drug Name	Panobinostat
Proposed Indication	
Clinical Division	CDER/Oncology
PBPK Consult request	Joseph Grillo, Pharm.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Joseph Grillo, Pharm.D.
Sponsor	Novartis

PBPK Review page 1

1. Objectives

The main objectives of this review are to 1) evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the DDI potential of panobinostat as a victim and time dependent perpetrator of the CYP3A4 metabolic pathway and 2) provide a dosing recommendation based on the predicted effect of rifampin on panobinostat PK and the effect of panobinostat on midazolam PK. Additional PBPK modeling and simulation using sponsor's model was conducted to evaluate the effect of food and increase in gastric pH on panobinostat PK. To support its conclusions the sponsor provided the following PBPK modeling and simulation reports:

1. "Simcyp® simulations of the clinical drug interaction potential of ketoconazole or rifampin with LBH589" [1]
2. "Risk assessment of the time-dependent inhibition of CYP3A by LBH589" [2]
3. "Updated Simcyp simulations of LBH589 pharmacokinetics and CYP3A drug interaction potential" [3].

2. Background

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) that is being evaluated in the current NDA for the treatment of patients with multiple myeloma (MM) who received at least one prior therapy (4). The proposed dosing regimen is oral administration of 20 mg three times a week (TIW), with a 2 weeks on/1 week off schedule in combination with bortezomib (BTZ) and dexamethasone (Dex). In advanced cancer patients, the extent of panobinostat after oral absorption was estimated to be more than 87% based on human mass balance study. After TIW (Monday/Wednesday/Friday) single agent dosing, steady state of panobinostat is reached on the 3rd dose with minimal accumulation. Panobinostat exposure appears to be dose-proportional over 10 to 30 mg after multiple dosing. Administration with Food does not have substantive effect on panobinostat exposure. The absolute bioavailability (F) for the oral anhydrous salt formulation (FMI) was estimated to be 21%, and the systemic clearance (CL) was estimated to be 33 L/hr based on population pharmacokinetic analysis. Panobinostat demonstrates extensive tissue distribution, with volume of distribution significantly exceeding blood volume. Panobinostat is metabolized by both non-CYP routes and CYP enzymes [4]. Detailed absorption and disposition characteristics can be found in the PBPK input parameter table (**Appendix Tables 1 and 2**).

The sponsor developed a PBPK model as part of the NDA submission [1,2] to evaluate two potential drug-drug interaction (DDI) scenarios and determine the need for additional in vivo trials. Specifically, it evaluated the effect of a strong CYP3A inducer rifampin on panobinostat PK and the effect of panobinostat on CYP3A probe substrate midazolam. Following the initial filing review the Agency sent two information requests to the sponsor on April 22, 2014 and July 07, 2014 (04222014IR and 07072014IR, Section 6.b) regarding model parameterization and requesting additional simulation scenarios be explored. In response, the sponsor submitted an updated study report and relevant electronic files of PBPK modeling on May 9, 2014[3], and additional simulations on July 10, 2014 [5].

This review evaluates the adequacy of sponsor's panobinostat PBPK model to predict the DDI potential, and provides dosing recommendations based on the predicted effect of rifampin on panobinostat PK and the effect of panobinostat on midazolam PK.

3. Methods

SimCYP® software (Sheffield, UK, [6,7]) was used by the sponsor to develop and verify the PBPK model of panobinostat. Earlier submissions used SimCYP version 8 for model development and simulations [1,2]. Simulations submitted in response to the Agency information request 04222014IR (Section 6.b), that included an updated panobinostat PBPK model, utilized SimCYP version 13 (release 1) [3]. This review focuses on this revised model and simulations [3]. Final drug-dependent parameters and their sources for panobinostat are summarized in **Appendix Tables 1 and 2** [3]. PBPK models of midazolam, rifampin, and ketoconazole (400 mg QD model) were provided within the software compound library. Software's "Healthy volunteer" population with an age range of 20-50 years and proportion of females of 0.5, was used for all simulations [5]. All simulations consisted of 10 trials of 10 subjects (n=100) and were designed as follows:

- PBPK simulations comparing panobinostat PK on day 8 with and without ketoconazole co-administration (400 mg once daily, q.d., on day 5-9 or 5 doses) assumed a two-way crossover study design. The sponsor also conducted a clinical panobinostat/ketoconazole DDI study (B2110), which used an open-label, single-sequence crossover DDI study design. In this study, panobinostat was given as a single oral dose of 20 mg on day 1 in 14 cancer patients (41-74 years old Caucasians, 36% females (5 out of 14)). Then, 400 mg ketoconazole was administered q.d. orally on day 5 to day 9 (5 doses). On day 8, 20 mg panobinostat was given orally 1 hour after ketoconazole dose. The study compared panobinostat PK between day 8 (with ketoconazole) and day 1 (control arm). Therefore the ketoconazole PBPK model and simulations were completed as a verification step rather than to address a specific regulatory question.   PBPK simulations of the effect of a strong CYP3A inducer rifampin (600 mg q.d. for 14 days) on the PK of panobinostat (single oral dose 20 mg on day 7) assumed a two-way crossover study design.

- Simulations of the effect of panaobinostat (20 mg Monday, Wednesday, Friday, MWF, for 15 days) on CYP3A probe midazolam (single oral dose 5 mg on day 15 with panobinostat) assumed a two-way crossover study design.

a. Model building

In vitro, panobinostat is a substrate of CYP3A. Results of in vitro ADME experiments, physicochemical properties, and results from several clinical PK studies including the parameters generated in population PK analysis were used to construct and optimize panobinostat PBPK model (**Appendix Tables 1 and 2**). In the updated PBPK report [3], the sponsor stated that the fraction of metabolism by CYP3A to hepatic clearance ($f_{m,CYP3A}$) and the hypothetical flow term for the intestine absorption model (Q_{gut}) were optimized during model building according to the observed magnitude of DDI between panobinostat and ketoconazole observed in Study B2110 (**Appendix Table 2**).

In vitro, panobinostat is also a time-dependent inhibitor of CYP3A and a reversible inhibitor of CYP2D6. The maximal inactivation rate constant (k_{inact}) and inactivation constant (K_I) for CYP3A were 1.37 ± 0.187 hr^{-1} and 12 ± 4.47 μM, respectively (mean± standard deviation from in vitro experiment). The reversible inhibition constant Ki for CYP2D6 was 0.167 μM. These parameters were integrated into the PBPK model.

b. Model verification

There were no independent studies used to verify panobinostat PBPK model (See discussions in Results 4.a). To confirm sponsor's assumption on $f_{m,CYPs}$, the FDA reviewer modified sponsor's model by

decreasing $f_{m,CYPs}$ from 0.55 to 0.3. This alternative model requires optimization of individual f_m by keeping the relative ratios for each CYP isoform and Q_{gut} to maintain overall first-pass metabolism.

c. Model applications

Two scenarios that have not been tested through clinical trials were predicted using panobinostat PBPK model. These include the effect of a strong CYP3A inducer rifampin on panobinostat PK and the effect of panobinostat on CYP3A probe substrate midazolam.

d. Additional PBPK modeling and simulation

Sponsor's PBPK model assumed first-order absorption for panobinostat (Appendix Table 2 and sources for input parameters therein). The FDA reviewer expanded this model by using the software's "Advanced Dissolution, Absorption, and Metabolism (ADAM)" model (mechanistic absorption model). Input parameters describing various processes responsible for oral absorption are summarized in **Appendix Table 3**, including a measured pH dependent solubility profile [8].The following scenarios were explored using mechanistic absorption model:

1. Food effect. The effect of food was evaluated by comparing the simulations under fasted and fed conditions. Physiological changes under these prandial conditions have been implemented in the PBPK software and include e.g. alterations in liver blood flow and composition of luminal fluids in terms of their pH and bile salt concentrations. Additional condition was tested by increasing gastric emptying time under fed condition from 1 hr to 3 hrs, partially mimicking the effect of high fat meal.

2. Sensitivity of panobinostat exposure to changes in gastric pH. A sensitivity analysis was conducted by varying gastric pH from 0.5-8.0 to explore the effect of changing gastric pH on panobinostat absorption and PK.

Unless otherwise stated, designs of these additional simulations used population representative (n=1 virtual subject) of "Healthy Volunteer" population taking a single oral dose of panobinostat. The duration was 48 hours.

4. Results

a. Can Panobinostat PBPK Model Be Used to Predict The Effect of CYP3A Modulation on Panobinostat Exposure?

Yes. Two major factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for panobinostat), and capability of the model to predict the PK profile under different dosing regimens.
The sponsor believes that the simulations using the updated panobinostat model are acceptable for describing the majority of the observed panobinostat single agent PK from three studies with patients taking oral panobinostat ([3], **Appendix Table 4**).

