Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Panobinostat lactate

Proprietary Product Name: Farydak

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

October 2018

TGA Health Safety Regulation

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
ASCT	Autologous stem cell transplantation
ALT	Alanine aminotransferase
APD	Action potential duration
aPTT	Activated partial thromboplastin time
AUC	Area under the curve is the definite integral in a plot of drug concentration in blood plasma versus time
BCRP	Breast cancer resistance protein
BJB432	Metabolite of panobinostat
BTZ	Bortezomib
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CNAE	Clinically notable adverse event
CMI	Consumer Medicine Information
CNS	Central nervous system
CSF	Clinical service formulation
CSR	Clinical study report
CV	Coefficient of variation
CVA	Cerebrovascular accident
CYP 450	Cytochrome P450
DILI	Drug-induced liver injury
DOR	Duration of response

Abbreviation	Meaning
EAD	Early after depolarisation
EBMT	European Bone Marrow Transplant Organisation
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA/EMEA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
Hb	Haemoglobin
Hct	Haematocrit
HCT	Hematopoietic cell transplantation
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitors
hERG	Human Ether a go go Related Gene
HR	Hazard ratio
hsp90	Heat shock protein 90
IC_{50}	Half maximal inhibitory concentration
IMiD	Immunomodulatory drug
IV	Intravenous
LD_{50}	Median lethal dose
MedDRA	Medical Dictionary for Regulatory Activities
mEMBT	Modified European Society for Blood and Bone Marrow Transplant

Abbreviation	Meaning
MM	Multiple myeloma
MR	Minimal response
MRP	Multidrug resistance-associated protein
MTD	Maximal tolerated dose
nCR	Near complete response
NHL	Non-Hodgkin's lymphoma
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OATPs	Organic anion transporting polypeptides
OCT	Organic cation transporter
ORR	Overall Response Rate
OS	Overall survival
PAN	Panobinostat
PBO	Placebo
PD	Progressive disease
P_{eff}	effective permeability of panobinostat
PFS	Progression free survival
P-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetics
PO	per oral
PTU	Propylthiourea
QD	Once daily
QLQ-C30	Quality of Life Questionnaire - Core Questionnaire
QLQ-MY20	Quality of Life Questionnaire – Myeloma Module
QoL	Quality of life

Abbreviation	Meaning
QTcF	Frederica's corrected QT interval
QW	Per week
RBC	Red blood cell
RDI	Relative dose intensity
RMP	Risk Management Plan
RRMM	Relapsed/refractory MM
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Standard deviation
SJS	Stevens-Johnson syndrome
SMQ	Standardised MedDRA Query
SOC	System Organ Class
t½	Half-life
T3	Triiodothryronine
T4	Thyroxine
TdP	Torsade de Pointes
TFI	Treatment free interval
TIW	Three times a week
t_{max}	Time to maximum concentration
TRPM	Transient receptor potential ion channels (M standing for melastatin)
TSH	Thyroid stimulating hormone
TTP	Time to disease progression
UGT	UDP glucuronosyltransferase
UK	United Kingdom

Abbreviation	Meaning
ULN	Upper limit of normal
US/USA	United States/United States of America
VGPR	Very good partial response
WBC	White blood cell
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	23 March 2016
Date of entry onto ARTG:	31 March 2016
ARTG numbers:	229941, 230845, 230844
Active ingredient:	panobinostat lactate
Product name:	Farydak
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd PO Box 101 North Ryde NSW 1670
Dose form:	Hard capsule
Strengths:	10 mg, 15 mg and 20 mg
Container:	Blister Pack
Pack sizes:	6, 12 and 24
Approved therapeutic use:	*Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.* *Treatment with Farydak should be initiated and monitored by a specialist physician with expertise in managing haematological malignancies.*
Route of administration:	oral
Dosage:	20 mg three times a week, with a 2 weeks on/1 week off schedule For further information on dosage and dosage adjustment please see the Product Information

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Farydak, panobinostat lactate 10 mg, 15 mg and 20 mg hard capsules for the following 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.

Despite the much improved survival outcome since the introduction of novel therapeutic agents including the immunomodulatory drugs (IMiDs) and proteasome inhibitors, multiple myeloma (MM) remains an incurable disease. However, the expansion of effective treatment options over the last two decades, has converted what was once a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long term control, often for 7 years or more. However, almost all patients will relapse after an initial response.

Treatment options for patients with relapsed or refractory MM include haematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include a risk stratification of myeloma (that is, high, intermediate or standard risk disease), prior treatments used, and the duration of response to these treatments.

For those not eligible for HCT, salvage treatment regimens include those based upon thalidomide, lenalidomide, pomalidomide or bortezomib which are used variously in combination with dexamethasone or cytotoxic agents, or treatment regimens with the alkylating agents, melphalan or cyclophosphamide. Additional options include novel agents available through clinical trial participation.

Panobinostat belongs to a novel class of compounds called histone deacetylase inhibitors (HDACi). It inhibits a broad range of histone deacetylases (HDACs) and targets epigenetic changes via gene expression modulation and inhibition of protein metabolism. Panobinostat has been shown to act synergistically with bortezomib through the simultaneous inhibition of the proteasome and aggresome pathways, resulting in cytotoxicity.[1]

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 31 March 2016.

At the date of submission, panobinostat had not been approved in any overseas jurisdictions. However, as outlined below there have been subsequent developments in the USA relating to the approval of panobinostat in that country. Similar applications to that submitted in Australia have been made in the USA (24 March 2014), the EU (7 May 2014), and Switzerland (6 June 2014). The dossier submitted to the FDA, EMA, Heath Canada and TGA is essentially the same, apart from the differences summarised (in a table, not included here). The sponsor stated that, as of 5 November 2014, no rejections, withdrawals or repeated deferrals had occurred in the USA, EU or Canada.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[1] Laubach J P et al, 2015 Panobinostat for the treatment of multiple myeloma. Clin Cancer Res 2015; 21: 4767-4773

II. Registration time line

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 1: Timeline for Submission PM-2014-03146-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 December 2014
First round evaluation completed	4 June 2015
Sponsor provides responses on questions raised in first round evaluation	5 August 2015
Second round evaluation completed	8 February 2016
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	22 February 2016
Sponsor's response to Delegate's overview	26 February 2016
Advisory Committee meeting	Was not presented to ACPM or ACM
Registration decision (Outcome)	23 March 2016
Completion of administrative activities and registration on ARTG	31 March 2016
Number of working days from submission dossier acceptance to registration decision*	214

*Statutory timeframe is 255 working days

III. Quality findings

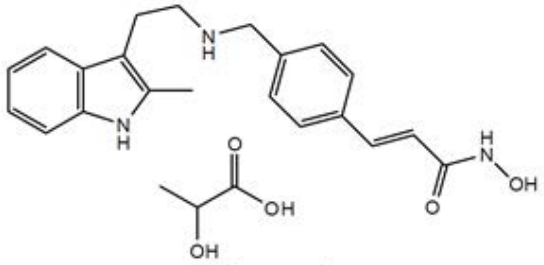
Introduction

Panobinostat is a new chemical entity which inhibits histone deacetylase (HDAC). The sponsor has applied to register Farydak panobinostat capsules for use in the treatment of multiple myeloma.

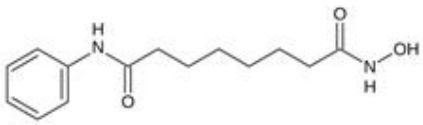
Drug substance (active ingredient)

Panobinostat is synthetic. The drug substance used is the lactic acid salt (2E)-N-hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl]-2-propenamide 2-hydroxypropanoate (1:1); the structure is shown below. Panobinostat has no chiral centres; lactic acid is chiral but the racemate is used here. The panobinostat double bond has controlled E (trans) stereochemistry. Like vorinostat, panobinostat has a hydroxamic acid group (-CONHOH).

Figure 1: Panobinostat lactate and vorinostat



panobinostat lactate
$C_{21}H_{23}N_3O_2 \cdot C_3H_6O_3$
MW 349.43 (free base)
439.51 (lactate)



vorinostat
ZOLINZA 100 mg capsules

(Febuxostat (adenuric 80 mg tablets) used in the treatment of gout is chemically unrelated; it does not have a hydroxamic acid group.)

The drug substance used to make the 'CSF' capsules used in early clinical studies was panobinostat lactate monohydrate. The drug substance used for later 'FMI' capsules and in the commercial capsules is the anhydrous form. This drug substance is crystalline (melting point 175°C); only one polymorphic form is known. Particle size control is limited which is acceptable given the solubility.

Panobinostat is basic (pKa 8.4 and 9.0). The aqueous solubility of panobinostat lactate is pH dependent, with maximum solubility at pH 2 or 3 (about 5 mg/mL) and low solubility at neutral pH (0.3 mg/mL at pH 6.8). Low solubility at pH 7.6 (0.07 mg/mL) makes it formally low solubility in the Biopharmaceutics Classification System. Nevertheless the recommended 20 mg dose should dissolve in less than 100 mL of fluids in most of the gastrointestinal tract.

Impurity levels in batches are generally low except for two impurities, a cyclisation product '014-06' and impurity '315-02' which is the main degradation product and also a metabolite. Impurity controls are considered acceptable. The drug substance is stable.

Drug product

Novartis seeks to register Farydak panobinostat 10 mg, 15 mg and 20 mg hard gelatin capsules. Labelled doses are the contents of the panobinostat base. Excipients are conventional. Proportional amounts of the same capsule fill are used in the different strengths. The strengths are well distinguished by different capsule sizes, colours and markings ('LBH 10 mg', 'LBH 15 mg', 'LBH 20 mg').

The recommended dose is 20 mg three times a week, with a 2 weeks on/1 week off schedule. Capsules are presented in blister packs; the blisters have calendar directions.

Routine in vitro dissolution testing of capsule batches uses a basket apparatus.

Degradation during manufacture and on capsule storage is slight. One impurity limit is subject to negotiation.

Capsules are stored below 30°C, 'Protect from moisture'. There is slight chemical degradation after long storage.

Biopharmaceutics

Panobinostat lactate is formally Class II (low solubility, high permeability) according to the Biopharmaceutical Classification System (BCS). The solubility classification is borderline (nearly high).

Absorption

An absorption, distribution, metabolism, and excretion (ADME) study (Study 2108) determined the fate of radiolabelled 20 mg capsule doses. 29 to 51% of radioactivity was excreted in urine over 168 hours, but negligibly as panobinostat (2%). Recovery was good, with 44 to 77% also recovered in the faeces. Metabolism was extensive. Novartis interprets the low recovery of unchanged panobinostat in faeces as indicating near complete oral absorption.

Absolute bioavailability has not been directly measured, but was estimated via cross trial comparison using pharmacokinetic measurements following intravenous (IV) doses (n = 69; two IV studies) and oral (n = 196; eight studies; PPK analysis). The absolute oral bioavailability of capsule was estimated as 21%, presumably due to extensive metabolism.

Clinical trial formulations

'Clinical service formulation' (CSF) 5 mg and 20 mg capsules were used in early clinical trials. These were formulated with panobinostat lactate monohydrate.

Subsequently 'final market image' (FMI) capsules were developed for manufacturing reasons. These use anhydrous panobinostat lactate, and the same set of excipients. FMI capsules were used in the pivotal Phase III Study D2308.This is almost the formulation proposed for registration (which has minor adjustments in the amounts of magnesium stearate and mannitol).

The bioequivalence of CSF, FMI and the proposed capsule formulations has not been directly tested in humans. Novartis notes a small bioequivalence study in beagles (9 dogs, non-Good Laboratory Practice (GLP), some excluded from pharmacokinetic analysis); this is not compelling. Novartis chiefly argues that the formulations and capsule dissolution profiles are so similar that a bioequivalence study is not required. Given also the use of the FMI capsules in the pivotal clinical trial, this argument is accepted.

Bioequivalence of strengths

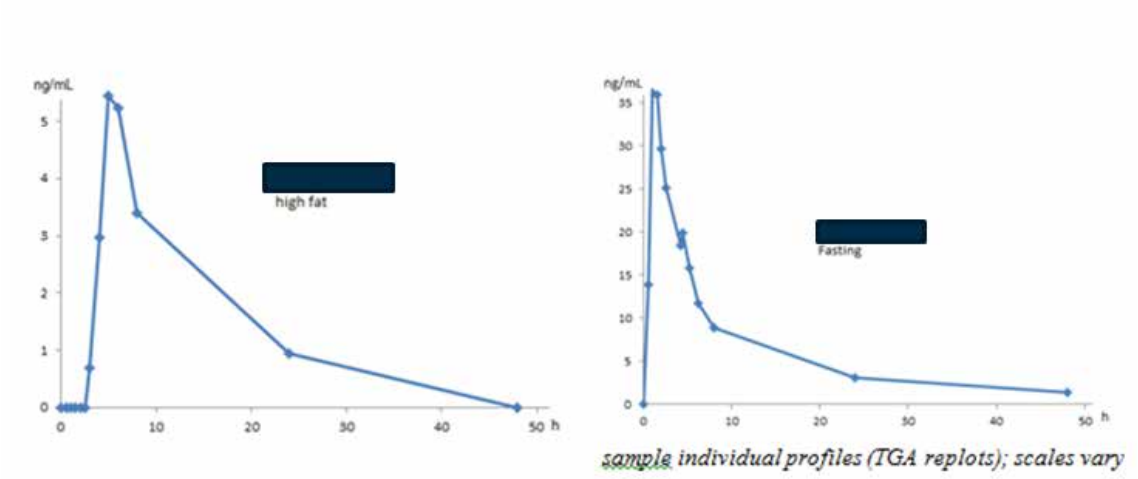
The bioequivalence of the different capsule strengths has not been tested in vivo. Novartis argues on the basis of scaled formulations and similar in vitro dissolution (at pH 1, 4.5 and 6.8) that studies are not required. This is accepted.

Effect of food

The effect of food was assessed in Study B2111, a multicentre, three way crossover trial in patients with advanced solid tumours, with 20 mg doses taken after an overnight fast, or 1 hour after a 'normal' breakfast (500 calories), or 30 minutes after a high fat breakfast (1000 calories). This study used 20 mg FMI capsules. Panobinostat pharmacokinetics were measured on Days 1, 8, and 15. In some cases there was significant carryover exposure detectable pre-dose and these subjects were excluded from analysis. There were 33 patients for whom pharmacokinetics were evaluable.

Panobinostat pharmacokinetic profiles are fairly conventional, with second peaks in some cases perhaps due to enterohepatic recycling. Plasma levels vary between subjects. Two individual profiles are shown below in Figure 2 as examples.

Figure 2: Two individual plasma profiles of panobinostat



sample individual profiles (TGA replots); scales vary

Administration with food clearly delays absorption (median time to maximum concentration (t_{max}) 1.5, 2.5 or 4.0 hours), with food also reducing maximum concentration (C_{max}) and somewhat reducing exposure as shown in Table 2.

Table 2: Tabular summary of panobinostat PK parameters by treatment (PK set)

PK parameter (unit)	Fasting (N = 33)	High Fat (N = 34)	Normal meal (N = 31)
T_{max} (h)	1.50 (0.50- 6.00)	4.00 (1.00- 8.07)	2.50 (0.50- 6.00)
C_{max} (ng/mL)	22.7 (86.02)	11.94 (63.36)	13.7 (64.87)
AUC(0-inf) (h.ng/mL)	176.4 (58.52)	143.89 (58.86)	152.7 (58.87)

The different dosing methods give C_{max} and area under the curve (AUC) outside standard bioequivalence limits. Nevertheless, Farydak was administered without regard to food in the pivotal trial Study D2308. The draft PI states that the capsules can be taken with or without food:

> Overall panobinostat exposure and inter-patient variability remained unchanged with or without food, whereas C_{max} was reduced by < 45% and t_{max} prolonged by 1.5 to 2.5 hours with food (that is, both normal and high fat breakfasts). Since food did not alter overall bioavailability (AUC), panobinostat can be administered with food in cancer patients.

Pharmaceutical subcommittee (PSC)

The dosage form is conventional and no unusual aspects have arisen in review of the chemistry or biopharmaceutic aspects, thus, in keeping with current policy, it is not planned to refer the submission to the PSC.

Comments and recommendations

Subject to resolution of one impurity limit, registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

IV. Nonclinical findings

Introduction

The quality of the nonclinical dossier was generally good. All pivotal safety related studies were conducted according to Good Laboratory Practice (GLP). Study designs included appropriate use of animal models, sufficient animal numbers, appropriate positive and negative controls, and in general, adhered to guidelines where relevant (for example ICH S9, S7A and S7B).[2,3,4] A relatively high number of cardiovascular safety pharmacology studies were submitted (not all GLP compliant) to further characterise the inhibitory action on hERG channels and assess risk of QT interval prolongation.[5] Attention is drawn to the fact that a number of toxicity studies used purified water as diluent in view of panobinostat's only slight water solubility, which may have reduced exposure and ensuing toxicities.

All *in vitro* pharmacokinetics studies the clinical module were evaluated, except for two *in silico* simulation studies (Studies DMPK-r00800469-01 and DMPK-r0600943-01) that concerned prediction of clinical drug interaction potential of panobinostat.

Pharmacology

Primary pharmacology

HDAC inhibitory activity

Assessment of the actions of panobinostat against purified recombinant human isoforms of HDACs found it inhibited all isoforms (HDACs 1 –11 of Class I, IIa, IIb and IV) to varying degrees, with greater activity against HDACs 1, 2, 3, 5, 6, 9, 10 and 11 (half maximal inhibitory concentration (IC_{50}) ranges 2.1 to 13.2 nM) than HDACs 4, 7 and 8 (IC_{50} ranges 203 to 531 nM) (Study RD-2008-51291). The IC_{50} against the former panel of HDACs were below or slightly above the clinical free fraction C_{max} 6.2 nM. The findings indicate that panobinostat is a pan-HDAC inhibitor.

Effect on acetylation of proteins and other markers

Panobinostat increased acetylation of HDAC substrate proteins: histones H3 and H4, heat shock protein 90 (hsp90) and tubulin in HCT116 (colon cancer cell line) and Hodgkin lymphoma cell lines. Panobinostat treatment of cells increased activation of the pro-apoptotic signalling molecule p21 (AC_{50}: 46 nM compared with vorinostat: 9800 nM. Markers for apoptosis (caspase 3/7 activity and Annexin V) were increased in cancer cells lines that were treated with panobinostat. As well, significant increases in expression of growth inhibitory genes Hep27, p21, TRPM were noted in panobinostat treated HCT116 cells (colon cancer cell line).[6]

In vitro anti-tumour activity

In a panel of different cancer cell lines (mix of solid and haematological tumour types), panobinostat induced cytotoxicity was observed in most haematological (leukaemia, lymphoma) and some solid (colon, prostate, small cell lung cancer) tumour types at

[2] ICH S9 Nonclinical evaluation for anticancer pharmaceuticals
[3] S7A Safety pharmacology studies for human pharmaceuticals
[4] S7B The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals
[5] hERG: Human Ether a go go Related Gene
[6] TRPM: transient receptor potential ion channels (M standing for melastatin)

median lethal dose (LD_{50}) < 50 nM. Panobinostat was more effective at halting proliferation and survival in cancer cell lines than non-cancer cells (IC_{50}: cancer cell range 0.7 to 15.9 nM compared with normal cell range 97.3 to 186 nM; LD_{90}: cancer cells range 14 to 541 nM compared with normal cells range > 5000 nM). Assessment of sensitivity across cancer cell lines found that haematological and lymphoid cancers (acute lymphocytic leukaemia, acute myeloid leukaemia, Non-Hodgkin's T-cell lymphoma and multiple myeloma) were the most responsive to panobinostat (Study RD-2013-50424). Some solid tumour cells (breast, prostate, colon and pancreatic cancer) were also responsive to panobinostat (Study RD-2008-51291). Anti-tumour effects (decreased proliferation, increased acetylation of histones, increased Annexin V levels) was shown in 5 established multiple myeloma cell lines as well in cells harvested from multiple myeloma patients.[7] In the same study panobinostat augmented the anti-tumour effects of bortezomib, dexamethasone and melphalan in these cell lines. As well, expression of the oncoproteins Bcl 2;[8] and Bcl X were downregulated by panobinostat treatment, while cells that overexpressed Bcl X were more resistant to panobinostat induced apoptosis.

Anti-tumour activity in animal cancer models

Assessment of anti-tumour activity of panobinostat was conducted using xenografted mouse models of various tumour types (HSD athymic nu/nu mice or CB17/SCID mice). Panobinostat was administered by the intravenous route in all studies and was formulated in either 5% dextrose solution (when lactate salt was used) or 0.03 M lactic acid in 5% dextrose (when free base panobinostat was used).

In HCT116 (colon cancer cell line) xenografted CB17/SCID mice peak tumour concentrations of panobinostat corresponded with peak levels of acetylated histone H4. Panobinostat concentrations persisted for up to 72 hours for single dose and 192 hours for repeat administrations of panobinostat (Study RD-2010-50113) (Study RD-2010-50113). In a xenograft mouse model of human cutaneous T-cell lymphoma panobinostat reduced tumour volume (Study RD-2007-50247). Dosing regimens were also compared to establish optimal efficacy. Lower doses (6 and 11.9 mg/kg, IV) at more frequent administrations (5 times per week (5QW)) yielded more favourable tumour responses than when less frequent administration (3QW) of higher doses (14.9 and 19.8 mg/kg, IV) was used. Panobinostat was well tolerated in the pharmacology studies with 5QW or 3QW dosing at up to 20 mg/kg, although body weight loss occurred in most treated groups (Study RD 2001-50288). Whilst tumour regression was more evident when more frequent dosing was used (that is 5QW compared with 3QW), tumour growth resumed once panobinostat treatment was withdrawn. In SCID mice injected with luciferase labelled human multiple myeloma cells, panobinostat at 10 or 20 mg/kg IP reduced tumour burden (Study RD-2008-51313). Paralleling the proposed dosing regimen, effects of panobinostat with dexamethasone and bortezomib were also determined in the SCID mouse MM xenograft model.[9] Suboptimal doses of dexamethasone and bortezomib (or lenalidomide) were used such that single agent anti-tumour effects (and toxicities) were relatively modest compared with panobinostat. Combination of panobinostat and dexamethasone with bortezomib (or lenalidomide) resulted in greater reductions of tumour volume/burden and survival rates.

Since bone lesions are a common symptom of multiple myeloma, effects on bone were also assessed. SCID beige mice were injected with labelled multiple myeloma cells (MM.1S), which distributed into bone, and effects of panobinostat on bone lesions (tumour burden),

[7] Maiso P et al., 2006 The Histone Deacetylase Inhibitor LBH589 Is a Potent Antimyeloma Agent that Overcomes Drug Resistance. *Cancer Res* 2006; 66: 5781-5789

[8] Bcl; B cell lymphoma cell Bcl2 a regulator protein that regulates cell death

[9] Ocio E M et al., 2010 In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. *Haematologica*; 2010; 95:794-803.

bone density and tolerability (as change in body weight) were observed (Study RD-2001-50288). Panobinostat produced a dose dependent reduction of bone lesions and provided protection against bone loss. Bortezomib also showed a dose dependent reduction of bone lesions and protection against bone loss. Combining panobinostat with bortezomib had a greater effect on reducing bone lesions, whereas effect on bone density was more modest. Tolerability to treatment was better in groups that received bortezomib alone. Panobinostat was also shown to improve bone density in proximal tibia from MM xenografted mice in a dose dependent manner.[9]

None of the primary pharmacology studies looked at potential anti-tumour properties of the major human metabolites of panobinostat, although a published study reported the lack of inhibitory activity of various metabolites (M37.8, M43.5 (AFN835), M40.8, M36.9, T24.0 and M44.6) against HDAC isoforms.[10] It is uncertain whether oral dosing (the clinical route) will have a different effect on tumour responsiveness. Pharmacokinetic studies indicated rapid absorption when the per oral (PO) route is used.

Secondary pharmacodynamics and safety pharmacology

The sponsor did not submit any studies that explored potential secondary or off-target effects (for example screens against a panel of receptors or proteins) of panobinostat or its known human metabolites.

Safety pharmacology studies explored the central nervous system (CNS), respiratory and cardiovascular systems. A large number of the *in vivo* studies were conducted using the IV administration route. In the CNS study mice injected with a single dose of panobinostat showed clinical signs indicative of a central effect (decreased motor activity, wobbly gait, convulsions) at 60 or 100 mg/kg (no effects at 30 mg/kg) (Study PCS-r0280108). Five out of the 10 animals in the 100 mg/kg group died and the deaths were preceded by these clinical signs, while the remaining five animals showed complete recovery at 2 hours post-dose. Clinical signs (including tremor) indicative of CNS effects were also observed in acute toxicity studies in mice and rats at ≥ 50 mg/kg IV and in repeat dose toxicity studies in rats at 2.5 mg/kg IV (3 times/week for 2 weeks) and in dogs after a single IV dose of 10 mg/kg or daily doses of 1 mg/kg IV for 4 days. Tissue distribution studies in rats showed distribution of drug related materials to the brain albeit at low levels. There are no pharmacokinetic data in mice. In rats and dogs, the lowest plasma C_{max} (first blood sample taken 5 to 30 minutes after injection) of panobinostat at doses eliciting clinical signs of CNS effects were approximately 10 times the clinical C_{max} (approximately 200 ng/mL compared with 21.6 ng/mL).

No treatment related effects on respiratory parameters were noted in rats that received 1, 3 and 10 mg/kg, IV panobinostat (Study PCS-r0280118).

Panobinostat was found to have inhibitory activity against hERG channels (IC_{50}: 3.5 and 5.8 μM in two assays and > 10 μM in another two assays). Clear additive effects were noted when combined with docetaxel, weak additivity with nilotinib and no additive effects with Herceptin or 5-azacytidine. Combined effects of panobinostat with bortezomib and dexamethasone were not tested. Exploration of hERG protein trafficking to cell surface found panobinostat had no inhibitory effect on wild type hERG, but increased trafficking of a mutant form SM-hERG (SM, G601S), a trafficking deficient mutant derived from a patient with long QT syndrome (Study PCS-r0516287), suggesting hERG channel inhibition.[11]

[10] Clive S et al., 2012 Characterizing the disposition, metabolism, and excretion of an orally active pan-deacetylase inhibitor, panobinostat, via trace radiolabelled 14C material in advanced cancer patients. *Cancer Chemother Pharmacol* 2012; 70: 513-522.
[11] Wible BA et al. (2005) HERG-Lite: A novel comprehensive high-throughput screen for drug-induced hERG risk. *Journal of Pharmacological and Toxicological Methods* 2005; 52: 136 - 145.

Metabolites of panobinostat were also tested, where it was found that BJB432[12] (519-07 or M37.8) inhibited hERG currents (approximately 40% at 1 μM, approximately 63% at 3 μM; IC_{50} 1.6 μM; Study PCS-r0870294), while AFN835 (315-02) and M36.9 only had a weak effect on hERG (AFN835: 16% inhibition at 30 μM; M36.9: 19% at 100 μM and 39% at 300 μM), and M40.8 (541-08) (only tested at up to 4.5 μM due to low solubility) and M24.0 (at up to 300 μM) had negligible or no effects (StudiesPCS-r0870532 and PCS-r0970190). The hERG IC_{50} values were considerably higher than the clinical free fraction C_{max} (6.2 nM), suggesting low potential for QT prolongation in patients. For BJB432 the sponsor cited a clinical C_{max} of approximately 120 nM. There were no plasma protein binding data for any metabolite. A risk assessment of BJB432 on its potential for QT prolongation from the hERG data cannot be made.

When tested using the perfused rabbit heart model, panobinostat at ≥ 1 μM (Study PCS-r0618523) increased action potential duration (APD_{60}), while at 5 μM also caused early after depolarisation (EAD) and induced Torsade de Pointes (TdP) (Study PCS-r0350418). No effects were seen at 0.5 μM panobinostat (approximately 70 times the clinical unbound C_{max}), but when combined with varying concentrations of docetaxel (up to 6 μM given 30 minutes after panobinostat) there was a 21 to 31% decrease in APD_{60}, reduction in conduction velocity and incidence of ventricular fibrillation and inexcitability (Study PCS-lr0618524). Panobinostat at 1 μM when combined with nilotinib (panobinostat given 90 minutes after nilotinib) exhibited higher APD_{60} and TdP-like activity. Metabolite BJB432 also exhibited increases in APD_{60} at ≥ 3 μM, while TdP and EADs were apparent at ≥ 10 μM.

In vivo telemetry studies in dogs showed panobinostat mediated prolongation of QT intervals at 1 and 3 mg/kg, IV, relative to vehicle control treated animals (QT_{CVdW} by 2.5 to 6 and 12.6 to 16%, respectively); Study PCS-r0110024). Prolongation at the low dose was accompanied by decreases in hazard ratio (HR) (by 2.5 to 10%), while at the higher dose there were modest increases in HR (by 3.7 to 5.1%). At lower doses, slight QT prolongation (by < 7%) was noted at ≥ 0.2 mg/kg, IV. Orally administered panobinostat also caused slight QT prolongation (by 10.6%); although only one dose (1.5 mg/kg) was tested (Study PCS-r0680202–02). At this dose peak plasma levels of panobinostat were approximately 2.4 folds higher than the clinical unbound C_{max} (16.4 ng/mL compared with 6.2 ng/mL). No other changes to cardiovascular parameters were reported. The sponsor did not provide *in vivo* studies with BJB432 (M37.8), but it was detected in rat and dog plasma under *in vivo* conditions, albeit at very low concentrations in the latter species.

Pharmacokinetics

Panobinostat has relatively low water solubility (0.1 to 1%). For oral dosing it was administered as either the lactate salt dissolved in purified water or in hydroxypropylcellulose, and for IV administration it was given as an aqueous dextrose solution with or without lactic acid. Studies that used hydroxypropylcellulose solution as the diluent generally exhibited greater bioavailability and more pronounced toxicities. The sponsor attributed the lower exposures in some studies (that is rat 13 week repeat dose toxicity study; Study PCS-r0680019) on differences in the particle size of the batches of drug substance used compared to other studies. However, the diluent used in the PK and toxicity studies may also have affected bioavailability for some studies. Nonetheless, systemic exposure data were available for all pivotal toxicity studies.

[12] BJB432 A metabolite of panobinostat

Absorption

Absorption of panobinostat with the PO route was rapid in all species, with t_{max} reached within an hour of dosing. Comparison of plasma AUC values of total radioactivity after an IV and PO dose indicated that the fraction absorbed after a PO dose was low in rats (17%, dosing vehicle lactic acid) and moderate in rabbits (62%, vehicle hydroxyethylcellulose) and dogs (68%, vehicle lactic acid). Oral bioavailability was low in rabbits (2.4%) and moderate in dogs (approximately 33 to 52%). In rats oral bioavailability was variable but low (approximately 6 to 22%). Plasma clearance with IV dosing was very high in the rat (22 L/hour/kg), while rabbits and dogs was on par with hepatic blood flow (3.6 L/hour/kg and 3.3 L/hour/kg, respectively). High plasma clearance, shorter elimination half-life and low oral bioavailability suggested a role for extrahepatic metabolism in rats. On the other hand, a pivotal 26 week oral toxicity study in rats found evidence of accumulation, with AUC values for doses 10, 30 and 75 mg/kg increasing by an average of 14, 9.3 and 5 fold of AUC values compared to the first sampling day, but this effect was not seen in other rat studies. The metabolite BJB432 (M37.8) was monitored in rat and dog IV studies, where similar t_{max} values to parent compound (< 1 hour) suggested rapid metabolism of panobinostat. AUC values of BJB432 were proportional to doses and there were no differences between males and females, nor was there evidence of accumulation.