The ratios of simulated exposure (AUC or Cmax) to the observed exposure for the 22 dosing conditions of these studies were calculated (**Table 1**). Based on sponsor's pre-defined, 2-fold prediction threshold, 4 conditions have ratios ≥2 (Cmax or AUC), and one condition has Cmax ratio of 0.5. One limitation is the use of healthy volunteer population to simulate all conditions. For example, healthy volunteer is not

considered by the FDA reviewer to represent patient cohort in Study B1101, because Asian race was a significant covariate in the population PK model with 17% higher clearance. In addition, there are diverse comorbidities in the cancer population that are not captured in the healthy volunteer population [9].

Sponsor compared simulated panobinostat PK in the absence and in the presence of ketoconazole (**Table 2**), and concludes that the model reasonably described the observed change in panobinostat exposure by ketoconazole. The predicted and observed geometric mean exposure ratios were 1.78 and 1.78 for AUC, and 1.71 and 1.62 for Cmax, respectively. Because the sponsor used ketoconazole DDI results to inform $f_{m,CYP3A}$ in the model (i.e., assumes the AUC ratio (with/without inhibitor) = $1/(1- f_{m,CYP3A})$ [3]), the ketoconazole study itself cannot be considered an independent study to verify the assumption on $f_{m,CYP3A}$ within panobinostat PBPK model. Thus, additional information is needed to confirm the assumption on $f_{m,CYP3A}$. In sponsor's model, the combined $f_{m,CYPs}$ of CYP isoforms is 0.55 (0.4, 0.12, and 0.03 for CYP3A4, CYP2D6, and CYP2C19, respectively, (**Appendix Table 2**). In response to 07072014IR (Section 5.2.2), sponsor states that the f_m values used the model for oxidative pathways can be supported by results of human mass balance study [5]. In fact, the $f_{m,CYPs}$ of 0.55 used in the sponsors model represents the higher value of the range of the fraction of oxidative metabolism observed in human mass balance study (0.3-0.47, [4]). The FDA reviewer tested the sensitivity of sponsor's assumption regarding the use of a higher $f_{m,CYPs}$ by predicting panobinostat PK using an alternative FDA developed model with a lower $f_{m,CYPs}$ (e.g., 0.3, see "Methods") This alternative model structure was also used to predict the effect of ketoconazole on panobinostat PK (**Appendix Table 5**). The additional simulations using FDA's model along with other data provided by the sponsor suggest that sponsor's assumption regarding $f_{m,CYPs}$ was reasonable.

Table 1. Ratios of PBPK simulated panobinostat exposure (AUC or Cmax) to the observed exposure for three studies

Study	Conditions	Comments	Simulated/Observed	
			AUC	Cmax
CLBH589B1101	10 mg day 1 (n=3)	A phase I dose-escalation study in Japanese advanced solid tumor and CTCL patients	0.7	**0.5**
	15 mg day 1 (n=4)		1.4	0.9
	20 mg day 1 (n=6)		1.7	1.8
	10 mg day 15 (n=3)		1.1	0.6
	15 mg day 15 (n=4)		1.6	1.2
	20 mg day 15 (n=6)		**2.1**	1.9
CLBH589B2101	15 mg day 1 (n=3)	A phase IA, 2-arm,multicenter, dose-escalation study in advanced solid tumor patients	NA	1.2
	20 mg day 1 (n=36)		0.7	0.8
	30 mg day 1 (n=31)		0.7	0.9
	15 mg day 15 (n=3)		1.2	1.3
	20 mg day 15 (n=18)		0.9	0.8
	30 mg day 15 (n=4)		1.6	**2.0**
CLBH589B2102	20 mg day 1 (n=9)	A phase IA/II, two-arm, multi-center, open-label, dose escalation study in advanced hematologic malignancy patients	1.0	1.0
	30 mg day 1 (n=18)		0.6	0.7
	40 mg day 1 (n=24)		0.9	0.7
	60 mg day 1 (n=53)		1.2	0.9
	80 mg day 1 (n=18)		1.6	1.2
	20 mg day 15 (n=8)		1.0	0.7
	30 mg day 15 (n=12)		1.3	0.9
	40 mg day 15 (n=22)		1.8	1.1
	60 mg day 15 (n=17)		**2.5**	1.3
	80 mg day 15 (n=4)		**2.8**	1.4

PBPK Review page 7

Table 2. Comparison of PBPK simulated PK parameters of LBH589 in the presence or absence of ketoconazole (Study CLBH589B2110)

	PBPK Simulated	Observed
Mean (CV%) panobinostat AUC (0-24hr) (ng/ml h)	104 (103)	111 (32)
Mean (CV%) panobinostat AUC (0-24hr) with ketoconazole (ng/ml h)	194 (110)	188 (56)
Geometric AUC mean ratio (90% CI)	1.8 (1.7-1.9)	1.8 (1.5-2.2)
Mean (CV%) panobinostat Cmax (ng/ml)	19 (146)	20 (36)
Mean (CV%) panobinostat Cmax with ketoconazole (ng/ml h)	37 (154)	40 (80)
Geometric Cmax mean ratio (90% CI)	1.7 (1.6-1.8)	1.6 (1.2-2.2)

Summarized from Table 6.3 of reference [3]. Simulation used 10 trials with 10 subjects each (n=100 total). Clinical data were available for panobinostat PK alone and with ketoconazole in 11 and 12 subjects.

Sponsor applied panobinostat PBPK model to predict the effect of a strong CYP3A inducer rifampin on panobinostat PK. **Table 3** shows the simulated panobinostat PK after 20 mg single oral dose on day 7 in the presence of rifampin (600 mg once daily for 14 days). Co-administration with rifampin decreased geometric mean AUC and Cmax by 65 and 55%, respectively. The default rifampin model in SimCYP software tends to underestimate its induction potential [10]. Therefore the strong CYP3A inducer rifampin will likely result in a decrease in panobinostat AUC that is greater than 65% reported from the simulations. This should be considered when drafting labeling for the effect of strong inducers on panobinostat exposure.

Table 3. PBPK simulated panobinostat PK parameters in the presence and in the absence of rifampin (Table 6.4 of reference [3])

	N	mean AUC_{0-24}	mean AUC_{0-Inf}	geometric mean AUC_{0-Inf}	mean C_{max}	geometric mean C_{max}
Simulated						
LBH589 alone	100	104 (103%)	256 (47%)	231	19.4 (146%)	9.67
Day 7 LBH589+rifampin	100	42.9 (109%)	97.4 (63%)	80.1	8.34 (149%)	4.34
Geometric mean ratio (90% CI)				0.35 (0.32-0.38) (65% decrease)		0.45 (0.41-0.49) (55% decrease)

Values are arithmetic mean (CV%) or geometric mean.
Units are: AUC, ng/mL*h; C_{max}, ng/mL; t_{max}, h

b. Can Panobinostat PBPK Model Be Used to Predict The Effect of Panobinostat on The PK of Midazolam?

Yes. **Table 4** shows the simulated midazolam PK after a single oral dose of 5 mg on day 15 in the presence of panobinostat given 20 mg MWF for 15 days (7 doses). The geometric mean increases in midazolam AUC and Cmax were 1.04 and 1.04, respectively. Sponsor conducted sensitivity analysis using a model that assumed a more potent time-dependent CYP3A inhibition (K_I of 7.5 μM and k_{inact} of 1.51 /h) and predicted a geometric mean increase in midazolam AUC of less than 1.08. Based on sponsor's prediction and sensitivity analyses, it appears that panobinostat will not significantly increase

midazolam exposure (e.g. AUC ratio of midazolam ≤1.25), when both drugs are co-administered through oral administration. The FDA reviewer conducted an additional sensitivity analysis by increasing k_{inact} by 10-fold. Simulated midazolam AUC ratio was 1.32 using the alternative model with 10-fold higher k_{inact} for CYP3A. The alternative model over predicted panobinostat exposure by >15%, suggesting nonlinear PK as a result of stronger auto inhibition of CYP3A, that was not observed in the dose escalation trials. Therefore, the 10-fold increase in k_{inact} appears implausible, and sponsor's assumption regarding k_{inact} for CYP3A is reasonable. Since the sponsor plans to conduct a clinical trial to further assess this potential DDI, interim labeling should communicate that PBPK simulations suggested that the effect of panobinostat on a sensitive CYP3A substrate midazolam is minimal (e.g. exposure increase less than 25%). The label should be updated once additional information becomes available from the proposed panobinostat-midazolam DDI trial.

Table 4. PBPK simulation of the effect of panobinostat on midazolam exposure (Table 6.5, reference [3]).

	N	mean AUC$_{0-inf}$	geometric mean AUC$_{0-inf}$	mean C$_{max}$	geometric mean C$_{max}$
Simulated					
midazolam alone	100	70.0 (64%)	56.2	17.1 (57%)	14.5
midazolam + LBH589	100	73.2 (64%)	58.7	17.8 (56%)	15.1
Geometric mean ratio (90% CI)			1.04 (1.04-1.05)		1.04 (1.03-1.04)

Values are median (range) for t$_{max}$, and arithmetic mean (CV%) or geometric mean for all other parameters.
Units are: AUC, ng/mL*h; C$_{max}$, ng/mL; t$_{max}$, h

    c. Additional modeling and simulations to evaluate the effect of food and elevated gastric pH on panobinostat oral absorption

Panobinostat has a pH dependent aqueous solubility, with high solubility at low pH and decreasing solubility with increasing pH [8]. In humans, normal breakfast and high fat breakfast delayed panobinostat Tmax by a median of 1.5 hours and 2.5 hours, decreased panobinostat Cmax by 36% (geometric mean ratio GMR of 0.64 (90% confidence interval CI: 0.50 – 0.81))and 44% (GMR of 0.56 (90% CI: 0.45 – 0.70)), respectively. However, food has marginal effect on panobinostat AUC [4]. In order to evaluate the effect of various factors on panobinostat absorption, especially the effect of gastric pH on panobinostat PK given a lower solubility at pH 7.6 [8], the FDA reviewer expanded sponsor's model by considering mechanistic oral drug absorption processes (**Appendix Table 3**). The mechanistic absorption model was used to simulate food effect and pH effect on panobinostat PK after single oral dose of 20 mg in healthy volunteers.

This model, under the assumptions provided in **Appendix Table 3**, predicts complete oral absorption (e.g. fraction absorbed or Fa of >99%) in both prandial states and under elevated gastric pH conditions. In a representative virtual healthy volunteer, simulated panobinostat PK using the mechanistic absorption model appears to be consistent with the observed data (**Table 5**). However, the model tends to over-predict panobinostat exposure (Cmax and AUC) when simulation was conducted in healthy volunteer virtual population (10 trials with10 subjects in each trial, data not shown). Because the post-absorption component of panobinostat PBPK model was kept unchanged with regard to hepatic metabolism and drug distribution, the over-prediction of panobinostat exposure can be attributed to a less significant first pass

metabolism in small intestine predicted by the mechanistic absorption model as compared to first order absorption model. A subsequent simulation of the effect of ketoconazole using the mechanistic absorption model (same design as in "a" above) shows that the effect of ketoconazole was less pronounced than using sponsor's first order absorption model, supporting the hypothesis that first pass metabolism needs to be optimized in the mechanistic absorption model in order to better describe panobinostat PK (see **Appendix Table A2** and discussions on optimization of Qgut parameter). Given the short review timeline and the primary focus on the effect on panobinostat oral absorption, the reviewer did not further optimize this mechanistic absorption model. The subsequent analyses of the factors affecting oral absorption of panobinostat should be considered exploratory.

1. Food effect

The FDA reviewer explored the effect of food on the exposure of panobinostat after a single oral dose of 20 mg. The results are shown in **Table 5**. Simulation shows that food has no effect on panobinostat AUC, fa, and Fg values. In addition, simulations under fed conditions (conditions 2 and 3 with prolonged gastric emptying time from fasted condition (condition 1) to 1 hr and 3 hr, respectively) show an increase in Tmax and a decrease in Cmax. These findings appear to be consistent with the observations in the food effect study [4]. The prolonged gastric emptying time (3h compared to the default value of 1h) assumed in the PBPK simulations can be reasonably justified with the fact that food, especially high-fat meals, decelerate gastric emptying.

Table 5. Additional simulations to evaluate the effect of food on panobinostat PK and oral absorption using mechanistic absorption model (GMR: geometric mean ratio. Data see Appendix Table 6)

Simulated compared to fasted condition (simulation Condition 1)		
	Default fed condition (gastric transit time 1 hr, Condition 2)	Modified fed condition (gastric transit time 3 hr, Condition 3)
Delayed T_{max} (hr)	0.4	1.2
% decrease in C_{max}	17%	51%
% change in AUC (0-48hr)	+4%	+1%
Observed compared to fasted condition		
	Normal Breakfast	High-fat Breakfast
Delayed median T_{max} (hr)	1.5	2.5
% decrease in GMR C_{max}	36%	44%
% change in GMR AUC $_{0-inf}$	-14%	-16%

2. Sensitivity analysis of gastric pH

When the default value of fasting gastric pH of 1.5 in the mechanistic absorption model of panobinostat was changed within a wide range from 0.5 to 8, value of Cmax, AUC0-48 hr, and Fa remained constant, suggesting the lack of effect of altered gastric pH on panobinostat PK.

5. Conclusion

Sponsor's PBPK model of panobinostat is considered sufficient to predict panobinostat PK in patients co-administered strong CYP3A inducers. The effect of a strong CYP3A inducer rifampin was predicted to decrease panobinostat exposure by >65%, suggesting that panobinostat should not be co-administered with strong CYP3A inducers. Sponsor's PBPK model of panobinostat predicted no effect (midazolam AUC ratio <1.25) on CYP3A in humans. The PBPK findings are not considered conclusive   (b) (4)
                                                        In addition, preliminary simulation using a mechanistic absorption model of panobinostat suggested that changing gastric pH in a physiological range (e.g. pH 1 – 7) does not significantly alter panobinostat oral absorption.

6. Appendices

a. Abbreviations

ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; AUC_{tau}, steady state AUC within a dosing interval; B/P, blood to plasma ratio; BTZ, bortezomib; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; C_{trough}, trough concentration; CL, clearance; CL_{int}, intrinsic clearance; DACi, Deacetylase inhibitors; DEX, dexamethasone; DDI, drug-drug interaction; F, bioavailability; F_a, fraction absorbed; F_g, fraction that escapes intestinal metabolism; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; f_p, fraction unbound in plasma; fu,mic, fraction unbound in microsomes; $f_{u,gut}$, apparent unbound fraction in enterocytes; GI: gastrointestinal; IR, immediate release formulation; k_a, first order absorption rate constant; K_i, reversible inhibition constant; K_I, inactivation constant (concentration of inactivator at 50% k_{inact}); k_{in}, first order rate constant into single adjusting compartment; k_{inact}, maximal inactivation rate constant; k_{out}, first order rate constant out of single adjusting compartment; LogP, logarithm of the octanol-water partition coefficient; MM: multiple myeloma; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, passive permeability; PBPK, Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; sac, single adjusting compartment; TDI, time-dependent enzyme inhibition; TIW, three times a week; Tmax, time at maximal concentration in plasma; V_{ss}, volume of distribution at steady state.

b. Information requests

Clinical Pharmacology Apr 22, 2014 (04222014IR)

Your submission includes PBPK modeling and simulations to predict the effect of strong inducer (rifampin, Study R0600943-01) on the exposure of panobinostat, and to predict the effect of panobinostat as a time-dependent inhibitor of CYP3A in vivo (Study R0800469-01). Based on our preliminary review of your study reports, you should address the following within ten business days:
a.Regarding report R0600943-01, your PBPK model appears to significantly over predict the exposure of panobinostat by nearly 10-fold. Optimize your drug model using available human PK data. The optimization should consider potential nonlinearity of the pharmacokinetics of panobinostat, when (if?) applicable. The updated model should be independently verified using drug interaction study results from Study CLBH589B2110 (ketoconazole inhibition study), before it can be used to predict the effect of rifampin and its inhibition of CYP3A. If the simulated exposure change of panobinostat by ketoconazole model does not describe the observed data, modify panobinostat model (e.g., by adjusting the relative contribution of CYP3A). Further, conduct simulations using the newer version of the PBPK software so that you can use the updated ketoconazole model.
b.Regarding report R0800469-01, conduct necessary sensitivity analysis (e.g. time-dependent CYP3A inhibition parameters) to justify your position for panobinostat as an inhibitor of CYP3A in vivo.
c. Submit the PBPK model files used to generate the results in the reports DMPK R0600943-01 and DMPK R0800469-01, and the final results requested above. The model files should be executable using SimCYP software Version 13 (such as .cmp, .lbr, and .wks). MS Excel files with the initial and revised simulation outputs should also be submitted. These files may be submitted via CD.