Distribution

Panobinostat showed moderate plasma protein binding in all tested species when tested at concentrations up to 100 µg/mL (Study DMPK-r0200414). Rank order of binding at 37°C was as follows: human (90%) > rat (79%) > dog (79%) > mouse (60%). At lower temperatures (4°C) binding was higher in mice (to 83%) and rats (to 89%), but only marginally increased in dogs (to 81%). Preliminary investigations found panobinostat was more stable at 4°C in mouse and rat plasma due to greater conversion of panobinostat into a carboxycylic acid metabolite at these temperatures. The fraction distributed to erythrocytes was highest in mouse (0.74), followed by dog (0.77), rat (0.68) and human (0.60). Tissue distribution of radiolabelled panobinostat in rats showed rapid and extensive distribution to tissues. Tissues with high tissue radioactivity included the uveal tract, colon wall, bile, liver, small intestine wall and oesophagus by the oral route (Study DMPK r0500724), and the kidney medulla, adrenals, thyroid and pituitary glands by the IV route (Study DMPK-r0101753). Low levels were detected in brain, eye and spinal cord. High levels noted in the uveal tract of pigmented rats indicated affinity for melanin. Radioactivity was mostly eliminated by 168 hours, with only trace levels detected in liver, kidneys and pituitary glands.

Metabolism

Extensive biotransformation of ^{14}C-panobinostat was noted in rat, rabbit, dog and humans. In humans the metabolic profile of panobinostat was considerably more complex with numerous (minor) metabolites formed and approximately 40 observed in plasma. Metabolism involved reduction, hydrolysis, conjugation (glucuronidation) and oxidation reactions. In human plasma unchanged panobinostat accounted for < 9% of total plasma exposure. Plasma metabolites common to all species (rat, rabbit, dog, human) were: M37.8 (BJB432): hydroxamic acid reduction product of panobinostat; M43.5 (AFN835): direct hydrolysis product of panobinostat; M40.8 1 carbon chain shortening product; M36.9: 2 carbon chain shortening product. None of these entities or the human species T24.0 and M44.6 exhibited inhibitory activity against HDACs.[10] Oxidation reactions are mediated by Cytochrome P450 (CYP 450) system enzymes with predominant involvement of CYP 3A4 and minor contributory roles by 2D6 and 2C19. UDP glucuronosyltransferase (UGT) enzymes also play a minor role in glucuronidation reactions mediated by isozymes UGT1A1, 1A3, 1A8 and 1A9. High levels of T24.0 (acyl glucuronide of M36.9, 17.3% of total plasma radioactivity) and T33a (carbamoyl glucuronide of panobinostat, 9.2% of total

plasma radioactivity) detected in humans were absent or at very low levels in rats and dogs.

Excretion

Mass balance studies found that irrespective of route (PO or IV) panobinostat and/or its metabolites were predominantly eliminated through the faecal route in rats (81 to 83% compared with 0.7 to 12% for urinary route), which was secondary to biliary excretion. In rabbit, dog and humans amount of radioactivity recovered from urine was higher than rats (28 to 41%, 33 to 34% and 40%, respectively) but the faecal route was still the predominant excretory pathway. Predominant metabolite species in excreta where M37.8 in rats (44.3%) and humans (21.1%), while M36.9 was the highest fraction in rabbits (30.3%) and dogs (44.8%).

Conclusion

Sufficient similarities between the pharmacokinetic profiles of animal species (rat, rabbit and dog) in toxicity testing and those discerned in patients allow these species to serve as adequate models of drug toxicity in humans. With regard to the discovery of numerous unique human metabolites in plasma, this was not considered to be a significant deficiency in view of the small proportion of individual metabolites and the ICH S9 guideline;**Error! Bookmark not defined.** recommending that extensive characterisation of metabolites unique to humans is not generally necessary for the product to be used in patients with advanced cancer.

Pharmacokinetic drug interactions

Oxidative metabolism of panobinostat by CYPs was attributed to CYP 3A4/5, with minor involvement of CYPs 2D6 and 2C19. Plasma panobinostat concentrations may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers.

Panobinostat weakly inhibited 3A4/5 (Range IC_{50} = 15 – 75 µM; K_i: 12 µM), while moderate inhibition of CYP 2D6 was seen under the studied conditions (IC_{50}: approximately 2 µM; K_i: 0.167 µM, approximately 24 times the clinical unbound C_{max} 21.6 ng/mL x 0.1 = 2.16 ng/mL or approximately 6.2 nM), suggesting potential for increasing exposures to CYP2D6 substrates (Study DMPK-r0201469). Panobinostat was not found to inhibit the activity of CYP1A2, 2C8, 2C9 or 2E1 or induce expression and/or the activities of CYPs 1A1/2, 2B6, 2C8/9, 2C19, 3A4/5 or UGT1A1 (Study DMPK-r0500725).

Panobinostat is a substrate of P-glycoprotein (P-gp), with an efflux ratio of 15 and a P_{appA-B} approximately 1 x 10^{-6} cm/s in the Caco-2 monolayer assay. The effective permeability of panobinostat (P_{eff}) was estimated to be approximately 5.8 x 10^{-6} cm/s (Study DMPK-r0500488). The study results suggest that plasma concentrations of panobinostat may be affected by P-gp inhibitors or inducers. The author of the P-gp study and the sponsor (in the Risk Management Plan (RMP)) argued that it was unlikely that P-gp would modulate the oral absorption of panobinostat for the following reasons:

1. high permeability based on the P_{eff} value
2. rapid absorption in animal species and humans and nearly complete absorption in dogs based on the comparison of radioactivity excretion in urine following an IV and oral dose
3. likely saturation of transporters at the clinical dose
4. physiochemical properties (polar, water soluble, low molecular weight)
5. different characteristics of Caco-2 cell monolayer (smaller tight junctions, homogeneous expression of P-gp) and human intestinal epithelium (heterogeneous expression of P-gp).

The nonclinical evaluator does not agree with the sponsor's interpretation. Firstly, the permeability of panobinostat in the Caco-2 cell monolayer was moderate compared to the values of model high permeability drugs (for example metoprolol, $P_{eff} > 10^{-5}$ cm/s at intestinal pH range;[13] and propranolol P_{appA-B} 80.8 x 10^{-5} cm/s in the same study for panobinostat (Study DMPK-r0500488)). Secondly, the oral absorption of panobinostat in rats, rabbits and dogs were low to moderate (17%, 62% and 68%, respectively) based on plasma radioactivity AUC values after an IV and oral dose. Thirdly, rapid absorption ($t_{max} \leq$ 1 hour) does not mean high (or near complete) oral absorption. Fourthly, the *in vitro* study in Caco-2 cell monolayers showed no saturation of P-gp at up to 130 μM (the highest text concentration). Therefore, potential interactions with P-gp inhibitors or inducers cannot be ruled out.

Panobinostat has no inhibitory activity against P-gp mediated efflux or induction of P-gp or multidrug resistance-associated protein (MRP) MRP2 expression. Nor did it inhibit breast cancer resistance protein (BCRP) activity. Uptake of panobinostat by hepatocytes occurred under *in vitro* conditions probably by passive diffusion since the uptake was not found to be mediated by transporters, OATPs, OATs or OCTs[14] and significant cellular uptake was observed at low temperature (4°C). Panobinostat caused modest inhibition of uptake transporters OAT3, OCT1 and OAT1B1 and weak inhibition of OCT3 and OATP1B3 (Studies DMPK-r01200559 and DMPK-r01200558) (Studies DMPK-r01200559 and DMPK-r01200558), but these effects are unlikely to be clinically significant as the lowest determined K_i was > 4 μM (compared with clinical unbound C_{max}). Circulating panobinostat levels are unlikely to approach these levels; even under conditions where the C_{max} of panobinostat may increase (the PI refers to clinical evidence of a 1.6 fold increase in the C_{max} following co-administration of strong inhibitors of CYPs 3A4/5).

Toxicology

Acute toxicity

Acute toxicity of panobinostat was examined in mice (Study PCS-r0270147) and rats (Study PCS-r0270147) using the IV route. Mortalities occurred in both species, with a maximum non-lethal dose of 50 mg/kg in mice and 10 mg/kg in rats. Clinical signs indicated a central effect (tremors, sedation, unconscious, decreased locomotor activity, ptosis). Most of the rodents found dead had no notable lesions that could be directly ascribed as cause of death. Overall, panobinostat exhibited a moderate to high order of acute toxicity when tested by the IV route in rodents. These studies did not use the clinical (PO) route; however extent of acute oral toxicity is readily discerned from Repeat dose toxicity study findings, as discussed below.

Repeat dose toxicity

The sponsor submitted 16 repeat dose toxicity studies that were up to 6 months in rats and 9 months in dogs. Studies used both the clinical (PO) and IV routes and all pivotal studies were GLP-compliant. Consistent with ICH S9;**Error! Bookmark not defined.** duration of pivotal studies (that is ≥ 3 months) were sufficient to support a product intended for patients with advanced disease. For most studies, dosing paralleled the proposed clinical dosing regimen (3 times a week on a Monday, Wednesday and Friday schedule). Choice of species used is acceptable, particularly in view of similarities of the plasma exposures of

[13] Ozawa M et al (2015) Intestinal permeability study of minoxidil: assessment minoxidil as a high permeability reference drug for biopharmaceutics classification. *Mol. Pharmaceutics* 2015; 12: 204-211
[14] OATPs : Organic anion transporting polypeptide; OAT: Organic anion transporter OCTs: organic cations transporters

dogs and humans. A high number of metabolites were unique to humans and could not be fully characterised in toxicity tests; however as in view of the proposed use, the low levels of these metabolites and recommendations outlined in ICH S9, extensive characterisation of these metabolites is not essential.

Relative exposure

Relative exposures have been calculated based on animal: human AUC_{0-24h} ratios. Human reference values were based on summary data obtained from clinical Studies CLBH589-B1101, B2101 and B2102 (from Clinical Pharmacology Summary), in which repeat dosing (3 doses/week for 4 weeks) was conducted in advanced cancer patients. Because of the moderate to high toxicity of panobinostat, relative exposures were very low (see below). None of the oral pivotal studies achieved a no observed adverse effect level (NOAEL). The exposure ratios for pivotal IV studies are not tabulated because the toxicity profile by the IV route was not different from that by the PO route, the weekly dosing schedule in the pivotal IV studies was different from the clinical dosing regimen, and the exposures in the IV studies were lower than those in the PO studies.

Table 3: Relative exposure in pivotal Repeat dose toxicity studies based on plasma exposure (AUC) ratios

Species	Study duration	Dose (mg/kg) 3 doses per week	C_{max} (ng/mL)	AUC0–t (ng·h/mL)	Exposure ratio*
Rat (SD)	4 weeks (PO) (PCS-r0370121-01) Diluent: purified water	3	1.17	2.9	0.01
		10	7.3	23.2	0.1
		30	70	188	0.9
	13 weeks (PO)† (PCS-r0680019) Diluent: hydroxypropyl cellulose	10	3	12.2	0.06
		30	21	87	0.4
		100	145	441	2.2
	26 weeks (PO) (PCS-r0680134) Diluent: hydroxypropyl cellulose	10	28	78	0.4
		30	131	290	1.5
		75	204	609	3.1
Dog (Beagle)	4 weeks (PO) (PCS-r0370122-01) Diluent: purified water	0.15	3.69/23.7§	11.6	0.06
		0.5	9.32/26.4	39	0.2
		1.5	51.5/52.7	137	0.7
	13 weeks (PO) (PCS-r0680020-01) Diluent: sterile water	0.15	3	15	0.07
		0.5	15	58	0.3
		1.5 (1.0)^	23	83	0.4
	39 weeks (PO)	0.15	3	15	0.07

Species	Study duration	Dose (mg/kg) 3 doses per week	C_{max} (ng/mL)	AUC0–t (ng·h/mL)	Exposure ratio*
	(PCS-r0680133) Diluent: sterile water	0.5	14	61	0.3
		1	20	82	0.4
Human (advanced stage patients)	steady state (Day 15) (CLBH589-B1101, B2101 and B2102)	20 mg (PO)	21.6	199	–

* = animal:human plasma AUC_{0-t} (199 ng·h/mL); ^ dose reduced from week 7 because of effects on body weight and food consumption; # evidence of accumulation noted in this study; †Used data from sampling Day 26 because of significantly lower values on Day 75; §Male/Female values.

Major toxicities

Primary target of panobinostat toxicity was the haematopoietic system. Significant changes to haematological parameters and haematopoiesis were consistently noted in toxicity studies irrespective of animal species, route of administration and duration of treatment. Other affected organ systems included the thyroid gland, gastrointestinal tract, thymus and lymphoid tissues. Rapidly emergent adverse effects (for example tremors, decreased locomotor activity, convulsions and unconsciousness) were noted at higher doses or when the IV route was used and suggested dose dependent neurotoxicity, an effect also corroborated by CNS safety pharmacology studies (in mice). Severity depended on extent of exposure. Specific toxicities are further discussed as follows below.

The haematopoietic system

Adverse effects on haematological parameters were consistently seen in both rats and dogs. These included reductions in total and differential white blood cell (WBC) counts, platelets and red blood cell (RBC), haemoglobin (Hb) and/or haematocrit (Hct), and gross and histological changes of the haematopoietic system such as the spleen, thymus and bone marrow. The effect of panobinostat on haematopoiesis is directly related to its intended pharmacological action since a number of transcription factors involved in haematopoiesis are dependent on HDAC-mediated deacetylation (for example HDACi mediated thrombocytopenia).[15]

Decreases in total WBC and differential leukocyte counts (lymphocytes, eosinophils, basophils and neutrophils), were noted in the rat and dog, irrespective of route of administration. Interval testing (for example weeks 4, 7, 13 in the 13 week dog PO study) of blood parameters showed most decreases occurred from the first sampling period, and remained low until treatment ceased. Erythrocyte parameters (RBC, Hb and Hct) were also reduced in both species irrespective of route. These changes often coincided with mild increases in reticulocyte numbers, regarded as a regenerative mechanism for restoring to normal erythrocyte and haemoglobin levels. Platelet counts were reduced in the rat, whereas in the dog platelet levels were either unaffected or higher with panobinostat treatment. The effects on RBC and platelets were less severe than on WBC. Haematological changes corresponded to bone smear and histological findings where there was evidence of treatment dependent myelosuppression (bone marrow aplasia, granulocytic hypoplasia, shifts in the proportion of erythroid and myeloid progenitor cells, marrow atrophy). Severe myelosuppression likely precipitated the congestion and haemorrhaging of

[15] Matsuoka H et al., 2007 Mechanisms of HDAC inhibitor-induced thrombocytopenia. *European Journal of Pharmacology* 2007; 571: 88-96

numerous organs reported in the dose range finding studies. Dose dependent atrophy was noted in the thymus. Lymphoid atrophy, depletion or necrosis was a recurrent observation in the spleen, thymus, Peyer's patch and lymph nodes.

Lower leukocyte counts brought on by panobinostat were severe enough to consider the likelihood of compromised host-defence mechanisms in the treated animals. Indeed pneumonia was noted in the 39 week and 13 week oral dog studies, indicating that treatment may increase vulnerability to infections. Prolongation of activated partial thromboplastin time (aPTT) was often seen at the high dose level in a number of the dog studies. The changes were discounted as biologically inconsequential because not all treated animals showed this effect; however as this was seen in male and female treated animals, occurred from week 4 onwards and was reversible once treatment ceased, the effect of aPTT is highly likely to be treatment related. Many of the blood cell effects were found to be reversible. Recovery was not always a complete restoration to control levels, but this may reflect a slower onset of recovery than the 4 week recovery period allowed. It is noted that for one dog oral study decreased bone marrow cellularity was still evident in high dose recovery animals; however blood cell counts had recovered to be comparable to control group levels, denoting recovery of haematopoietic processes.