Clinical Pharmacology 07-Jul-2014 (07072014IR)

We note in your clinical pharmacology summary that you state that the "Oxidative metabolism by CYP P450 accounts for approximately 40% of panobinostat metabolism [study B2110],.." We reviewed your final report for

PBPK Review page 12

trial B2110 and the basis for this statement is not obvious. Provide additional context regarding how the 40% estimate was derived, and please respond within 3 business days (July 10, 2014).

c. Appendix tables and figures

Appendix Table 1. Physicochemical parameters of panobinostat for PBPK model

Input parameter	Value	Unit	Comment
Molecular weight	349.44	g·mol-1	
logPo:w	(b) (4)		cLogP, not measured
pKa1			DSP5.1R5001203B, measured amine group
pKa2			DSP5.1R5001203B, measured hydroxamic acid group

Appendix Table 2. Input parameters of panobinostat for PBPK model using SimCYP (V13 release 1)

Parameter	Value (%CV)	Unit	Comment
Absorption: First order kinetics			
fa	(b) (4)	fraction	Mass balance data >87% absorbed, only 3.5% unchanged drug in feces. Value of (b)(4) was assumed based on high permeability in vitro in Caco 2 cells.
ka		hr^{-1}	Estimated from population PK report
Qgut		L/hr	Optimized by user to capture PK profile of panobinostat after oral administration
Distribution: minimal PBPK model with a single adjusting compartment (sac)			
B/P (blood to plasma ratio)	(b) (4)		Measured. Study Report DMPK(US) R0200414
fu plasma		fraction	Measured. Study Report DMPK(US) R0200414
Predicted V_{ss}		L/kg	Fitted using in vivo IV data
kin		h-1	Population PK report parameter K24 (which assumed three compartment model)
kout		h-1	Population PK report parameter K42 (which assumed three compartment model)
Vsac		L/kg	Manually optimized for fit of clinical PK data by user
Vss		L/kg	Population PK report based on mean body weight of 76.8 kg. (b) (4) coefficient of variation (CV) was chosen by sponsor with the intention to reduce predicted variability

PBPK Review page 13

Parameter	Value (%CV)	Unit	Comment
Metabolism/Excretion			
Hepatic elimination: enzyme kinetics model. Systemic clearance of (b) (4) (Population PK report), renal CL (CLr, (b) (4) and fractional metabolism (fm CYPs) for CYP3A4, 2D6, and 2C19 ((b) (4) , respectively, in vitro CYP phenotyping study using enzyme inhibitors) were used for retrograde calculation of CLint for each metabolic pathway.			
$CL_{int,CYP3A4}$	(b) (4)	µL/min/pmol	Assuming fm of (b) (4)
$CL_{int\ CYP2D6}$		µL/min/pmol	Assuming fm of (b) (4)
$CL_{int\ CYP2C19}$		µL/min/pmol	Assuming fm of (b) (4)
$CLint,\ other$		µL/min/mg	Assuming additional fractional metabolism happened in the liver through unidentified enzymes in human liver microsomes
CL_r		L/h	Mean CLr from mass balance study
Interaction			
CYP2D6 Ki		µM	DMPKR021469
CYp2C19 Ki		µM	DMPKR021469 (from IC50 of 35 µM)
CYP3A4 Ki		µM	DMPKR021469 (from IC50 of 15 µM)
CYP3A4 k_{inact}		1/h	DMPKR0700973
CYP3A4 K_I		µM	DMPKR0700973

Appendix Table 3. FDA's modification of sponsor's panobinostat PBPK model (Appendix Tables 1 and 2) by integrating parameters of Advanced Dissolution, Absorption, Metabolism (ADAM) model (Simcyp V13, release 2)

Parameter	Value	Comment
Input form	Solid formulation	Formulation administered in vivo
Formulation	Immediate release (IR)	Formulation administered in vivo
Solubility (mg/mL) at given pH		
Water	(b) (4)	Ref [8], Water
pH 1.2		Ref [8], in HCL
pH 2.0		Ref [8], in HCL
pH 4.5		Ref [8], acetate
pH 6.0		Ref [8], phosphate
pH 6.8		Ref [8], phosphate, simulated intestinal fluid
pH 7.6		Ref [8], phosphate
Precipitation rate (1/h)		Simcyp V13 default value
Maximal super saturation ratio		Simcyp V13 default value
Radius (micro meters)		Estimated from sponsor's data [1]
Dispersion type		Assumed due to a lack of actual data
Particle density (g/mL)		Simcyp V13 default value

PBPK Review page 14

OCP PBPK Review_NDA205494 Panobinostat (SimCYP)

Diffusion coefficient, ionized (10⁻⁴ cm²/min)	(b) (4)	Simcyp V13 calculated value from molecular weight
Diffusion coefficient, micelle (10⁻⁴ cm²/min) mean		Simcyp V13 default value
Diffusion coefficient, micelle CV (%)		Simcyp V13 default value
Diffusion coefficient. (10⁻⁴ cm²/min)		Simcyp V13 calculated value from molecular weight, assuming the same as ionized (default)
Effective diffusion layer thickness (µm)		Simcyp V13 calculated value from particle size
Effective human permeability (10⁻⁴ cm/s)		Ref [8] based on caco-2 permeability in the presence of P-glycoprotein inhibitor
Bile Micelle mediated solubilization		Simcyp V13 calculated. No information on the effect of bile salt on pH dependent solubility by sponsor

Appendix Table 4. Observed and predicted panobinostat PK (Table 6.2 of reference [3])

Study	dose (mg)	Study day	N	Mean AUC (ng/mL*h) (0-48 hr)	CV% for AUC	Mean Cmax (ng/mL)	CV% for Cmax	Tmax (hr)	range for Tmax
Actual									
CLBH589B1101	10	1	3	93.0	82%	20.5	92%	1.00	(0.5-1.97)
	15	1	4	69.5	64%	16.6	69%	1.23	(0.483-4.00)
	20	1	6	75.1	54%	10.8	28%	1.45	(0.517-2.98)
	10	15	3	111	74%	19.4	94%	1.00	(0.500-4.00)
	15	15	4	112	27%	14.4	30%	1.50	(0.417-2.03)
	20	15	6	114	54%	11.6	52%	1.97	(0.500-7.97)
CLBH589B2101	15	1	3	n/a	na	12.2	65%	1	(0.5-2)
	20	1	36	198.1	(48%)/n=28	23.6	57%	1	(0.5-4.5)
	30	1	31	261.5	(49%)/n=27	34.0	56%	1	(0.5-8)
	15	15	3	148.7	48%	13.2	58%	1	(1-2)
	20	15	18	263.8	56%	28.8	62%	1	(0.5-3)
	30	15	4	235.0	62%	17.3	61%	2.1	(1-4)
CLBH589B2102	20	1	9	131	58%	19.5	61%	2.1	(0.5-3.1)
	30	1	18	310	117%	39.8	69%	1	(0.5-28)
	40	1	24	299	76%	58	59%	0.8	(0.5-3.1)
	60	1	53	330	62%	66.9	70%	1	(0.5-45.7)
	80	1	18	342	54%	63.5	58%	1	(0.5-6)
	20	15	8	245	87%	33.6	49%	1	(0.5-2.1)
	30	15	12	280	59%	38.4	61%	2	(0.7-4.0)
	40	15	22	271	59%	41.6	88%	1.1	(0.5-4.0)
	60	15	17	306	50%	51.8	56%	1.1	(0.5-6.0)
	80	15	4	369	52%	69.6	39%	1.5	(0.7-2.0)
Simulated									
	10	1	100	64.1	87%	9.71	146%	1.3	(0.28-1.8)
	15	1	100	96.5	87%	14.6	146%	1.3	(0.28-1.8)
	20	1	100	129	87%	19.5	146%	1.3	(0.28-1.8)
	30	1	100	195	88%	29.2	146%	1.3	(0.28-1.8)
	40	1	100	262	88%	39.1	146%	1.3	(0.28-1.8)
	60	1	100	398	88%	58.8	146%	1.3	(0.28-1.8)
	80	1	100	538	89%	78.7	146%	1.3	(0.28-1.8)
	10	15	100	119	47%	11.1	126%	1.3	(0.3-1.7)
	15	15	100	180	47%	16.7	126%	1.3	(0.3-1.7)
	20	15	100	242	48%	22.4	126%	1.3	(0.3-1.8)
	30	15	100	368	48%	33.9	126%	1.3	(0.3-1.8)
	40	15	100	498	48%	45.6	126%	1.3	(0.3-1.7)
	60	15	100	765	48%	69.6	126%	1.3	(0.3-1.8)
	80	15	100	1044	49%	94.2	126%	1.3	(0.3-1.8)

Values are median (range) for tmax, and arithmetic mean (CV%) for all other parameters.
n/a: not available
n: a subset of patients who had evaluable PK parameters (e.g., AUC). This "n" is smaller than patients who had PK collection
The multiple dose regimen was MWF every week

CLBH589B2101 CLBH589B2102. A phase IA/II,two-arm, multi-center, open-label, dose escalation study of LBH589 administered orally via different dosing schedules in adult patients with advanced hematological malignancies.