Thyroid gland

Changes to the thyroid were reported in a number of the studies; however extent of these changes varied. In the 26 week rat oral study (Study PCS-r0680134), whilst there was a clear treatment dependent increase in the incidences of thyroid follicular cell hypertrophy in both males and females, as well as a single occurrence of follicular cell adenoma in a high dose male, there were no changes in thyroid weight and changes in serum thyroid hormones were inconsistent (triiodothryronine (T3) decreased in mid and high dose females and only slightly lower in high dose males, thyroxine (T4) tended to be lower in high dose males and thyroid stimulating hormone (TSH) unchanged). Follicular cell vacuolation was also noted in the 4 week study at ≥ 10 mg/kg (Study PCS-r0370121-01). On the other hand a rat 13 week IV study (Study PCS-r0670757-01) showed treatment dependent increases in T4 and decreases in TSH levels in mid and high dose females and increases in T3 levels in all treated male groups (no clear dose-response relationship), but these were not associated with any gross or microscopic changes. Nor were histological thyroid lesions observed in the 13 week oral study in rats (Study PCS-r0680019), although serum T4 levels were increased in high dose males. In the dog, the 9 month oral study(Study PCS-r0680133) showed lower thyroid weights in treated males but there were no other thyroid changes (including changes to T3, T4 and TSH), while the 13 week oral study (Study PCS-r0680020-01) showed significant decreases in T3 levels in the high dose group that persisted in recovery animals. On the other hand the 13 week IV study revealed microscopic changes (follicular cell hypertrophy and decreased colloid) but changes to thyroid hormones (T4 levels in mid- and high dose males and females) were transient (at week 5 only). Thyroid effects were not reported in animal studies with two other HDAC inhibitors, vorinostat and romidepsin. A four week study in rats compared panobinostat to an agent (propylthiourea (PTU)) known to bring on genetic and morphological changes to the thyroid (Study PCS-r0770979). Repeat dosing of panobinostat (75 mg/kg, PO; 3 doses/week up to 4 weeks) did not evoke notable histological changes or changes to thyroid hormone levels compared with PTU. There were also transcriptional differences between the two agents. PTU induced expression of the Na+/I- symporter, as well as genes associated with mitosis and proliferation, angiogenesis and remodelling, while panobinostat affected genes related to HDAC and chromatin-dependent pathways, as well as genes related to downstream processes (oxidative stress, cell cycle arrest and apoptosis). In spite of these variable changes, an effect on thyroid

function is anticipated based on evidence that ligand-bound thyroid hormone receptor relies on recruitment of HDACs to signal negative feedback regulation of thyroid function.[16]

Gastrointestinal tract

The GI tract was a notable target of toxicity in dogs, particularly when the oral route was used. Gross pathology examinations noted treatment dependent reddening of parts of the GIT. There were also instances of abnormal faeces (soft or liquid faeces, diarrhoea) and emesis observed in high dose animals from a number of dog studies. Five day consecutive dosing also had a notable effect on the GI epithelium with effects extending from the stomach (necrosis of glands and mucosal congestion), duodenum (necrosis of crypt epithelium), ileum (mucosal haemorrhage and mixed cell mucosal inflammation), colon (depletion of goblet cells and lymphoid tissue necrosis) and rectum (goblet cell depletion). These effects were also reported in a 4 week oral dog study, and were generally absent in recovery groups indicating that GI effects were reversible. While direct contact mediated irritation through oral dosing might be a plausible cause for GIT toxicities, a 4 day rising dose IV study in dogs (Study PCS-r0170106) also reported adverse GIT findings (mucosal congestion, atrophy of villi, crypt necrosis). Due to a key role of HDACs (in particular, HDACs 2 and 3) in crypt cell proliferation and maturation, degenerative effects on the intestinal tract are expected adverse effects of HDAC inhibitors.

Male reproductive system

Oligospermia in epididymis was a recurrent observation in males from both rat and dog studies. Frequency of observations however was higher in dogs. While the study authors of the 13 week oral study attributed epididymal oligospermia and presence of debris in the epididymis to the young age of animals used in this study (approximately 4 to 5 months old), similar observations were made in older dogs used in other toxicity studies (approximately 9 to 11 months old). Attenuation of the prostatic epithelium and reduced secretory granules and testicular seminiferous tubule degeneration were reported in high dose dogs in the 4 week oral study, and oligospermia and testicular seminiferous tubule degeneration were noted in a dog from the recovery group. Testicular epithelial degeneration was also noted in all high dose animals (1.2 mg/kg/week) in the 13 week IV study (weekly AUC 220 ng.h/ml compared with clinical weekly AUC 597 ng.h/mL).

Other toxicities

Hyperostosis of the femur was noted in the 13 week PO study in rats at 100 mg/kg. Treated rats in this study also exhibited elevated serum calcium and phosphate levels, which suggest a panobinostat mediated interference on bone metabolism. However, no other aberrant effects on bone metabolism were noted in other rat toxicity studies nor in dogs and the sponsor surmised that these effects might be rodent and age specific. Given that HDACs are intricately involved in chondrocyte and osteoblast maturation and terminal differentiation;[17] an abnormal effect on bone metabolism is not unexpected. Focal osseous metaplasia (differentiation of fibroblasts into osteoblasts) noted in the 39 week oral toxicity study in the lungs of two high dose dogs could also reflect aberrant bone signalling and differentiation.

Serum chemistry analyses also highlighted notable findings. Oral rat studies showed elevated total bilirubin levels. A similar effect which was surmised to be related to increased intravascular red blood cell destruction. Observed increases in pigmentation and presence of haemosiderin in spleens of panobinostat treated rats and the lack of evidence of liver toxicity (no increases in serum ALP, alanine aminotransferase (ALT) or AST and no

[16] Sasaki et al., 1999 Ligand-induced recruitment of a histone deacetylase in the negative-feedback regulation of the thyrotropin β gene. The EMBO Journal 1999; 18: 5389-5398
[17] Bradley E W et al., 2011 HDAC-mediated control of endochondral and intramembranous ossification. *Crit Rev Eukaryot Gene Expr*, 2011; 21: 101-113

histological hepatic lesions) would support this assertion. Some studies showed clear treatment dependent and reversible reductions in ALT and ALP activities by panobinostat, which are of uncertain toxicological significance. Treatment dependent decreases in serum potassium were also observed in rats, while in dogs there was a slight increase. In the 13 week study this effect was not completely reversed by the end of the 4 week recovery period, although this could again reflect a longer lag time to recovery. The low serum potassium levels correlated with low platelet counts. Low platelet counts were associated with decreased plasma potassium levels in rats while in dogs higher platelet counts were associated with increased potassium. It is worth noting that hypokalaemia (as well as thrombocytopaenia) are very common adverse effects in patients.

Genotoxicity

Genotoxicity was assessed in a number of *in vitro* assays concerning mutagenicity (Ames bacterial reverse mutation assay), clastogenicity (chromosomal aberration assay in human lymphocytes) and DNA damage (comet assay in mouse lymphoma cells). Studies were consistent with ICH guidelines S2(R1) and ICH S9.**Error! Bookmark not defined.**,[18] Assays were appropriately validated and panobinostat was tested to its limits of solubility and cytotoxicity.

In silico analysis (DEREK Ver. 4.0.1) did not identify structural alerts for mutagenicity.[19] However *in vitro* investigations found panobinostat caused dose dependent increases in mutations in Ames assays, with higher numbers of revertants for strains TA1535 and TA97a (with or without metabolic activation). Panobinostat also caused concentration-dependent cytotoxicity and DNA damage in mouse lymphoma cells in a comet assay. Whilst panobinostat was not found to be clastogenic in human lymphocytes, there was a higher frequency of endoreduplication at all concentrations tested (≥ 0.04 μg/mL, or 0.11 μM) with or without metabolic activation. Endoduplication is associated with modulation of mitotic activity;[20] and may reflect pharmacologically mediated cell cycle arrest by panobinostat.[21]

Thus, under *in vitro* conditions panobinostat was mutagenic in bacterial strains, induced DNA damage in mammalian cells and showed higher frequency of endoreduplication in human lymphocytes. Therefore panobinostat is considered to be genotoxic. Genotoxicity was also demonstrated for vorinostat. Consistent with ICH guideline (S1A) no carcinogenicity studies were conducted nor are they required; however on the basis of genotoxicity findings, carcinogenic potential is likely.[22]

Reproductive toxicity

Reproductive toxicity studies were conducted in rats and rabbits and encompassed most stages of development (fertility and embryofetal development). Pre-/postnatal development was not assessed which is acceptable under ICH S9.**Error! Bookmark not defined.** Study designs were satisfactory with regard to group sizes, route of administration, timing and duration of treatment, as per the relevant Note for Guidance on reproductive toxicity.[23] Dosing used in the embryofetal development studies attained moderate levels of

[18] ICH guidelines S2(R1) Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.
[19] DEREK Ver. 4.0.1 an expert software system for prediction of toxicity.
[20] Chang B-D et al., 2000 p21Waf1/Cip1/Sdi1-induced growth arrest is associated with depletion of mitosis-control proteins and leads to abnormal mitosis and endoreduplication in recovering cells. Oncogene 2000; 19: 2165-2170
[21] Bolden J E et al., 2006 Anticancer activities of histone deacetylase inhibitors. Nature Reviews Drug Discovery 2006; 5: 769-784
[22] ICH guideline (S1A) Guideline on the need for carcinogenicity studies of pharmaceuticals
[23] ICH S5R2 Detection of toxicity to reproduction for medicinal products and toxicity to male fertility

exposure to panobinostat (up to 6 fold and 8 fold the clinical AUC for rats and rabbits, respectively; see below). Because fertility studies did not include toxicokinetic measurements, AUC values from Day 26 of the 13 week repeat dose study that used the same doses (Study PCS-r0680019) are used for comparison with the clinical value.

Table 4: Relative exposure in reproductive toxicity studies based on plasma levels (AUC_{0-t})

Species	Study	Dose (mg/kg/day; PO)	AUC0–t (ng•h/mL)†	Exposure ratio
Rat (SD)	Fertility PCS-r670511	10	12.6/11.8*	0.06/0.06
		30	72.1/102*	0.4/0.5
		100	1180/763*	6/4
Rat (SD)	Embryofetal development PCS-r670511	30	289	3#
		100	816	8#
		300	nd	–
Rabbit (NZW)	Embryofetal development PCS-r0670512	10	49.6	0.5#
		40	305	3#
		80	585	6#
Human (patients)	steady state (Day 15)	20 mg	199	–

† animals AUC_{0-24h}, human AUC_{0-48h}; # = animal (AUC_{0-24h} x 2):human plasma AUC_{0-48h} ; * AUC values on Day 26 in the 13 week repeat dose toxicity study (PCS-r0680019); nd = not determined due to early terminations

Whilst panobinostat was found to readily cross the placenta in rats, transfer of panobinostat and/or its metabolites in milk was not investigated by the sponsor.

In the rat fertility and early embryofetal development study (dosing every other day, 3 doses per week), both sexes at ≥ 30 mg/kg exhibited decreases in body weight gain and food consumption indicating general toxicity. Adverse effects on male fertility were not immediately evident with sperm counts and motility from treated males being comparable to those from the vehicle treated group. However, males at ≥ 30 mg/kg had significantly lower cauda epididymis weights, suggesting potential effects on male fertility. Oligospermia in epididymis in both rats and dogs and, prostate atrophy and reduced secretory granules, testicular epithelial degeneration and increased epididymal debris in dogs were observed in repeat dose toxicity studies (discussed above). Panobinostat caused a treatment dependent decrease in fertility index (number of pregnancies/number of females placed for mating) at 100 mg/kg. There were higher resorptions/post-implantation losses at ≥ 30 mg/kg, which accounted for the significantly lower number of live embryos in these groups and indicated embryotoxicity. The NOAEL for fertility and early embryofetal development was 10 mg/kg (< 1/10th the clinical exposure based on AUC).

In the rat embryofetal development study there was profound maternal and embryofetal toxicity in all treated groups at daily doses of 30, 100 and 300 mg/kg (Study PCS-

r0670511). There were high mortalities and/or unscheduled sacrifices in the mid- and high groups such that incidences of fetal variations and malformations could not be determined in these groups. Maternal clinical signs and necropsy findings were consistent with signs of general systemic toxicity (decreased activity, weakness, body weight loss and decreased food consumption). Litter findings showed high numbers of early resorptions in all treated groups, which corresponded to either high or complete losses of litters. In the low dose group there were significantly higher instances of skeletal anomalies (extra pre-sacral vertebrae, extra 14th rib and incomplete ossification of sternebrae) and decreased fetal weights, suggesting adverse developmental effects across all tested dose levels. Based on these findings a NOAEL for embryofetal toxicity was not established.

In rabbits (Study PCS-r0670512) at a dose range of 10, 40 and 80 mg/kg/day, maternal toxicity was observed at the high dose (mortalities, reduced food consumption, decreased faecal output, tremors and weakness). Litter parameters showed high post–implantation loss in the high dose group, although the increase was not statistically significant. Statistically significant decreases in mean fetal weights were noted at 40 and 80 mg/kg/day. Examination of fetuses found a number of malformations at 80 mg/kg/day (interventricular septal defect and interrupted aortic arch in one fetus; interrupted aortic arch and missing forepaw digit in another fetus from a different dam), which, although were of a low incidence (n = 1 to 2 fetuses), were absent in all other treatment groups and thus cannot be entirely excluded as a treatment related effect. More compelling and consistent were the significantly higher incidences of skeletal anomalies (incomplete ossification of hyoid, pubic and interparietal bones) in the mid (hyoid bone only) and high dose group. Higher incidences of extra sternabrae were also noted in the high dose group. The sponsor considered these skeletal effects to be secondary to the lower fetal weights noted at these dose levels, which is plausible and suggests general fetotoxicity of panobinostat.

Overall, panobinostat had a detrimental effect on rat fertility, exhibited embryotoxicity (as noted by the higher post–implantation losses) and caused impairments to skeletal developments; an effect that might be both a direct pharmacological action and secondary to generalised fetotoxicity and maternotoxicity. Malformations in a few rabbit fetuses might also be related to panobinostat treatment.

Pregnancy classification

The sponsor proposed Pregnancy Category D for panobinostat;[24] which is considered appropriate in view of embryotoxicity and skeletal abnormalities noted in two different animal species following maternal exposure to panobinostat. It is also consistent with the pregnancy classification for vorinostat.

Local tolerance and immunotoxicity

Single dose panobinostat administration via the intravenous, intra-arterial and perivenous routes caused slight local irritation in rabbits (Study PCS-r0770115). Perivenous administration caused mild erythema and inflammation that resolved at 15 days post-dose.

Sensitising potential of panobinostat was evaluated using a modified mouse local lymph node assay (Study PCS-r0670352). The studies indicated that panobinostat is a skin irritant and skin sensitiser at 0.1 to 1% based on increased ear weight and thickness, and local draining lymph node weight and lymph node cell counts after topical administration

[24] Pregnancy Category D is Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

to the ear. The threshold concentration for skin irritation and sensitisation was estimated to be 0.03% and 0.1%, respectively. Higher concentrations (≥ 5%) caused systemic toxicity (decreased body weight and decreased local lymph node weights and cell counts).

Repeat dose toxicity studies also corroborated panobinostat's high contact mediated irritation potential. Higher incidences of local irritation (reddening, scabbing and discolouration) were seen in both rats and dogs dosed via the IV route. The effects on GI tract (reddening of colon, intestine and mesenteric lymph node, emesis and watery/soft faeces) in dogs could also be partly attributable to local irritation.