PBPK Review page - 16 -

Appear this way on original

Appendix Table 5. PBPK simulated panobinostat PK parameters in the presence and in the absence of ketoconazole – comparison between sponsor's model and FDA's model

		Sponsor's model	FDA's model
Model conditions	Combined $f_{m,CYPs}$ [a]	0.550	0.300
	$f_{m,CYP3A4}$ [a]	0.400	0.218
	$f_{m,CYP2D6}$ [a]	0.120	0.065
	$f_{m,CYP2C19}$ [a]	0.030	0.016
	Q_{gut} (L/h) [b]	2.8	2.0
$AUC_{0-24 hr}$ (ng/mL.h)	Mean	104.17	111.73
	Geometric Mean (95% confidence interval)	68.99 (57.97, 82.11)	74.57 (62.71, 88.67)
Cmax (ng/mL)	Mean	19.44	20.90
	Geometric Mean (95% confidence interval)	9.67 (7.78, 12.04)	10.47 (8.42, 13.02)
AUC ratio (with/without ketoconazole)	Mean	1.77	**1.48**
	Geometric Mean (95% confidence interval)	1.73 (1.66, 1.80)	**1.46 (1.42, 1.50)**
Cmax Ratio (with/without ketoconazole)	Mean	1.74	**1.47**
	Geometric Mean (95% confidence interval)	1.71 (1.64, 1.78)	**1.46 (1.42, 1.50)**

[a.] *FDA's model assumed fm,CYPs of 0.3, the lower value of a range reported in human mass balance study for oxidative pathways [4], individual fm values were adjusted according to the relative ratios in sponsor's model.* [b.] *A lower Q_{gut} value was used to offset an over-prediction of panobinostat exposure (in the absence of inhibitor) potentially due to decreased gut wall metabolism.*

Appendix Table 6. Model simulated PK parameters of panobinostat under fasted and fed conditions

Parameters	Condition 1. Fasted (default gastric transit time of 0.25 hr)	Condition 2. Fed (default gastric transit time of 1 hr)	Condition 3. Fed (Gastric transit time of 3 hr)	Ratio condition 2/condition 1	Ratio condition 3/condition 1
C_{max} (ng/mL)	18.1	15.0	8.8	0.83	0.49
T_{max} (h)	1.4	1.9	2.7	1.3	1.86
AUC (ng/mL.h)	111.5	116.0	113.1	1.04	1.01
f_a	0.99	0.99	0.99	1.00	1.00
F_g	0.95	0.96	0.96	1.01	1.01

Appear this way on original

PBPK Review page 19

References

1. Novartis. Drug Metabolism and Pharmacokinetics Report DMPK R0600943-01: Simcyp® simulations of the clinical drug interactionpotential of ketoconazole or rifampin with LBH589.

2. Novartis. Drug Metabolism and Pharmacokinetics Report DMPK R0800469-01: Risk assessment of the time-dependent inhibition of CYP3A by LBH589.

3. Novartis. Drug Metabolism and Pharmacokinetics Report DMPK 1400354: Updated Simcyp simulations of LBH589 pharmacokinetics and CYP3A drug interaction potential.

4. Novartis. Clinical Development Panobinostat (LBH589). CTD 2.7.2. Summary of Clinical Pharmacology.

5. Novartis. Response to FDA Request for Clinical Information (IR-19) received 07-Jul-2014.

6. SimCYP manual: A Guide for IVIVE and PBPK/PD Modeling using the Simcyp Population-based Simulator version 12, CERTARA^{TM} 2013.

7. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.

8. Novartis. Study 1400363. ACAT absorption model for LBH589 in humans and the assessment of varying stomach pH on LBH589 absorption in humans.

9. Cheeti S, Budha NR, Rajan S, Dresser MJ, Jin JY. A physiologically based pharmacokinetic (PBPK) approach to evaluate pharmacokinetics in patients with cancer. Biopharm Drug Dispos. 2013 Apr;34(3):141-54

10. Xu Y, Zhou Y, Hayashi M, Shou M, Skiles GL. Simulation of clinical drug-drug interactions from hepatocyte CYP3A4 induction data and its potential utility in trial designs. Drug Metab Dispos. 2011 Jul;39(7):1139-48.

4.3 Cover sheet and OCPB Filing/Review Form

See filing memo posted in DARRTs by JA Grillo on 04/28/2014.

4.4   Cited References

Appear this way on original

The antitussive effect of dextromethorphan in relation to CYP2D6 activity

R. Abdul Manap,[1] **C. E. Wright,**[1] **A. Gregory,**[2] **A. Rostami-Hodjegan,**[2] **S. T. Meller,**[3] **G. R. Kelm,**[3] **M. S. Lennard,**[2] **G. T. Tucker**[2] **& A. H. Morice**[1]

[1]*Pulmonary Medicine, Division of Clinical Sciences, University of Sheffield, Northern General Hospital, Sheffield, S5 7AU, UK,* [2]*Section of Molecular Pharmacology and Pharmacogenetics, Division of Clinical Sciences, University of Sheffield, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK and* [3]*OTC-HCTD, The Procter and Gamble Company, 8700 Mason-Montgomery Road, Mason, OH 45040, USA*

COPYRIGHT MATERIAL WITHHELD

Pharmacokinetics of Dextromethorphan After Single or Multiple Dosing in Combination With Quinidine in Extensive and Poor Metabolizers

Laura E. Pope, PhD, M. H. Khalil, PhD, James E. Berg,
Mark Stiles, Gerald J. Yakatan, PhD, FCP, and Edward M. Sellers, MD, PhD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO

09/26/2014

BAHRU A HABTEMARIAM

09/26/2014

SARAH E DORFF

09/26/2014

LIAN MA

09/26/2014

PING ZHAO

09/26/2014

NITIN MEHROTRA

09/26/2014

NAM ATIQUR RAHMAN

09/26/2014

BIOPHARMACEUTICS REVIEW - ADDENDUM

Office of New Drug Quality Assessment

Application No.:	NDA 205353	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	March 24, 2014		
Division:	Division of Hematology Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Novartis Pharmaceuticals Corporation	**Acting Supervisor:** Paul Seo, PhD	
Trade Name:	Farydak® Capsules (proposed)	**Date Assigned:**	March 26, 2014
Generic Name:	Panobinostat Capsules	**Date of Review:**	September 22, 2014
Indication:	Indicated, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma, who have received at least one prior therapy	**Type of Submission:** 505(b)(1) Original New Drug Application - Priority	
Dosage form/ strengths	Capsules/ 10, 15, and 20 mg/capsule		
Route of Administration	Oral		

SUMMARY:

Submission:
NDA 205353 is a 505(b)(1) priority submission for hard gelatin capsules containing 10, 15, or 20 mg of panobinstat (LBH589).

Review:
ONDQA-Biopharmaceutics reviewed the original NDA 205353 submitted 3/24/2014, and a Biopharmaceutics review authored by Dr. Elsbeth Chikhale was placed in DARRTS on 8/27/2014. The Original Biopharmaceutics review concluded the following:

"At this time of the review process (GRMP date), because the Applicant has not provided the dissolution information that is needed to finalize the regulatory acceptance criterion for the dissolution test of the proposed drug product, from the Biopharmaceutics perspective, the recommendation for NDA 205353 for Panobinostat Capsules (10, 15, and 20 mg/capsule) is **PENDING***."*

This Addendum to the Original Biopharmaceutics review is focused on the evaluation of the data supporting the acceptance criterion for the dissolution test.

Additionally, since the risk assessment table for dissolution was not included in the Original Biopharmaceutics review, this table is included in this Addendum.