In view of the prominent myelosuppression (and anticipated immunosuppression) by panobinostat, the sponsor did not conduct specialised studies on immunotoxicity, which is acceptable and consistent with guideline recommendation (ICH S9).**Error! Bookmark not defined.**

Paediatric use

Panobinostat has not been proposed for paediatric use and no specific studies using juvenile animals were submitted.

Nonclinical summary and conclusions

- The nonclinical module was of satisfactory quality and all pivotal safety related studies were GLP compliant.
- Panobinostat is a histone deacetylase (HDAC) inhibitor, with activity against all HDAC isoforms (HDAC 1, 2, 3, 5, 6, 9, 10 and 11 IC_{50}: 2.1 to 13.2 nM; HDAC 4, 7 and 8 IC_{50} ranges 203 to 531 nM). Panobinostat induced acetylation of substrate proteins (histones, hsp90 and tubulin) was associated with increased p21 expression/activity. Panobinostat treatment also resulted in higher levels of markers for apoptosis (caspases, Annexin V) in a range of cancer cell lines, including multiple myeloma cell lines.
- Panobinostat was cytostatic and cytotoxic against multiple myeloma cell lines and cells from multiple myeloma patients. Cancer cells were more sensitive to panobinostat than normal cells. In a mouse multiple myeloma xenograft model, the combination of panobinostat with bortezomib and dexamethasone resulted in greater reductions in tumour burden and improved survival rates. As well, panobinostat dose dependently improved bone density. Frequent dosing in tumour-presenting mice resulted in more effective tumour regression than less frequent dosing. Higher dosing was limited by tolerability.
- Secondary effects on unrelated receptor targets were not assessed. Both panobinostat and metabolite BJB432 inhibited hERG at concentrations (IC_{50} 3.5 and 1.6 μM, respectively) above the C_{max} for unbound drug (approximately 6.2 nM). Panobinostat increased action potential duration, induced TdP and early after depolarisations in isolated perfused rabbit hearts, and caused QT prolongation in dogs by both the clinical (oral) and IV routes. IV administration caused CNS toxicity.
- Rapid oral absorption was demonstrated in all species. Panobinostat exhibited moderate plasma protein binding (human (90%), rat (79%), dog (79%), mouse (60%)) and in rats showed wide distribution in tissues (high levels in kidney medulla, adrenals, thyroid; low or trace levels in brain, eye and spinal cord). Extensive metabolism involved reduction, hydrolysis, glucuronidation and oxidation reactions. Numerous (mostly minor) metabolites identified in human plasma were not present in other species. Plasma metabolites common to all species were M37.8 (BJB432), M43.5, M40.8 and M36.9.

- Oxidative metabolism of panobinostat is mainly by CYP3A4/5, with minor involvement of 2D6 and 2C19. Panobinostat exhibited inhibitory activity against CYP2D6 (K_i 0.167 μM) and uptake transporters OAT3, OCT1 and OAT1B1 (K_i > 4 μM). Panobinostat is a substrate of P-glycoprotein transporter (P-gp.) Excretion of panobinostat is predominantly through the faecal route for all species. Significant biliary excretion was demonstrated in rats.
- Panobinostat exhibited a moderate to high order of acute toxicity in rodents when tested by the IV route. Clinical signs suggested a centrally-mediated cause (tremors, ataxia, sedation and decreased locomotor activity) of death. Acute toxicities were less frequent in repeat dose studies using the clinical (PO) route. However, acute maternotoxicity in rat oral embryofetal development studies suggests a moderate order of acute toxicity via this route too.
- Repeat dose toxicity studies were conducted in rats (up to 26 weeks) and dogs (up to 9 months) using both the PO and IV routes. Because of the moderate toxicity of panobinostat, relative exposures were low (up to 3 x clinical AUC in rats and 0.7 x clinical AUC in dogs by the oral route) and none of the pivotal toxicity studies achieved a NOAEL.
- Significant toxicities were noted for both species and routes. Target organs/systems were:
  - the haematopoietic system (myelosuppression, leukopenia, anaemia, thrombocytopenia in rats, lymphoid atrophy, altered bone marrow cellularity);
  - gastrointestinal tract (mucosal haemorrhage, goblet cell depletion);
  - thyroid (follicular cell hypertrophy, decreased colloid, altered hormone levels);
  - the reproductive system (oligospermia, testicular degeneration).

  Decreased body weights and food consumption were also common to all species. In rats changes in serum potassium were associated with treatment, while slight prolongation of aPTT was common in dogs. Partial recovery of tested parameters indicated that toxicities may be reversible.
- Panobinostat was mutagenic in the Ames test, induced DNA damage in mammalian cells in the COMET assay. Panobinostat was not found to be clastogenic in human lymphocytes, but it caused an increase in endoreduplication, which was likely due to pharmacologically-mediated cell cycle arrest. Carcinogenic potential was not assessed.
- Panobinostat readily crosses the placenta. Male and female rat fertility was adversely affected by panobinostat, with a NOAEL of 10 mg/kg/day (0.06 fold the clinical AUC). Teratogenicity was demonstrated in rabbits. Maternotoxicity was noted in pregnant rats and rabbits at doses that were 8 and 3 fold the clinical AUC, respectively, while higher resorptions and post-implantation losses occurred at doses that were 3 fold the clinical AUC. At these doses incomplete ossification and incidences of extra sternebrae or ribs were noted in fetuses from both species. Interventricular septal defects, interrupted aortic arches and missing forepaw digit were seen in rabbit fetuses.
- Panobinostat evoked tolerance reactions when administered via the perivenous route and also brought on contact mediated/dermal irritation and sensitisation. Panobinostat did not have phototoxic potential.

Conclusions and recommendation

- An adequate module data package for panobinostat has been presented for review. However, there are no studies investigating the potential toxicological interactions for panobinostat and the co-administered drugs, bortezomib and dexamethasone.

- Primary pharmacology studies provided *in vitro* proof of inhibition of HDACs by panobinostat with downstream anti-tumour effects demonstrated under both *in vitro* and *in vivo* conditions.
- Safety pharmacology studies indicated pro-arrhythmogenic effects of panobinostat, as evidenced by hERG channel inhibition, action potential prolongation in isolated perfused hearts and QT interval prolongation under *in vivo* conditions. CNS effects in patients may also be possible if the systemic exposure is high.
- Primary target of panobinostat toxicity was the haematopoietic system, the gastrointestinal tract, bone, thyroid gland and the (male) reproductive system. Toxicities showed signs of recovery when panobinostat treatment was withdrawn.
- Panobinostat was mutagenic in an Ames test, caused DNA damage in mouse lymphocytes and endoreduplication in human lymphocytes. Carcinogenicity was not tested.
- Panobinostat adversely affected male and female fertility, was embryotoxic, teratogenic and caused skeletal abnormalities. In view of its teratogenic effects, the proposed pregnancy category of D is considered appropriate.
- There are no nonclinical objections to the registration of panobinostat provided the safety of the panobinostat in combination with bortezomib and dexamethasone has been demonstrated in clinical studies and appropriate risk mitigation strategies are adopted to minimise the severity of expected adverse effects.

The nonclinical evaluator also made comment regarding the draft PI and Risk Management Plan (RMP) but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The submission included a local (Australian) expert statement outlining the management of high risk patients with multiple myeloma (MM) who have not benefited from treatment with currently available agents. The local expert notes that, 'collectively', for high risk patients (representing approximately 25% of patients with MM) the median survival is ≤ 2 years. Therefore, the local expert considers that there is a 'very clear unmet need for alternative classes of anti-MM therapeutics that may potentially improve the outcome for high risk MM patients who have not benefited from the novel agents and build upon the benefit that non-high risk patients have achieved with novel agents and where applicable (autologous stem cell transplantation)'.

Clinical rationale

There are no HDACi anticancer agents currently on the Australian Register of Therapeutic Goods (ARTG) for the treatment of MM. However, there are two histone deacetylase (HDAC) inhibitors currently on the ARTG for the treatment of other haematologic malignancies (romidepsin and vorinostat). Romidepsin (Isotodax) is approved for the treatment of peripheral T cell lymphoma in patients who have received at least one prior systemic therapy. Vorinostat (Zolina) is approved for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease subsequent to prior systemic therapies.

Contents of the clinical dossier

The submission included comprehensive clinical pharmacology and clinical efficacy and safety data provided to support registration of panobinostat in combination with bortezomib and dexamethasone for the proposed indication. The submission was presented in Common Technical Document (eCTD) format. It included a 'Notes to Reviewers', dated 3 November 2014, provided as an annex to the Application Letter to facilitate the review of the eCTD. The clinical evaluation report (CER) is based on the data provided on the CD.

The submission contained the following clinical information:

- 12 clinical pharmacology studies including pharmacokinetic and/or pharmacodynamic data.
- 1 population pharmacokinetic study.
- 1 population pharmacokinetic/pharmacodynamic study (exposure/platelet count).
- 1 pivotal Phase III efficacy and safety study.
- 2 supportive, uncontrolled, single arm Phase Ib and Phase II clinical efficacy and safety studies.
- 6 other Phase II clinical efficacy and safety studies assessing various panobinostat dosing regimens for various solid tumour and haematological malignancy indications.
- 4 reports detailing the analytical methods used to measure panobinostat and its metabolites in human plasma and bortezomib in human plasma.
- 14 reports involving human biomaterials aimed at the in vitro identification of enzymes relevant to the hepatic metabolism of panobinostat and protein transporters relevant to potential drug-drug interactions.
- Literature references.

The submission also contained: A clinical overview, summary of biopharmaceutic studies and associated analytical methods, summary of clinical pharmacology studies, summary of clinical efficacy in MM, summary of clinical safety in MM, and literature references.

Paediatric data

No paediatric data were included in the submission. The sponsor indicates that it has not submitted paediatric data in the EU or the USA for patients aged < 17 years. The sponsor indicates that it does not have an agreed Paediatric Investigation Plan (PIP) in Europe. The requirement to submit a PIP in Europe was waived because panobinostat is intended to treat multiple myeloma, a condition that occurs only in adults and is included in the 'class waiver' list. The sponsor indicates that it does not have an agreed Paediatric Plan under the Paediatric Research Equity Act (PREA) in the USA. Under USA legislation, the sponsor is exempt from assessing the efficacy and safety of panobinostat in a paediatric population as the FDA has designated it to be an orphan drug for the treatment of MM.

The absence of paediatric and adolescent efficacy and safety data for panobinostat in the regulatory dossier submitted to the TGA is acceptable, given the proposed indication.

Good clinical practice

The dossier indicated that all studies sponsored by the sponsor complied with the principles of Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Overview

- All pharmacokinetic (PK) data relating to panobinostat were based on patients with advanced cancer. There were no PK data for panobinostat in healthy subjects due to genotoxicity being observed with the drug in nonclinical assays.
- The PK of panobinostat as a single agent have been assessed in 17 Phase I/II clinical studies in approximately 650 patients with solid tumour or haematological malignancies. These 17 studies included, fifteen Phase I/II clinical trials assessing the oral (PO) PK of panobinostat and two Phase I/II clinical studies assessing the intravenous (IV) PK of panobinostat. The main focus in the submission was on the PK data from the 15 PO studies, while the 2 IV studies were primarily included for estimation of absolute bioavailability.
- Characterisation of the PK of single agent panobinostat was primarily based on a pooled PK analysis and a population PK (PPK) analysis. The pooled PK analysis included data from 14 studies, comprising 12 studies with PO administration (Studies B1101, B2101, B2102, B2201, B2202, B2203, B2211, B2109, B2110, B2111, X2101 and X2105) and two studies with IV administration (Studies A2101 and A2102). The PPK analysis was also based on data from 14 studies, including all studies in the pooled PK analysis apart from Studies X2101 and X2105 (that is, the hepatic and renal impairment studies), and 2 studies not included in the pooled analysis (that is, Study E2214, a Phase II study in Hodgkin's lymphoma, and Study B1201, a small study in 4 Japanese subjects with T-cell lymphoma).
- The PK of panobinostat (PAN) in combination with bortezomib (BTZ), with and without dexamethasone (Dex), were investigated in Study B2207, a Phase Ib study in patients with MM, and in Study D2308, a Phase III, placebo controlled study in patients with relapsed or relapsed and refractory MM (that is, the pivotal efficacy and safety study).
- The submission included 14 in vitro human biomaterial studies assessing hepatic pathways relating to the metabolism of panobinostat, and transporter proteins relevant to potential drug-drug interactions (DDI) with the drug. The evaluation of these studies is a matter for the nonclinical evaluator. However, relevant information from these in vitro studies relating to the clinical use of panobinostat has been provided in this CER. The human biomaterial studies were provided.
- The submission included reports detailing the analytical methods used to estimate the concentration of panobinostat in human plasma and urine, the concentration of one of the metabolites of panobinostat in human plasma (BJB432), and the concentration of bortezomib in human plasma. The evaluation of the analytical reports is a matter for the pharmaceutical chemistry evaluator, but clinically relevant information from the studies is summarised below.
- Panobinostat was analysed in human plasma and human urine using specific liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods, with a lower limit of quantification (LLOQ) of 0.500 ng/mL (expressed in base) and a dynamic range of 0.500 to 500 ng/mL using 100 µL of human plasma or human urine. Plasma concentrations of panobinostat and BJB432 were analysed simultaneously in human plasma using a specific LC-MS/MS method with a LLOQ of 0.100 ng/mL (expressed in base), and a dynamic range of 0.100 to 100 ng/mL for each analyte using 100 µL of human plasma. In most studies the human plasma concentration of panobinostat was reported in ng/mL. However, in some studies, molar units were used to express

panobinostat concentration, in order to have comparative stoichiometric data with one of its major metabolites, BJB432. The molecular weights of panobinostat (free base) and BJB432 are 349.4 g/mole and 333 g/mole, respectively.

- The approach to evaluating the PK data has been; to broadly review the individual single agent panobinostat studies, the pooled PK analysis and the PPK analysis. The PK characteristics of PAN based on the single agent data are then reviewed, followed by a summary of the PK data for PAN when administered in combination with BTZ and Dex.

Individual PO studies with PK data; single agent panobinostat

- The submission included 17 Phase I/II studies assessing the PK of panobinostat when administered as a single agent in both single dose and multiple dose regimens to patients with haematological malignancies and solid tumours. Of the 17 studies, 15 assessed the PK of panobinostat following PO administration and 2 assessed the PK of panobinostat following IV administration. Most of the studies were in patients with malignancies other than MM. The PK parameters of panobinostat in the individual studies were calculated using standard non-compartmental methods. In addition, synopses of each of the studies were provided.
- The PK data from 16 of the studies were included in the pooled analysis and/or the PPK analysis. The data from the key mass balance study (Study B2108) was not included in either of the integrated analyses and have been evaluated separately. In addition, PK data from the food effect study (Study B2111), the two intrinsic factor studies (Studies X2101, X2105) and the two extrinsic factor studies (Studies B2109, B2110) have also been evaluated separately. The single agent panobinostat PO and IV doses assessed in the 17 submitted studies with relevant PK data are summarised below in Table 5.

Table 5: Single agent panobinostat doses assessed in the submitted studies with relevant PK data

ID	Patients	PK Data	N	Dosage
B2101 Phase IA	Solid tumours NHL	First PO study MTD / DLT	33	PAN 10 mg to 60 mg; dense PK sampling through to 48 hours Day 1, Day 15 or Day 17; complex dosing schedules.
B2102 Phase IA/II	Haematological malignancy	Dose escalating MTD / DLT	140	PAN 20 mg to 80 mg; dense PK sampling through to 48 hours Day 1 and Day 15.
B2108 Phase I	Solid tumours NHL	Mass balance ADME	4	(14C)-PAN 20 mg single dose taken on Day 1; dense PK sampling through to 168h following dosing on Day 1; urine and faecal collection over the same period.
B2111 Phase Ib	Solid tumours	Food effect	33	PAN 20 mg taken on Day 1 and Day 4 (fasting, normal meal, high fat meal); dense PK sampling through to 48 hours following dosing on Day 1, Day 8, and Day 15.
X2101 Phase I	Solid tumours	Hepatic impairment	24	PAN 30 mg single dose (core phase) with dense PK sampling through to 96 hours.
X2105 Phase I	Solid tumours	Renal impairment	37	PAN 30 mg single dose (core-phase) with dense PK sampling through to 96 hours.