1

DISSOLUTION ACCEPTANCE CRITERION:

On **August 25, 2014**, the following **information request** was send to the Applicant:
> *Based on the provided dissolution data in your response dated 8/18/14, showing complete dissolution in* (b)(4) *minutes, we recommend that you implement a dissolution acceptance criterion of Q=* (b)(4) *% at 15 minutes for your product. Please submit a revised drug product specification table and stability protocol with the updated dissolution acceptance criterion by Aug 26, 2014.*

Applicant's response dated August 29, 2014:
> *Novartis believes the Agency's request to revise the release and stability dissolution acceptance criteria to Q=* (b)(4) *% in 15 minutes is reasonable. However, Novartis proposes to maintain the release and stability dissolution acceptance criteria of Q=* (b)(4) *% in* (b)(4) *minutes and commits to reassess the appropriateness of the acceptance criteria as a post-approval commitment to be fulfilled no later than February 2015.*

On **September 11, 2014**, the following **feedback and information request** was send to the Applicant:
> *Your proposal (dated 8/29/14) to maintain the release and stability dissolution acceptance criteria of Q=* (b)(4) *% in* (b)(4) *minutes and commitment to reassess the appropriateness of the acceptance criteria as a post-approval commitment is not acceptable. Based on the provided dissolution data showing complete dissolution in* (b)(4) *minutes, we recommend that you implement the dissolution acceptance criterion of Q=* (b)(4) *% at 15 minutes for your drug product. Please submit the revised drug product specifications table and stability protocol with the updated dissolution acceptance criterion. Note that revisions to the dissolution acceptance criterion (if appropriate), can be requested post-approval via a prior approval supplement with complete dissolution data supporting such request.*

Applicant's response dated September 18, 2014:
> *The dissolution acceptance criteria is revised as requested by the Agency in the FDA IR, dated September 11, 2014. Specifically, the Agency recommendation to implement the dissolution acceptance criterion of Q=* (b)(4) *% at 15 minutes based on the dissolution data showing complete dissolution in* (b)(4) *minutes is formally submitted herewith. The current dissolution method is also revised specifically to include the 15 minute time-point. The revision of the dissolution method allows for the appropriate dissolution profiling to be conducted at the 15, 20 and 30 minute intervals at the 36 month time-point.*

Reviewer's overall assessment of the dissolution acceptance criterion: **ACCEPTABLE**

The revised dissolution acceptance criterion of Q= (b)(4) % at 15 minutes for Panobinostat Capsules is found acceptable.

2

RISK ASSESSMENT EVALUATION: *ACCEPTABLE*

The risk assessment evaluation for the dissolution CQA component of Panobinostat Capsules is presented in the next table.

Risk Assessment of Panobinostat Capsules

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	M	The dissolution method and the dissolution acceptance criterion are adequate to control the quality of the drug product	Acceptable (M)	The dissolution method is shown to be capable to reject batches with unacceptable dissolution profiles due to (b) (4) during the drug product manufacturing process.

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

CONCLUSION:

The dissolution acceptance criterion, which was a pending issue in the Original Biopharmaceutics review dated 8/27/14, has been revised and is now acceptable.

In summary, the following dissolution method and acceptance criterion for Panobinostat Capsules (10, 15, 20 mg) are found acceptable for release and stability testing.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
I (Basket)	100 rpm	900mL	37°C	0.01 N HCl pH ~ 2	Q = (b)(4)% at 15 minutes

RECOMMENDATION:

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

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Paul Seo

3

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 205353	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	March 24, 2014		
Division:	Division of Hematology Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Novartis Pharmaceuticals Corporation	**Acting Supervisor:** Paul Seo, PhD	
Trade Name:	Farydak® Capsules (proposed)	**Date Assigned:**	March 26, 2014
Generic Name:	Panobinostat Capsules	**Date of Review:**	August 27, 2014
Indication:	Indicated, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma, who have received at least one prior therapy	**Type of Submission:** 505(b)(1) Original New Drug Application - Priority	
Dosage form/ strengths	Capsules/ 10, 15, and 20 mg/capsule		
Route of Administration	Oral		

SUMMARY

Submission:

This is a 505(b)(1) priority NDA for hard gelatin capsules containing 10, 15, or 20 mg of panobinstat (LBH589). The proposed drug product is indicated, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy. The Applicant has performed numerous clinical safety and efficacy studies. The Applicant is seeking a waiver from conducting in-vivo bioavailability studies for the 10 mg and 15 mg hard gelatin capsule strengths based on the establishment of bioequivalence between the commercial formulation and the pivotal study formulation of the highest strength (20 mg).

The dissolution for the proposed drug product will be evaluated as part of the drug product release and stability testing.

Review:

The Biopharmaceutics review for this NDA is 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

1

CONCLUSIONS:

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:**
   Due to an outstanding information request on the recommended dissolution acceptance criterion, the setting of the regulatory dissolution acceptance criterion for the proposed product could not be finalized at the time of this review (GRMP date) and therefore it still is **PENDING**.

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:

At this time of the review process (GRMP date), because the Applicant has not provided the dissolution information that is needed to finalize the regulatory acceptance criterion for the dissolution test of the proposed drug product, from the Biopharmaceutics perspective, the recommendation for NDA 205353 for Panobinostat Capsules (10, 15, and 20 mg/capsule) is **PENDING**.

After the requested information is received and reviewed, an Addendum to this Original Review with the final Biopharmaceutics recommendation on the approvability of this NDA will be filed in DARRTS.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

2

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

This is a 505(b)(1) priority NDA for hard gelatin capsules (HGC) containing 10, 15, or 20 mg of panobinstat (LBH589). The proposed drug product is indicated, in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma, who have received at least one prior therapy. The proposed commercial formulation ⬚⬚⬚⬚⬚⬚ (b) (4) ⬚⬚⬚⬚⬚⬚ is representative of the formulation utilized in the pivotal Phase III clinical study. In addition, the 20 mg panobinostat hard gelatin capsules are the highest proposed commercial strength utilized in the pivotal Phase III clinical study (D2308). The Applicant has performed numerous clinical safety and efficacy studies.

The Applicant is seeking a waiver from conducting in-vivo bioavailability studies for the 10 mg and 15 mg hard gelatin capsule strengths, based on the establishment of bioequivalence between the commercial formulation and the pivotal study formulation of the highest 20 mg strength and comparative dissolution profiles. The dissolution of the proposed drug product will be evaluated as part of the drug product release and stability testing.

BACKGROUND:

The drug product's development involved the following two stages:
  a) Development of the Clinical Service Form (CSF) to support early clinical studies
  b) Optimization of the CSF into the Final Market Image (FMI) to support pivotal clinical studies and commercialization.

(b) (4)

After the Phase I clinical studies, the hard gelatin capsule was chosen as the dosage form for further development and future commercialization with minimal changes in the formulation compared to the CSF.

During the continued development of the capsule formulation, both drug substance and drug product challenges were encountered. (b) (4)

(b) (4)

3

REVIEW:

The Biopharmaceutics review for this NDA is 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

BIOPHARMACEUTICS INFORMATION:

PROPOSED FORMULATION:

The table below lists the composition of panobinostat 10mg, 15mg and 20mg hard gelatin capsules.

Ingredient	Theoretical amount [mg]			Function	Reference to standards
	10mg	15mg	20mg		
LBH589 lactate, anhydrous corresponding to drug substance	(10.000)	(15.000)	(20.000) (b) (4)	Active ingredient	Novartis monograph
Mannitol				(b) (4)	Ph.Eur., NF, JP
Cellulose, microcrystalline / Microcrystalline cellulose					Ph.Eur., NF, JP
Starch, Pregelatinized / Pregelatinized starch					Ph.Eur., NF, JPE
Magnesium stearate[1]					Ph.Eur., NF, JP
(b) (4)					Ph.Eur., USP
Fill weight					-
Capsule shell, size 3					Novartis monograph
Capsule shell, size 1					Novartis monograph
Capsule shell, size 1					Novartis monograph
Total weight (approx.)					-

1 (b) (4)

2

DISSOLUTION INFORMATION:

Proposed dissolution method:
Apparatus 1 (basket), 900 mL 0.01 N HCl, pH ~2 at 100 rpm.

Dissolution Method Development Report:
The dissolution method development report was requested by the FDA in an information request dated May 13, 2014 and was provided in a response dated May 21, 2014. The dissolution method development report included the following information:

➤ *Solubility of panobinostat drug substance, lactate salt at 37 °C, batch 0724011 (lactate anhydrous):*

Solvent	Solubility in mg/ml of solution	Solubility % m/V (g/100 ml solution)	Description term[1]
Water	4.775	0.48	sls
0.1 N HCl (simulated gastric fluid)	1.452	0.15	sls
0.01 N HCl[3]	8.759	0.88	sls
Buffer pH 1.2 (HCl)[2]	1.017	0.10	sls
Buffer pH 2.0 (HCl)[2]	1.256	0.13	sls
Buffer pH 4.5 (acetate)[2]	4.771	0.48	sls
Buffer pH 6.0 (phosphate)[2]	3.845	0.38	sls
Buffer pH 6.8 (phosphate, Simulated intestinal fluid)[2]	0.261	0.03	vsls
Buffer pH 7.6 (phosphate)[2]	0.064	<0.01	ins
Sodium chloride 0.9% in water	1.146	0.11	sls

[1]　According to USP, Pharm. Eur., J.P.

[2]　Triplicate determination performed (others are duplicate determination)

[3]　Prepared by dilution of 0.1N HCl. In comparison, buffer pH 2.0 (HCl) was prepared by adjusting the pH of commercially available buffer pH 1.0 HCl to pH 2.0 using 2M NaOH. As a result, there is possible salt conversion to the chloride salt due to a common ion effect and subsequent change in solubility.

Sls　slightly soluble

Vsls　very slightly soluble

Ins　practically insoluble

➤ *Selection of dissolution medium:*
According to the Applicant, the in vivo dissolution of the proposed drug product is likely to be completed   (b) (4)

Additionally, the Applicant states that the pH/solubility data at 37 ± 0.5°C batch 0724011, shows that the panobinostat drug substance, lactate salt has a good solubility in phosphate buffer pH 6.8 of 0.261 mg/ml   (b) (4)). Therefore, the Applicant believes that complete dissolution occurs   (b) (4)

                                                                                    Consequently, 0.01N HCl (~ pH 2) dissolution medium was selected since it is expected to best reflect the dissolution behavior under physiological conditions. The dissolution method meets sink conditions, because at the highest concentration of 20 mg (worst case of the three dosage strengths) and 900 ml dissolution medium (volume is

5

typically 500, 900 or 1000 mL), the drug concentration would be [(b) (4)] mg/ml. [(b) (4)]

> ### *Paddle Speed:*

Since the dosage form is a hard gelatin capsule (HGC), a USP apparatus 1 (basket method) at rotational speed of 100 rpm was selected. There is no history of an evaluation of different basket speeds; the Applicant states that different speeds were not evaluated since 100 rpm is the standard speed used for basket methods.

> ### *Discriminating power of the method:*

Due to a drug product manufacturing site change from Novartis East Hanover to [(b) (4)]

The following panobinostat HGC 20 mg, technical batches of similar size (approximately [(b) (4)] kg) and manufacturing process (using the same equipment) as pilot scale batches were manufactured at [(b) (4)]

Experiment #	Batch	Experimental parameter	[(b) (4)]
1	08JM-328E	[(b) (4)]	Yes
2	08JM-327E		No
3	08JM-329E		No

[(b) (4)]

It should be noted that the commercial drug product launch site is Novartis Barbera, Spain. The commercial drug product manufacturing process at Novartis Barbera, Spain uses [(b) (4)]

Dissolution data (generated per the proposed dissolution test method in 0.01N HCl) representing in-process control (IPC) samples based on experiments 1 and 2 are as follows (n=3 beginning, n=3 middle, and n=3 end of the batch):

1 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

6

Based on the overall data, the proposed dissolution method described for panobinostat HGC is found to be discriminatory and is suitable to distinguish subtle changes following process changes during manufacturing. The proposed dissolution method can detect the ▓▓▓▓ (b) (4) ▓▓

Reviewer's assessment of the proposed dissolution method: *ACCEPTABLE*
The proposed dissolution method is shown to be capable to reject batches with unacceptable dissolution profiles due to ▓▓▓ (b) (4) *during the drug product manufacturing process.*

DISSOLUTION ACCEPTANCE CRITERION:

The Proposed drug product dissolution acceptance criterion is Q = ▓ (b) (4) **% at** ▓ (b) (4) **minutes**

The Applicant claims that the acceptance criterion for release and stability control of 'Not less than ▓ (b) (4) % (Q value after ▓ (b) (4) minutes)' of the declared content, according to USP, Ph. Eur., and JP is a standard requirement for immediate release solid oral dosage forms and is supported by the dissolution data obtained at release and stability up to 24 months for the clinical, pre-validation, validation and stability batches (see Table below). The data are presented as minimum and maximum value observed between all batches.

Dissolution data for clinical, pre-validation, validation and stability batches of LBH589 HGC:

Dissolution	Q = ▓(b)(4)% in ▓(b)(4)minutes (Range)		
	10mg	15mg	20mg
Release (average) Stability (Min-Max)[1]	▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4)		

It is noted that the stability data only show results for the dissolution at ▓ (b) (4) minutes.

Reviewer's initial assessment of the dissolution acceptance criterion: *NOT ACCEPTABLE*

*Based on provided dissolution data, the following **information request (IR)** was sent to the Applicant on **August 13, 2014**:*

> ***Provide the dissolution profile data for the registration stability batches (and clinical batch if available) at the current stability time point, measuring dissolution at 10, 15, 20, and 30 minutes, using the proposed dissolution method. For each batch, provide information such as age of batch, packaging, strength, batch number, storage conditions etc.***

Applicant's Response dated August 21, 2014:
> *Novartis would like to inform the Agency that dissolution profile data have not been generated as part of the on-going registration stability program. All samples have been analyzed as per the proposed testing monograph, see Module 3, assessing dissolution only after ▓ (b) (4) minutes. Profiles have been generated as part of release testing for all batches used in clinical studies. The profile data according to the current analytical method associated with batch H717EF/B0006 used as part of the Multiple Myeloma (MM) pivotal*

8

trial is available in the request for bio-waiver previously provided to the Agency and summarized in the following Table.

Table 1-1   **LBH589 cumulative percent released, H717EF (20 mg) at pH 2 (0.01N HCl)**

	Cumulative percent released (%)	
Capsules		(b) (4)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Average		
RSD (%)		

*Considering the data provided in this response, the following **information request (IR)** was sent to the Applicant on **August 25, 2014**:*

Based on the provided dissolution data in your response dated 8/21/14, showing complete dissolution in (b)(4) **minutes, we recommend that you implement a dissolution acceptance criterion of Q=** (b)(4) **% at 15 minutes for your product. Please submit a revised drug product specification table and stability protocol with the updated dissolution acceptance criterion by Aug 26, 2014.**

Applicant's Response dated August 26, 2014:
The Applicant proposes to respond to the FDA IR dated Monday, August 25, 2014 on Friday, August 29, 2014 rather than on the FDA requested response date of Tuesday, August 26, 2014.

<u>Reviewer's overall assessment of the dissolution acceptance criterion</u>: PENDING
Due to the above mentioned outstanding information request on the recommended dissolution acceptance criterion, the setting of the regulatory dissolution acceptance criterion for the proposed product could not be finalized at the time of this review (GRMP date) and therefore this issues still is pending.

9

BIOWAIVER REQUEST:

The proposed commercial strengths of panobinostat (LBH589) hard gelatin capsules are 10 mg, 15 mg and 20 mg. The proposed commercial formulation ▓▓▓▓▓▓▓ (b) (4) is representative of the formulation utilized in the pivotal Phase III clinical study (CLBH589D2308, hereafter referred to as D2308). In addition, the 20 mg panobinostat hard gelatin capsules are the highest proposed commercial strength utilized in the pivotal Phase III clinical study. The Applicant is seeking a waiver from conducting in-vivo bioavailability studies for the 10 mg and 15 mg hard gelatin capsule strengths based on the following supporting information:

- ▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4)

- The three proposed commercial dosage strengths are manufactured by the same manufacturing process;
- Appropriate in-vitro dissolution data* were provided to support the adequacy of waiving the in-vivo bioavailability testing. The dissolution profile comparison data demonstrate that the product exhibits similar dissolution in at least three dissolution media (▓▓▓▓ (b) (4) ▓▓▓▓▓▓▓▓▓▓ for the 20 mg, 15 mg and 10 mg strengths based on the f_2 test; and
- Panobinostat PK is linear in the clinically relevant dose range between 10 and 30 mg.

   *The dissolution profile comparisons were performed in three different media ▓▓ (b) (4) (▓▓ (b) (4) ▓▓ (b) (4) ▓▓▓▓▓▓▓▓▓▓▓ using Apparatus 1 (baskets), n=12 and 100 rpm agitation speed used and dissolution vessel volume of 900 mL. The 20 mg validation batch (H117BJ/B8008) was used as the reference batch to compare the dissolution profiles (obtained during release testing) for the 10 mg validation batch (H121DJ/B8002) and the 15 mg validation batch (H118CJ/B8003) manufactured at the commercial launch site in Barbera, Spain.

The dissolution profile comparisons for the reference and tested products are presented in the following plots.