ID	Patients	PK Data	N	Dosage
B2109 Phase IB	Solid tumours	DDI with CYP2D6 substrate	16	DM 60 mg on Day 1 with dense PK sampling through to 48 hours; PAN 20 mg on D3, Day 5, and Day 8; DM + PAN on Day 8 with dense PK sampling for DM through to 48 hours.
B2110 Phase IB	Solid tumours	DDI with CYP3A4 inhibitor	14	PAN 20 mg on Day 1 and Day 8 with dense PK sampling through to 48 hours on both days; KZ 400 mg + PAN 20 mg on Day 8.
B1101 Phase I	Solid tumours CTCL	Dose-escalation Japanese	13	PAN 10 mg (n = 3), 15 mg (n = 4), 20 mg (n = 6) dose escalation (single dose); dense PK sampling through to 48 hours following each dose (Day 1, Day 8, Day 15).
B1201 Phase II	CTCL ATC	PK profile Japanese	4	PAN 20 mg three times a week; PK sampling through to 24 hours following dosing on Day 1 and Day 8.
B2201 Phase II	CTCL	Efficacy and safety study	114	PAN 20 mg on Day 1, D3, and Day 5; PK sampling (limited) through to 24 hours on Day 1 (n = 109) and Day 8 (n = 60).
B2202 Phase II	Ph+ CML-CP resistant	Efficacy and safety study	19	PAN 20 mg on Day 1, D3, and Day 5; PK sampling (limited) through to 24 hours on Day 1 and Day 8.
B2203 Phase II	MM refractory	Efficacy and safety study	30	PAN 20 mg on Day 1, D3, and Day 5; PK sampling (limited) through to 24 hours on Day 1 (n = 27) and Day 8 (n = 22).
B2211 Phase II	CML accelerated	Efficacy and safety study	17	PAN 20 mg on Day 1, D3, and Day 5; PK sampling (limited) through to 24 hours on Day 1 (n = 17) and Day 8 (n = 16).
E2214 Phase II	HL refractory /relapsed	Efficacy and safety study	14	PAN 40 mg on Day 1; PK sampling (limited) through 28h on Day 1
A2102 Phase IA/II	Haematological malignancies	MTD and DLT IV	15	PK parameters assessed on Day 1 following PAN IV at doses of 4.8, 7.2, 9, 11.5 and 14 mg/m^2, with trough concentrations on D2, D3, Day 4, Day 5 and D7.

Source: CSR reports. Note: ATC = adult T-cell leukemia/lymphoma; CTCL - cutaneous T-cell lymphoma; D = day; DM = dextromethorphan; h = hours; HL = Hodgkin's lymphoma; KZ = ketoconazole; MM = multiple myeloma ; NHL = non Hodgkin's lymphoma; PAN = panobinostat; Ph+ CML-CP = Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase; TIW - three times a week; MTD = maximum tolerated dose; DLT toxicities

Evaluator's conclusions on pharmacokinetics

- There were no PK studies in healthy subjects due to the genotoxicity of panobinostat observed in the nonclinical studies. Furthermore, the pharmacokinetics of panobinostat were primarily characterised following single agent administration (rather than in combination with bortezomib and dexamethasone) in patients with solid tumours and haematological malignancies other than MM. There were limited PK

data on panobinostat administered in combination with bortezomib and dexamethasone in the target patient population.

- One of the problems with the panobinostat oral PK studies was the inadequate characterisation of the terminal elimination phase due to short sampling times (that is, 48 to 96 hours) relative to the estimated terminal elimination half-life (that is, 37 hours (PPK study)). In order to adequately characterise the terminal elimination phase, sampling should continue to at least 3 times the terminal half-life (that is, to at least 111 hours for panobinostat). Therefore, oral PK parameters estimated from data derived from the terminal elimination phase based on sampling for less than 3 times the terminal half-life are likely to be inaccurate (that is, AUC_{inf}, t½, CL/F[25], Vz/F). In the current submission, the only study in which PK sampling was greater than 3 times the half-life of panobinostat was the mass balance/ADME study in 4 patients with advanced cancer (Study B2108). In this study, PK sampling was continued through to 168 hours following a single radio labelled dose of panobinostat 20 mg administered as a capsule.
- The human biomaterial data were reported to show than panobinostat can be categorised as a highly permeable drug as regards transport across the intestinal mucosa, and that it may be a substrate for the P-gp efflux transporter. The physicochemical data showed that the aqueous solubility of panobinostat was pH-dependent, but the sponsor states that the drug would be completely soluble at the maximum proposed dose of 20 mg over the physiological pH range in the upper GIT.
- The single agent clinical studies showed that panobinostat was rapidly absorbed following oral administration with the median t_{max} being 2 hours, followed by excretion with a terminal elimination half-life of approximately 37 hours (PPK). The drug was well absorbed following oral administration with ≥ 87% of an administered radio labelled dose of panobinostat 20 mg being recovered in the urine and faeces and < 3.5% of the dose being excreted unchanged in the faeces. There was no formal absolute bioavailability study in the submission, but the absolute bioavailability derived from the PPK analysis was estimated to be approximately 21%.
- The effect of food on the bioavailability of panobinostat 20 mg administered on Days 1, 8, and 15 was assessed in a crossover study (fasting, high fat meal, normal meal) (Study B2111). Relative to fasting administration, the AUC_{inf} was reduced by 16% when panobinostat 20 mg was administered with a high fat meal and by 14% when administered with a normal meal. The 90% confidence interval (CI) for the AUC_{inf} ratio (fed relative to fasting) was outside the standard bioequivalence interval of 0.8 to 1.25 for both the high fat and normal meals. Relative to fasting administration, the C_{max} was reduced by 44% when panobinostat 20 mg was administered with a high fat meal and 36% when administered with a normal meal. The 90% CI for the C_{max} ratio (fed relative to fasting) was outside the standard bioequivalence interval of 0.8 to 1.25 for both the high fat and normal meals. The inter subject variability (coefficient of variation (CV)%) remained constant for the AUC_{inf} for each of the three treatments (approximately 59%), while inter subject variability in C_{max} for fasting was notably higher than for both fed treatments (86% (fasting) versus 63% (high fat) to 65% (normal meal)). t_{max} was prolonged with a high fat meal compared to both a normal meal and fasting (4.0 versus 2.5 versus 1.5 hours, respectively). Overall, the PK data suggest that panobinostat can be administered with or without food. However, the adverse event (AE) data indicated that nausea and vomiting occurred more frequently when panobinostat was administered in the fasting state. Therefore, panobinostat should be administered following a mean (that is, on a full stomach).

[25] CL/F: apparent clearance t½: Half-life

- There were no clinical data on the effect of food on the two lower doses of panobinostat proposed for registration (that is, 10 mg and 15 mg). The sponsor provided a justification for not submitting a food study with the two the lower doses (and by extension a justification for not submitting a bioequivalence study comparing the three proposed doses). The justification for not submitting food effect studies for the two lower dose capsules is considered to be reasonable, based on the physicochemical and PK properties of panobinostat.
- Pooled data showed that the single dose PK of panobinostat based on the C_{max} and AUC_{inf} were approximately dose proportional over the dose range 10 mg to 30 mg, but that the multiple dose PK of panobinostat based on the C_{max} and $AUC_{0 \text{ to } 48 \text{ hours}}$ were less than dose proportional over the dose range 10 mg to 30 mg. The inter subject PK of panobinostat are extremely variable with CV% for most PK parameters ranging from 60% to 100%.
- *In vitro*, panobinostat was reported to be 89.6% bound to plasma proteins, and binding was independent of panobinostat concentrations over the 0.1 to 100 µg/mL range evaluated in human plasma (Study R0200414). In vitro protein binding was not significantly affected by either renal or hepatic impairment (Studies X2101, X2105). In human plasma the mean fraction of panobinostat in erythrocytes *in vitro* was reported to be 0.60 and the mean blood to plasma concentration ratio was reported to be 1.4, with the values being independent of panobinostat concentration over the evaluated range of 0.1 to 100 µg/mL (Study R0200414). In the ADME study (Study B2108), the apparent volume of distribution was estimated to be 9464 L in 4 patients with PK sampling through to 168 hours post dose following radio labelled panobinostat 20 mg. The large volume of distribution indicates that panobinostat is extensively distributed to the tissues.
- Panobinostat undergoes extensive hepatic metabolism. A least 77 distinct metabolites have been identified of which approximately 40 were observed in circulating plasma. The primary metabolic pathways involved modifications of the hydroxamic acid side chain to form an amide via reduction (M37.8 or BJB432), three distinct carboxylic acids via hydrolysis (M43.5) and one- (M40.8), and two-carbon chain shortening (M36.9) of the hydroxamic acid side chain. Additionally, double bond reduction along with multiple oxygenations and glucuronidations (with and without carbamoylation) occurred both alone and in combination with the modifications of the hydroxamic side chain. The sponsor estimates that approximately 40% of the total hepatic metabolism of the drug is accounted for by CYP3A4, with minor contributions from CYP2D6 and CYP2C19.
- At least 87% of a single 20 mg oral dose of radio labelled panobinostat was recovered in the urine and faeces within 7 days of administration in all 4 treated patients with advanced cancer (Study B2108). Of the administered dose, median recovery in the faeces was 47.8% and median recovery in the urine was 41.3%. The excretion of panobinostat was primarily in the form of metabolites, with unchanged panobinostat accounting for approximately 1.1% to 2.4% of the dose in urine (0 to 48 hours) and 0% to 3.3% of the dose in faeces (0 to 108 hours to 148 hours). The high total recovery of the administered dose and the low fecal excretion of the unchanged drug suggests that oral absorption is nearly complete. Based on this observation and the estimated absolute bioavailability of 21% it can be concluded that panobinostat undergoes extensive first pass hepatic metabolism.
- In Study B2108, the median apparent oral clearance of panobinostat was 209 L/hour, and the estimated mean renal clearance of the drug was approximately 4 L/hour. In the PPK analysis, the oral clearance of panobinostat was estimated to be approximately 160 L/hour, with a large inter subject variability (CV% = 65%). The

large apparent oral clearance estimated from the PPK was consistent with the median oral apparent clearance reported in Study B2108.

- Exposure to panobinostat increased in patients with advanced solid tumours and hepatic impairment (Study X2101). The geometric mean AUC_{inf}, increased by 43% and 105% in patients with mild (n = 7) and moderate hepatic impairment (n = 7), respectively, compared to patients with normal hepatic function (n = 10). The geometric mean C_{max} increased by 57% and 83% in patients with mild and moderate hepatic impairment, respectively, compared to patients with normal hepatic function. There were data on 1 patient with severe hepatic impairment, and the PK parameters in this patient were consistent with the mean PK parameters observed for the patients with moderate hepatic impairment. It is recommended that the starting dose of panobinostat be reduced to 10 mg in subjects with moderate hepatic impairment and 15 mg in patients with mild hepatic impairment. Treatment should be avoided in patients with severe hepatic impairment.
- Exposure to panobinostat either decreased or remained largely unchanged in patients with advanced solid tumours and mild (n = 10), moderate (n = 10), or severe (n = 6) renal impairment relative to patients with normal renal function (n = 6). Geometric mean $AUC_{0\text{-}inf}$ values in patients with mild, moderate and severe renal impairment were 64%, 99% and 59%, respectively, of the value in patients with normal renal function. Geometric mean C_{max} concentrations in patients with mild, moderate and severe renal impairment were 59%, 95% and 45%, respectively, of the value in patients with normal renal function. Overall, the data suggest that no dosage modifications are required in patients with impaired renal function. There were no data in patients with ESRD. It is not known whether panobinostat is dialysable.
- Simulations (PPK) showed that panobinostat clearance and central compartment volume increased with age. Simulations showed that compared to a typical 61 year old patient a typical 31 year old patient would have a 12% lower clearance and a 25% lower central compartment volume. The PPK analysis also predicts that patients older than 80 years will have a 5% higher panobinostat clearance than patients aged 61 years. Overall, the data suggest that no dosage adjustments are required based on age.
- The PPK analysis indicates that gender has no significant effect on the clearance or central compartment volume of panobinostat. There was some evidence that Asian patients have a higher clearance and central compartment volume compared to Caucasian patients. However, the data are too limited to recommended dosage adjustments in Asian patients.
- Simulations (PPK) showed that panobinostat clearance and central compartment volume increased with BSA. The simulations predict that a typical patient with a BSA of 1.5 m^2 would have a 21% lower clearance and a 27% lower central compartment volume compared to a typical patient with a BSA of 1.9 m^2, while a typical patient with a BSA of 2.5 m^2 would have a 32% higher clearance and a 45% higher central compartment volume compared to a typical patient with a BSA of 1.9 m^2. The proposed dosing regimen is not based on BSA.
- The data indicate that approximately 40% of the hepatic clearance of panobinostat is accounted for by CYP3A4. In the clinical DDI study (Study B2110), the geometric mean C_{max} and the AUC_{inf} of panobinostat increased by 62% and 78%, respectively, when panobinostat (20 mg single dose; n = 11 to 14) was administered in combination with ketoconazole (400 mg once daily (QD) x 5 days; n = 12-14). It is recommended that the panobinostat starting dose be reduced to 10 mg when administered with strong CYP3A4 inhibitors. There were no clinical DDI studies with CYP3A4 inducers. However, on the basis of Symcyp *in vitro* modelling the AUC of panobinostat is predicted to decrease by 67% when co-administered with rifampin 600 mg QD (a

CYP3A4 inducer). Consequently, it is recommended that co-administration of panobinostat and strong CYP3A4 inducers be avoided.

- In vitro human biomaterial studies reported that panobinostat was a competitive inhibitor of CYP2D6. In the clinical DDI study (Study B2109), when the CYP2D6 substrate dextromethorphan (60 mg, single dose; n = 14) was administered in combination with panobinostat (20 mg single dose; n = 12-14) the C_{max} and $AUC_{0\text{-}48\ h}$ of dextromethorphan increased by 83% and 52%, respectively. Based on FDA criteria relating to drug interactions, panobinostat can be classified as a weak inhibitor of CYP2D6 (that is, dextromethorphan AUC increase ≥ 1.25 but < 2 fold for combination dextromethorphan plus panobinostat compared to dextromethorphan alone). It is recommended that co-administration of panobinostat with sensitive CYP2D6 substrates or with CYP2D6 substrates with a narrow therapeutic index be avoided.
- In vitro Symcyp modelling predicts a median increase in the AUC of midazolam (a sensitive CYP3A4 substrate) of 1.18 fold when co-administered with panobinostat using a time based model and 1.76 fold when using an 'over-predictive' steady state model. The clinical significance of these findings are uncertain. Definitive conclusions relating to the potential clinical effects of co-administration of panobinostat and midazolam should await the outcome of the planned clinical study.
- In vitro human biomaterial studies reported that panobinostat was not an inducer of CYP1A1/2, CYP2B6, CYP2C8/9/19, CYP3A, UGT1A1, ABCB1 (P-gp) or ABCC2 (MRP2). In vitro human biomaterial studies reported that panobinostat was not an inhibitor of the organic anion transporter OAT1, but was an inhibitor of the organic anion transporter OAT3. It was reported that panobinostat was an *in vitro* inhibitor of the organic cation transporters OCT1 and OCT2, and the organic uptake transporters OATP1B1 and OATP1B3. However, the sponsor stated that, based on a 20 mg oral dose ($C_{max,ss}$ of 21.6 ng/mL or 0.062 μM) no clinical DDI with respect to OATP1B1/3, OAT3, OCT1, or OCT2 inhibition is expected.
- It was reported in the human biomaterial studies that panobinostat was not an *in vitro* inhibitor of the P-gp transporter or the breast cancer resistant protein (BCRP) transporter. It was reported that panobinostat was a substrate for P-gp mediated efflux, but not for MRP mediated efflux. It was reported that panobinostat, *in vitro*, was not an inducer of the UDP-glucuronosyl transferase transporter (UGT1A1), the P-gp transporter or the multi drug resistance protein 2 (MRP2) transporter.
- There was no clinical DDI study in the submission exploring co-administration of panobinostat and drugs that increase gastro-intestinal pH (for example, PPIs). No human biomaterial or simulated (Symcyp) modelling studies investigating potential DDI between panobinostat and drugs that increase gastro-intestinal pH could be identified in the submission. This is considered to be a deficiency in the data, given that the aqueous solubility of panobinostat is pH-dependent.
- In Study B2207 (dose expansion phase) in patients with MM, PAN exposure in the PAN+BTZ+Dex arm was approximately 20% lower than in the PBO+BTZ+Dex[26] arm, based on both the $AUC_{0\text{-}24\ hours}$ and C_{max}. Both PAN and BTZ are metabolised by CYP3A4 (40% and 25%, respectively). It is likely that reduced exposure to PAN observed in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm was due to CYP3A4 induction mediated by the addition of Dex to PAN+BTZ. The C_{max} of BTZ decreased by approximately 25% when Dex was added to PAN+BTZ, while the $AUC_{0\text{-}24\ hours}$ increased by approximately 3%. Overall, the addition of Dex to PAN+BTZ combination is unlikely to result in clinically significant reduced exposure to either PAN or BTZ.

[26] PBO: Placebo

- In the pivotal Phase III Study D2308, exposure to PAN increased by approximately 67% (C_{max}) and 56% (AUC_{0-48h}) following multiple dose treatment with PAN+BTZ+Dex compared to single dose administration of this regimen. The results suggest that PAN accumulates following multiple dosing. In this study, exposure to BTZ in the PAN+BTZ+Dex arm was greater than in the PBO+BTZ+Dex arm (AUC_{0-24h} approximately 32% greater, C_{max} approximately 21% greater). The increased exposure to BTZ in the presence of PAN might be due to competition between the two drugs for binding sites on CYP3A4 (given that the two drugs are metabolised by this enzyme), resulting in decreased metabolism of BTZ.

Pharmacodynamics

Studies providing pharmacodynamic data

The pharmacodynamic data included three exposure response analyses:

1. panobinostat versus thrombocytopaenia
2. panobinostat versus Frederica's corrected QT interval (QTcF)
3. panobinostat versus efficacy.

The results of these three analyses are discussed in Section 5 of Attachment 2.

Evaluator's conclusions on pharmacodynamics

- The exposure response relationship between panobinostat and thrombocytopenia appears to have been designed to explore a proposed panobinostat dosing regimen for the treatment of patients with classical HL. Therefore, the dosing regimens explored in this analysis are not directly applicable to the treatment of patients with MM. Simulations of platelet dynamics based on the model predictions showed a strong dependence of the response to panobinostat on baseline platelet count, as well as on panobinostat dose and dose regimen. These predictions are likely to be relevant to panobinostat for the treatment of MM.
- The exposure response relationship between panobinostat plasma concentration and QTcF did not provide a signal indicating that treatment with panobinostat is associated with clinically significant prolongation of the QTcF. However, electrocardiogram abnormalities are a known class effect of HDACi. In addition, both panobinostat and BJB432 inhibit hERG potassium channel activity at IC_{50} values of 3.5 µM and 1.6 µM, respectively. Therefore, concomitant administration of panobinostat with drugs known to increase the QTc interval may result in clinically significant prolongation of the QTc due to possible synergistic effects. In addition, patients with baseline QTc prolongation might be at an increased risk of clinically significant QTc prolongation when exposed to panobinostat.
- The exposure-response relationship between panobinostat AUC_{0-24h} and efficacy (best overall response) showed a positive relationship for PAN 20 mg + BTZ 1.3 mg/m^2 and suggested a synergistic effect when Dex 20 mg was added to the regimen.

Dosage selection for the pivotal studies

The panobinostat dose regimen selected for the pivotal Study D2308 was based on the results of the Phase Ib dose escalating study (Study B2207) designed to assess the combination of panobinostat (PAN) with bortezomib (BTZ) in patients with relapsed or relapsed and refractory MM, following at least 1 prior line of therapy. Prior to this study,

single agent oral PAN had been tested in patients with advanced haematological malignancies in the Phase IA/II dose escalation Study B2102 and in the Phase II Study B2203 in patients with MM who had received at least 2 lines of previous therapy, which must have included bortezomib or lenalidomide. Based on these results and nonclinical data suggesting a potential synergistic effect for the combination of PAN plus BTZ, the sponsor stated that 'development of PAN in combination with other anti-myeloma agents was prioritized'.

The primary objective of the dose escalating phase of Study B2207 was to determine the maximum tolerated dose (MTD) of PAN and BTZ when administered in combination to patients with advanced MM. The primary endpoint of the study was the MTD, which was defined as the highest dose level of PAN in combination with BTZ in the specified dosing schedule that met the dose limiting (DLT) criteria. DLT was defined as clinically relevant AEs or abnormal laboratory values occurring ≤ 21 days following the first dose of study treatment in Cycle 1. Each cohort consisted of a minimum of six patients and dose escalation was to end when at least 12 MTD evaluable patients had been enrolled at the recommended dose level. The MTD dose level cohort was then to be expanded to a total of 22 patients treated at that level, in order to assess safety and tolerability of the MTD (Phase II period of the study).

In the dose escalation phase, PAN was initiated at a dose of 10 mg, which was lower than the dose used in the single agent PAN studies (that is, 20 mg). Doses of PAN 10 mg to 30 mg (three times a week, until progression) in combination with BTZ 1.0 or 1.3 mg/m^2 BTZ IV (on Days 1, 4, 8, and 11) were tested. The addition of Dex to the combination was discretionary in the dose escalation phase for patients who had worsening disease or suboptimal response, but mandatory for all patients in the dose expansion phase starting at Cycle 2. The planned treatment cycle duration throughout the study was 21 days, which was based on the standard cycle duration for BTZ. The dose cohorts for the dose escalation phase of the study are summarised below in Table 6.

Table 6: Study D2307; Dose levels for PAN, BTZ and Dex

Dose level escalation phase [1]	PAN dose (mg) [2]	BTZ dose (mg/m^2) [3]	Dex dose (mg)
Cohort I (n=7)	10	1.0	
Cohort II (n=7)	20	1.0	
Cohort III (MTD) (n=8)	20	1.3	
Cohort IV (n=7)	30	1.3	
Cohort V (n=9)	25	1.3	
Cohort VI (MTD) (n=9)	20	1.3	
Dose level expansion phase [4]			
Cohort VII (n=15)	20	1.3	20 [5]

Source: CSR D2308, Table 9-1.
[1] Dex was optional in the dose escalation phase for patients with suboptimal responses but was not considered to be an investigational or a control drug.
[2] Administered three times a week (TIW) on Mon, Wed, Fri
[3] Administered IV on Days 1, 4, 8, 11 of a 21-Day cycle.
[4] Treatment was 2-weeks on and 1-week off.
[5] Dex was mandatory in the expansion phase starting at Cycle 2.

The MTD dose was declared to be PAN 20 mg + BTZ 1.3 mg/m^2, based on 15 evaluable patients in Cohorts III plus VI. Dose limiting toxicities were reported in 3 out of 15 patients (20%) in the MTD cohort. This was considerably lower than in the cohorts receiving higher doses of PAN. The following DLTs were reported in different dose level cohorts during dose escalation phase:

- In the PAN 30 mg + BTZ 1.3 mg/m2 (Cohort IV), DLTs were reported in 4 out of 6 evaluable patients (66.7%). These included thrombocytopenia (2 patients), weakness (2 patients), and anorexia, asthenia and fatigue (all in 1 patient). This led to de-escalation in PAN dose from 30 mg to 25 mg in the next cohort (Cohort V), keeping the BTZ dose at 1.3 mg/m2.

- In the PAN 25 mg + BTZ 1.3 mg/m2 (Cohort V), DLTs were observed in 2 out of 6 evaluable patients (33.3%), including tumour lysis syndrome (1 patient) and thrombocytopenia (1 patient). This led to de-escalation in PAN dose from 25 mg to 20 mg in the next cohort (Cohort VI) keeping the BTZ dose at 1.3 mg/m2, and bringing the dose back to the dose tested in Cohort III.
- In the PAN 20 mg + 1.3 mg/m2 (Cohort VII), DLTs were observed in 3 out of 15 (20%) evaluable patients (6 patients from cohort III and 9 patients from cohort VI) and included thrombocytopenia, vomiting and orthostatic hypotension (1 patient each).

Thrombocytopenia as a disease limiting toxicity (DLT ≥ Grade 3) was reported by 6.7% (1 out of 15) of patients in the MTD cohort of PAN 20 mg + BTZ 1.3 mg/m^2 compared to 25% (3 out of 12) of patients in the cohorts with higher doses of PAN. Based on the results of the dose escalation phase, the MTD of PAN 20 mg + and 1.3 mg/m^2 BTZ was selected for the Study B2207 expansion phase. The dosing schedule of 2 weeks on / 1 week off (similar to that of BTZ) was introduced into the dose expansion phase of in order to manage thrombocytopenia and to allow for accelerated platelet recovery.

Based on the results of the dose escalation phase of Study B2207, the PAN 20 mg + BTZ 1.3 mg/m^2 + Dex 20 mg dose regimen selected for the pivotal efficacy and safety study (Study D2308) is considered to be appropriate.

Efficacy

Studies providing efficacy data

The submission included three efficacy and safety studies relevant to the proposed dose for the proposed usage (see Table 7). The most important of these studies is the Phase III study (Study D2308) which provides pivotal clinical efficacy data, while the other two studies are considered to provide limited supportive efficacy data. The evaluation of clinical efficacy focuses on the data from the pivotal Phase III study (Study D2308).

Table7: Overview of efficacy studies

	Study D2308	Study DUS71	Study B2207 Dose escalation phase	Study B2207 Dose expansion phase
Study design features	Phase III	Phase II	Phase Ib	Phase Ib
	Confirmatory	Proof of concept	Dose escalation	Dose expansion
	Placebo-controlled	Uncontrolled	Uncontrolled	Uncontrolled
Population	Relapsed or relapsed-and-refractory, excluding BTZ-refractory	Relapsed and refractory, selectively including BTZ-refractory	Relapsed or relapsed-and-refractory, including BTZ-refractory	Relapsed or relapsed-and-refractory, including BTZ-refractory
FPFV	21-Dec-2009	22-Jun-2010	18-Oct-2007	N/A
Database-lock / Type of analysis	29-Nov-2013 Final PFS and interim OS analysis	28-Jun-2013 Primary analysis	10-Aug-2011 Primary analysis	10-Aug-2011 Primary analysis
Study status	Ongoing[1]	Ongoing[2]	Completed	Ongoing[3]
Primary efficacy endpoint	PFS based on mEBMT criteria	ORR based on mEBMT criteria	MTD of PAN in combination with BTZ	N/A
Secondary efficacy endpoints	OS (key secondary), ORR, MRR, TTR, DOR, TTP, all based on mEBMT criteria, PRO	Rate of MR or better (≥ MR), TTR; DOR, PFS, TTP, all based on mEBMT criteria, OS, PRO	Preliminary efficacy (ORR based on IMWG criteria)	ORR based on IMWG criteria
Exploratory efficacy endpoints	VGPR and sCR based on updated IMWG criteria	VGPR based on updated IMWG criteria	Rate of minor response based on the updated IMWG criteria	Rate of minor response based on the updated IMWG criteria

Source: SCE (CTD 2.7.3), Table 1-2. DOR: Duration of response, IMWG: International Myeloma Working Group, mEBMT: modified European Group for Blood and Marrow Transplantation, MR: minimal response, MRR: minimal response rate, MTD: maximum tolerable dose; ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PRO: patient reported outcomes, RR: response rate, sCR: stringent complete response, TTP: time to progression, TTR: time to response, VGPR: very good partial response

[1] Study D2308: At the time of the data cut-off on 10 September 2013, 58 patients were being followed for disease progression and 416 patients were being followed for survival.

[2] Study DUS71: At the time of the data cut-off on 04 December 2012, 2 patients were on-going and 21 patients were being followed for survival.

[3] Study B2207: At the time of the data cut-off on 10 August 2011, 8 patients were on-going treatment.

Evaluator's conclusions on efficacy

The submitted efficacy data for the PAN+BTZ+Dex regimen for the proposed indication was primarily derived from the pivotal efficacy and safety study (Study D2308), and two supportive open label, single arm studies (DUS71, B2207).

In the pivotal study (Study D2308), the primary efficacy analysis was investigator assessment of progression free survival (PFS) using modified European Society for Blood and Bone Marrow Transplant (mEMBT) criteria. This analysis showed a statistically significant 3.9 month increase in median PFS for patients in the PAN+BTZ+Dex arm (n = 387) compared to patients in the PBO+BTZ+Dex arm (n = 381). The median PFS was 12.0 months (95% CI: 10.3, 12.9 months) in the PAN+BTZ+Dex arm (n = 387) and 8.1 months (95% CI: 7.6, 9.2 months) in the PBO+BTZ+Dex arm; HR = 0.63 (95% CI: 0.52, 0.76); $p < 0.0001$. The study was powered on an assumption that the difference in the median PFS between the two treatment arms would be 2.7 months.

In the primary PFS analysis (disease progression/relapse/death), disease progression was reported more frequently in the PBO+BTZ+Dex arm compared to the PAN+BTZ+Dex arm (60.6% versus 42.4%, respectively), while death was reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (5.3% versus 3.7%, respectively) as was relapse (5.2% versus 3.9%, respectively).

The major limitation of the primary analysis of the PFS was the significant proportion of the total number of patients in the study who were censored in both, the PAN+BTZ+Dex and the PBO+BTZ+Dex arms (46.5%, n = 180 and 31.8%, n = 121, respectively).

Furthermore, censoring was high in non-ongoing patients (that is, dropouts) who contributed no data to the primary analysis of PFS due to the censoring rules (that is, n = 145 (37.5%) in the PAN+BTZ+Dex arm; n = 106 (27.8%) in the PBO+BTZ+Dex). The high dropout rate in both treatment arms due to the censoring rules has the potential to bias the results of the primary analysis of PFS, leading to uncertainty about the accuracy of the observed treatment effect.

In a PFS sensitivity analysis aimed at assessing the impact missing data from non-ongoing censored patients had on the primary analysis, the difference in median PFS between the PAN+BTZ+Dex arm and the PBO+BTZ+Dex arm was 1.8 months (that is, 9.46 months versus 7.62 months, respectively); HR = 0.71 (95% CI: 0.61, 0.83); $p < 0.0001$. This PFS sensitivity analysis ('dropout') reduced the median PFS difference between the two treatment arms by 54% relative to the primary PFS analysis (that is, from 3.9 to 1.8 months). The results of the PFS sensitivity analysis ('dropout') suggest that missing data from these patients might have biased the primary analysis towards the PAN+BTZ+Dex arm.

In another key PFS sensitivity analysis based on IRC assessment using mEMBT criteria, the difference in the median PFS between the two treatment arms was 2.3 months (that is, median PFS of 10 months in the PAN + BTZ + Dex arm and 7.7 months in the PBO+BTZ+Dex arm): HR = 0.69 (95% CI: 0.58, 0.83); $p < 0.0001$. In general, IRC assessment of PFS can be considered to be less prone to bias than investigator assessment due to all assessments being undertaken by the same group of assessors, with less scope for subjective interpretation among site specific investigators.