   Comparison between Panobinostat HGC 20 mg and 10 mg batches at ▓▓▓▓ (b) (4))

(b) (4)

.
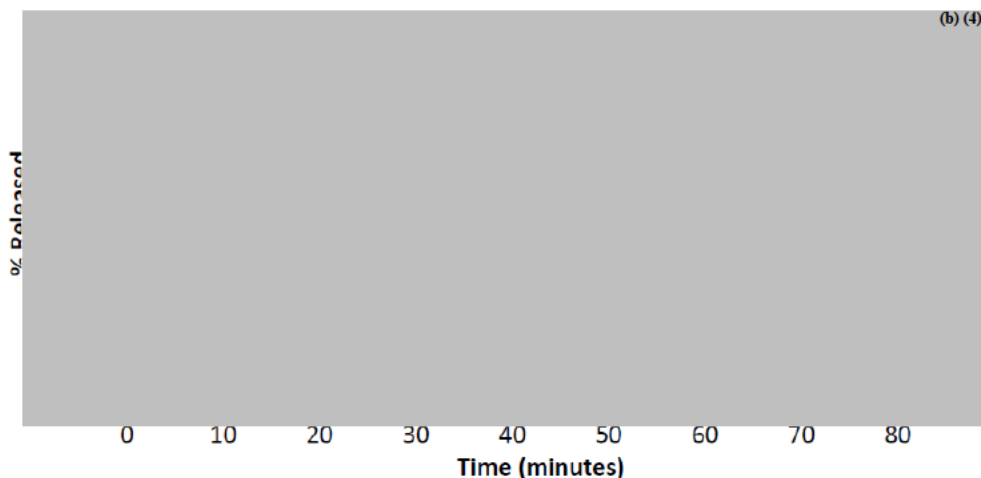
Reviewer's assessment of the Biowaiver request: ACCEPTABLE

Based on the provided information (b) (4) *, sameness of manufacturing process, comparative dissolution profiles in 3 media, and PK linearity), 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**.*

BRIDGING OF FORMULATIONS USED DURING PRODUCT's DEVELOPMENT:

The following drug products have been used during the development of the proposed drug product:

(b) (4)

13

The clinical service formulation (CSF) used in several early Phase I oral studies was a ▓▓▓▓ (b) (4)

▓▓▓▓ This early clinical formulation was subsequently modified to improve the manufacturing process by using a ▓▓▓▓ (b) (4) anhydrous salt formulation (final market image, FMI). Subsequently, six Phase II studies and three studies in patients with MM, and five clinical pharmacology studies were conducted using this FMI formulation which is intended for commercialization.

The FMI is the investigational product used in the three studies (B2207, DUS71 and D2308) supporting the present market application and is representative of the proposed commercial drug product (final FMI). The compositions of the FMI formulation utilized in the Phase III pivotal study (D2308) and the proposed commercial supplies are similar. In the formulation intended for commercialization (final FMI) the amount of ▓▓▓▓ (b) (4)

▓▓▓▓.

The compositions of the formulations used in early Clinical Service Form (CSF) and Final Market Image (FMI) are provided in the Table below.

Table 1-1   Compositions of CSF and FMI batches of panobinostat 20 mg hard capsules used for dissolution profile comparison

Batch no.	AEUS/2005-0183 (CSF)	TRD 2218-056 (FMI)
Ingredients	Amount per capsule (mg)	Amount per capsule (mg)
▓▓▓▓ (b) (4)	▓▓ (b) (4)	- ▓ (b) (4)
LBH589 lactate salt, anhydrous		
Mannitol		
Microcrystalline cellulose/ Cellulose, microcrystalline		
Pregelatinized starch		
Magnesium stearate[3]		
▓▓▓▓ (b) (4)		
Fill weight		
Approx. weight of shell		
Total weight (approx.)	315.0	315.00

The Applicant claims that the CSF and FMI are considered equivalent based on the similar in-vitro dissolution profiles in multi-media (see dissolution profiles below), comparable absolute bioavailability data generated in various phase 1/phase 2 studies, and demonstration of in-vivo bioequivalence in dogs (DMPK R0600179). The Applicant claims that the CSF and FMI showed similar dissolution behavior in the low (physiologically relevant) pH range, and therefore, no difference in the relative extent of bioavailability between the CSF and the FMI is expected in humans. A formal bioequivalence study was not conducted in patients during the clinical development program. The FMI oral capsule was used in the pivotal Phase III efficacy and safety trial D2308.

The comparison of the dissolution profiles between CSF (early clinical studies, manufactured at

14

East Hanover) and FMI batches (manufactured at [redacted (b) (4)] of 20mg hard gelatin capsules at pH 2 is illustrated below.

[redacted (b) (4)]

The comparison of dissolution profiles between CSF (early clinical studies) and FMI batches of panobinostat 20mg hard gelatin capsules at pH 4.5 is presented below.

[redacted (b) (4)]

The comparison of dissolution profiles between CSF (early clinical studies) and FMI batches of panobinostat 20mg hard gelatin capsules (manufactured in [redacted (b) (4)] at [redacted (b) (4)] illustrated below.

[redacted (b) (4)]

To demonstrate the equivalence of the pivotal clinical batch (FMI) to full scale batches made with the final commercial process (final [redacted (b) (4)]

15

(b) (4) dissolution profiles from release testing of the pivotal batch (H717EF/B0006) were compared to the 20 mg validation batch(H117BJ/B8008) in 3 different media. The plots are presented next.

Comparison between clinical (B0006) and validation (B8008) batch (20 mg) at (b) (4)

(b) (4)

Time (minutes)
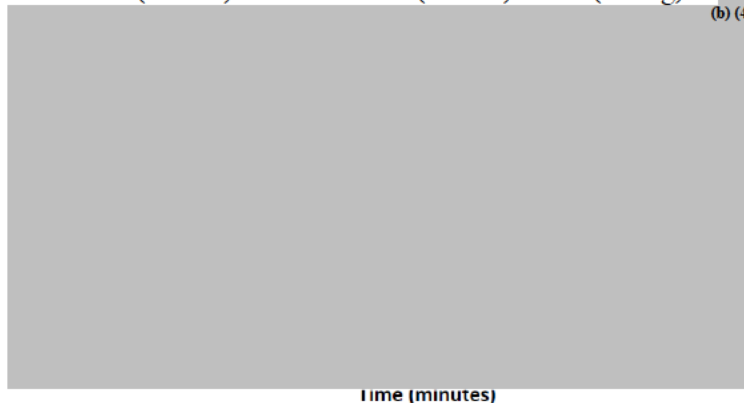
Comparison between clinical (B0006) and validation (B8008) batch (20 mg) at pH (b) (4))

(b) (4)

Comparison between clinical (B0006) and validation (B8008) batch manufactured in Novartis Barbera, 20 mg at pH (b) (4))

(b) (4)

% Released

No bioequivalence study was performed in patients during the clinical development. The absolute and relative bioavailability of panobinostat was assessed through comparison of data across studies following a single dose.

16

A formal food effect study was conducted using the FMI formulation in patients with advanced cancer (Study B2111). The human ADME study (Study B2108) used the CSF with radioactive panobinostat dose. The absolute bioavailability of panobinostat was estimated from all available intravenous studies (A2101 and A2102) and oral studies (Studies B1101, B2101, B2102, B2201, B2202, B2203, B2211, B2109, B2110, B2111, B1201 and E2214) using either the CSF or FMI oral capsules in a population pharmacokinetic (PPK) analysis. These studies are being reviewed by the Clinical Pharmacology Reviewer at OCP.

__Reviewer's assessment of the bridging of the formulations:__ ***SATISFACTORY***

Early clinical studies (phase 1/2) were conducted using the CSF and FMI drug product batches which are manufactured at three different manufacturing sites and using different formulations and drug substance forms ____(b) (4)____ *The provided comparative dissolution profile data at* ____(b) (4)____ *support the bridging of the manufacturing sites, formulations, and drug substance forms; however, comparative dissolution data at* ____(b) (4)____ *showed differences in the dissolution profile. The Applicant justified this difference by claiming that the dissolution method at* ____(b) (4)____ *is overly discriminating and bioavailability data* were also provided to support the bridging between the CSF and FMI drug products.*

Bridging of the FMI (manufactured at Novartis Barbera, Spain) to the final FMI is important since the pivotal clinical studies are conducted using the FMI and the final FMI is the commercial product. The drug product batch B00006/H717EF (20 mg, FMI) used in the pivotal clinical study has the same manufacturing site (Novartis Barbera, Spain) and practically the same formulation as the registration batches/proposed commercial drug product (final FMI). Comparative dissolution data indicate that the pivotal clinical batch B0006/H717EF is representative of the proposed commercial product.

> **It is noted that the absolute and relative bioavailability of the proposed drug product is being reviewed by the Clinical Pharmacology Reviewer from OCP.*

REVIEWER'S OVERALL CONCLUSIONS:

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:**
   Due to an outstanding information request on the recommended dissolution acceptance criterion, the setting of the regulatory dissolution acceptance criterion for the proposed product could not be finalized at the time of this review (GRMP date) and therefore this issues still is **PENDING**.

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:

At this time of the review process (GRMP date), because the Applicant has not provided the dissolution information that is needed to finalize the regulatory acceptance criterion for the dissolution test of the proposed drug product, from the Biopharmaceutics perspective, the recommendation for NDA 205353 for Panobinostat Capsules (10, 15, and 20 mg/capsule) is **PENDING**.

After the requested information is received and reviewed, an Addendum to this Original Review with the final Biopharmaceutics recommendation on the approvability of this NDA will be entered in DARRTS.

18