Although the difference in median PFS between the two treatment arms was statistically significant for both the investigator and IRC assessments using mEMBT criteria, the numerical difference between the two analyses raises uncertainty about the true effect size (that is, 3.9 months versus 2.3 months, respectively). Furthermore, the difference between the two treatment arms in median PFS based on IRC assessment using mEMBT criteria of 2.3 months was less than the pre-specified difference of 2.7 months between the two treatment arms used to power the study. Based on the power calculation assumptions, it is reasonable to infer that a PFS difference of 2.7 months represents the minimum clinically meaningful difference between the two treatment arms for patients with relapsed or relapsed/refractory MM included in the pivotal study. Consequently, the numerical difference in PFS between the two treatment arms of 2.3 months based on IRC assessment using mEMBT criteria is not only inconsistent with the corresponding result observed for the primary analysis, but is also of doubtful clinical significance in the context of the pivotal study.

In addition, it is of concern that censoring for the primary PFS analysis due to withdrawal of consent was reported in a notably higher proportion of patients in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex Arm (74 (19.1%) versus 45 (11.8%), respectively). This raises the possibility that treatment with PAN+BTZ+Dex was less well tolerated than treatment with PBO+BTZ+Dex, resulting in more patients withdrawing consent to continued treatment in the 'PAN' arm than in the 'PBO' arm. In contrast, censoring due to new cancer therapy being added was reported in a similar proportion of the total number of patients in both treatment arms (that is, n = 23 (5.9%) in the PAN+BTZ+Dex arm and n = 24 (6.3%) in the PBO+BTZ+Dex arm).

OS was a key secondary efficacy endpoint in the pivotal study. However, the OS data at the data cutoff date were immature as only 68.9% (n = 286) of the 415 OS events planned for the final analysis had occurred. In the interim analysis, OS based on investigator assessment was not statistically significantly different between the two treatment arms with a median OS of 33.6 months for patients in the PAN+BTZ+Dex arm and 30.4 months for patients in the PBO+BTZ+Dex arm; HR = 0.87 (95% CI: 0.69, 1.10), p = 0.2586.

There were a number of other key secondary efficacy endpoints based on investigator assessment of mEMBT criteria. The analyses of these endpoints consistently showed a numerical advantage for the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm (that is, overall response rate (ORR), near complete response (nCR)/CR rate, median TTR, median duration of response (DOR), and median TTP). However, there was no statistically significant difference between the ORR based on investigator assessment using mEMBT criteria in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm (60.7% versus 54.6%; p = 0.0873).

Patient reported outcomes showed no advantage for patients treated with PAN+BTZ+Dex compared to patients treated with PBO+BTZ+Dex (for example, EORTC;[27] QLQ-C30, QLQ-MY20;[28] and FACT/GOG-NTX questionnaires).

Limited data from the open label Study DUS71 showed that the ORR (primary efficacy endpoint) was 34.5% (19/55) (95% CI: 22.2%, 46.7%; p < 0.0001) after PAN+BTZ+Dex for 8 treatment cycles, based on investigator assessment per modified European Bone Marrow Transplant Organisation (EBMT) criteria. The ORR was statistically significant for the test of null hypothesis of response rate ≤ 10%. No patients achieved a CR, 1 (1.8%) patient achieved nCR and 18 patients (32.7%) achieved a PR. Limited data from Study B2207 showed that in the dose escalation phase, the ORR (stringent complete response (sCR) + CR + very good partial response (VGPR) + PR) for treatment with PAN+BTZ+Dex was 71.4% (95% CI: 41.9%, 91.6%); that is, 10 out of 14 patients (sCR = 0, CR = 0, VGPR = 3, PR = 7).

Safety

Studies providing safety data

The approach to the evaluation of safety adopted in this CER focuses on the data from the pivotal Study D2308 provided in the clinical study report (CSR), supplemented by additional data from this study provided in the Summary of Clinical Safety (SCS). Study D2308 was the only study in the submission with controlled data (PBO+BTZ+Dex) for the PAN+BTZ+Dex regimen for the proposed indication. In this study, 381 patients were exposed to PAN+BTZ+Dex and 377 patients were exposed to PBO+BTZ+Dex.

The submission also included two single arm studies in patients with relapsed and relapsed and refractory MM treated with the PAN+BTZ+Dex regimen consistent with that proposed for registration. Overall, a total of 451 patients from the pivotal and supportive studies were exposed to PAN+BTZ+Dex at doses relevant to the proposed indication, including 381 (84.4%) patients from the pivotal Study D2308, 55 (12.2%) patients from the supportive Study DUS71, and 15 (3.3%) from the dose expansion phase of supportive Study B2207. The SCS included an integrated safety assessment of the 451 patients in the PAN+BTZ+Dex arm from the pivotal and supportive studies, and separate safety assessments from each of the studies. The integrated safety data for the 451 patients treated with PAN+BTZ+Dex have been examined and are consistent with the safety data for the 381 patients in the pivotal study treated with this combination. This is not unexpected as the pivotal study contributed the majority of the patients (n = 381, 84.4%) to the integrated safety data (n = 451).

The SCS also included an integrated safety assessment of 278 patients treated with single agent panobinostat 20 mg, including 39 patients with MM. The data from the panobinostat 20 mg single agent integrated safety assessment have not been evaluated as it is

[27] EORTC: European Organization for Research and Treatment of Cancer
[28] QLQ-C30: Quality of Life Questionnaire - Core Questionnaire; QLQ-MY20: Quality of Life Questionnaire – Myeloma Module

considered that these data are not directly relevant to the purposes of the submission. Neither the patient population nor the dosage regimen in the single agent integrated analysis was consistent with those being proposed for approval.

Patient exposure

The safety set consisted of all randomised patients who received at least one dose of any component of the study treatment. Of the 768 randomised patients, 758 (98.7%) patients were included in the safety set: 381 patients in the PAN+BTZ+Dex arm and 377 patients in the PBO+BTZ+Dex arm.

The median duration of exposure to study treatment was 5.0 months for patients in the PAN+BTZ+Dex arm (152 days (range: 3, 411 days)) and 6.1 months for patients in the PBO+BTZ+Dex arm (187 days (range: 3, 443 days)). In total, 178 patients (46.7%) were treated with PAN+BTZ+Dex and 202 patients (53.6%) with PBO+BTZ+Dex for ≥ 24 weeks, and 5 (1.3%) and 3 (0.8%) patients, respectively, were treated for ≥ 56 weeks. The exposure data are summarised in Table 8.

Table 8: Study D2308; Overall duration of exposure to study treatment by treatment group; safety set

	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
Exposure categories (cycle) – n (%)		
< 3 weeks	29 (7.6%)	20 (5.3%)
≥ 3 and <6 weeks	28 (7.3%)	19 (5.0%)
≥ 6 and <12 weeks	60 (15.7%)	53 (14.1%)
≥ 12 and <24 weeks	86 (22.6%)	83 (22.0%)
≥ 24 and <48 weeks	118 (31.0%)	153 (40.6%)
≥ 48 and ≤ 56 weeks	55 (14.4%)	46 (12.2%)
≥ 56 weeks	5 (1.3%)	3 (0.8%)
Duration of study treatment exposure (days)		
n	381	377
Mean	183.5	195.0
SD	125.75	118.33
Median	152.0	187.0
Minimum	3.0	3.0
Maximum	411.0	443.0

Treatment Phase 1 (Cycle 1 to Cycle 8) has a cycle length of three weeks; Treatment Phase 2 (Cycle 9 to Cycle 12) has a cycle length of six weeks.

Duration of study treatment exposure (days) = [date of last administration of study treatment] - [date of first administration of study treatment] + 1.

Dose intensity

The median relative dose intensity (RDI) for PAN and PBO in the combination treatment arms was 80.7% (range: 40.6%, 104.2%) and 95.1% (range: 44.7%, 250.0%), respectively. The median RDI for BTZ was higher in the PBO+BTZ+Dex arm, 86.7% (range: 30.8%, 104.7%) than in the PAN+BTZ+Dex arm, 75.7% (range: 30.7%, 105.8%). The median RDI for Dex was 87.5% (range: 35.0%, 106.1%) in the PAN+BTZ+Dex arm and 95.1% (range: 27.0%, 106.3%) in the PBO+BTZ+Dex arm. Dose intensity and RDI are summarised in Table 9.

Table 9: Study D2308; Dose intensity and relative dose intensity of study treatment component by treatment group; safety set

	PAN+BTZ+Dex N=381			PBO+BTZ+Dex N=377		
	PAN	BTZ	Dex	PBO	BTZ	Dex
Number of patients receiving component – n (%)	381 (100.0)	381 (100.0)	381 (100.0)	377 (100.0)	377 (100.0)	377 (100.0)
Dose intensity[1]						
Mean	4.8	0.2	6.1	5.3	0.2	6.3
SD	1.30	0.06	1.88	1.01	0.05	1.46
Median	4.7	0.2	5.7	5.5	0.2	6.2
Minimum	2.4	0.1	2.6	2.6	0.1	2.1
Maximum	10.0	0.4	13.3	14.3	0.4	13.3
Relative dose intensity [2]						
Mean	79.4	75.8	83.1	90.5	83.3	89.4
SD	16.64	16.25	16.89	14.60	14.05	14.12
Median	80.7	75.7	87.5	95.1	86.7	95.1
Minimum	40.6	30.7	35.0	44.7	30.8	27.0
Maximum	104.2	105.8	106.1	250.0	104.7	106.3
Relative dose intensity categories – n (%)						
<50%	19 (5.0)	24 (6.3)	19 (5.0)	2 (0.5)	8 (2.1)	6 (1.6)
50 to <70%	94 (24.7)	122 (32.0)	78 (20.5)	26 (6.9)	68 (18.0)	36 (9.5)
70 to <90%	140 (36.7)	139 (36.5)	112 (29.4)	107 (28.4)	146 (38.7)	91 (24.1)
90 to <110%	128 (33.6)	96 (25.2)	172 (45.1)	241 (63.9)	155 (41.1)	244 (64.7)
≥ 110%	0	0	0	1 (0.3)	0	0

[1] Dose intensity = cumulative dose / sum of all actual cycle lengths; cumulative dose = total dose given during the study treatment exposure ; cycle length (except for last cycle) = (date of Day 1 of next cycle – date of Day 1 of current cycle);last cycle length = [date of last administration of study treatment component + X) – (Day 1 of last cycle date)] where X is number of days remaining to complete exposure time of last dose of study treatment component or number of days from last administrated dose to next planned dose. Units: mg/day for PAN/PBO and Dex, mg/m^2 day for BTZ.

[2] Relative dose intensity (%) = 100*dose intensity/planned dose intensity.

For further detail please see Attachment 2, Extract from the Clinical Evaluation Report.

Safety issues with the potential for major regulatory impact

Liver toxicity

The sponsor comments that based on the cumulative clinical experience to date, hepatic dysfunction has been identified as a safety risk for patients treated with PAN.

In the pivotal Study (Study D2308), clinically notable adverse events (CNAEs) (all Grades) grouped as hepatic dysfunction were reported more frequently in patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (16.5%, n = 63 versus 12.2%, n = 46), while CNAEs (Grade 3/4) were reported in a similar proportion of patients in the two treatment arms (4.2%, n = 16 versus 3.4%, n = 13, respectively).

Haematological toxicity

This has been discussed (please see Attachment 2). Haematological toxicity, particularly thrombocytopenia, is the major safety concern associated with panobinostat treatment. In the pivotal Study (Study D2308) myelosuppression resulting in thrombocytopaenia and leukopenia occurred markedly more frequently in patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm.

Serious skin reactions

In the pivotal Study (Study D2308), skin and subcutaneous tissue disorder (System Organ Class (SOC)) AEs (any Grade) were reported in 28.3% (n = 108) of patients in the PAN+BTZ+DEX arm compared to 24.4% (n = 92) of patients in the PBO+BTZ+Dex arm, and AEs (Grade 3/4) were reported in 3.4% (n = 13) and 0.8% (n = 3) of patients, respectively. The only AE (any) reported in ≥ 5% of patients in either of the two treatment arms was rash (8.7% versus 6.4%). AEs (Grade 3/4) reported in the PAN+BTZ+Dex arm versus the PBO+BTZ+Dex arm were rash (1.0%, n = 4 versus 0%), swelling face (0.5%, n = 2 versus 0%), pruritis (0.3%, n = 1 versus 0%), urticaria (0.3%, n = 1 versus 0), night sweats (0.3%, n = 1 versus 0%), acute febrile neutrophilic dermatosis (n = 1, 0.3% versus 0.3%, n = 1), exfoliative rash (0.3%, n = 1 versus 0.3%, n = 1), hidradenitis (0.3%, n = 1 versus 0%), and Stevens Johnson Syndrome (SJS) (0.3%, n = 1 versus 0%). As mentioned above (see Attachment 2), the one case of SJS in the PAN+BTZ+Dex arm was confounded by other factors that might have caused the condition.

Cardiovascular safety

Cardiac disorders

For the details please see Attachment 2.

Comment: Overall, the data suggest an increased risk of cardiac disorders in the pivotal study (Study D2308) for patients in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. However, the sponsor states that review of the medical history of patients in this study indicated that 16.8% of patients in the 'PAN' arm had underlying cardiac disorders as part of their medical histories compared to 13.9% of patients in the 'PBO' arm. Therefore, the sponsor considers that there is insufficient evidence from the pivotal study to suggest that panobinostat may increase cardiac risk, due to the presence of significant confounding factors associated with each patient reporting ischaemic heart disease.

Unwanted immunological events

In the pivotal study (Study D2308), immune system disorder (SOC) AEs (any Grade) were reported in 5 (0.3%) patients in the PAN+BTZ+Dex arm and 4 (1.1%) patients in the PBO+BTZ+Dex arm.

Post-marketing data

Not applicable.

Evaluator's conclusions on safety

The safety data relating to the proposed dosage regimen for the proposed indication are derived primarily from the pivotal Study D2308. In this study, 381 patients were exposed to PAN+BTZ+Dex for a median duration of 5.0 months and 377 patients were exposed to PBO+BTZ+Dex for a median duration of 6.1 months. In total, 178 patients (46.7%) were treated with PAN+BTZ+Dex and 202 patients (53.6%) with PBO+BTZ+Dex for ≥ 24 weeks, and 5 (1.3%) and 3 (0.8%) patients, respectively, were treated for ≥ 56 weeks.

Overall, it is considered that the data from the pivotal study (Study D2308) indicate that the safety profile of PAN+BTZ+Dex for the proposed indication is notably inferior to the safety profile of PBO+BTZ+Dex. The major safety concerns relating to treatment with PAN+BTZ+Dex are myelosuppression (including severe thrombocytopaenia, neutropaenia and anaemia), haemorrhage, severe infections including sepsis, diarrhoea, cardiac

disorders (including ischaemic heart disease and tachyarrhythmias), hepatic dysfunction, renal dysfunction, and fatigue.

AEs (all Grades) were reported in 99.7% of patients in both treatment arms. Most AEs in both treatment arms were Grade 3/4 in severity and were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (95.5% versus 82.5%). AEs (Grade 3/4) reported in ≥ 10% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were thrombocytopenia (57.0% versus 24.9%), diarrhoea (25.5% versus 8.0%), neutropenia (24.1% versus 8.0%), hypokalaemia (19.2% versus 6.4%), fatigue (17.1% versus 8.8%), anaemia (16.5% versus 15.9%), pneumonia (12.6% versus 10.3%), and lymphopenia (12.3% versus 7.4%).

AEs leading to discontinuation of the study drug (PAN or PBO) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (36.2% versus 20.4% (all Grades) and 25.5% versus 13.3% (Grade 3/4), respectively). AEs requiring dose interruption or study drug interruption were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (88.7% versus 75.6% (all Grades) and 77.2% versus 52.0% (Grade 3/4), respectively). In both treatment arms AEs requiring dose interruption or study drug interruption occurred notably more frequently than AEs leading to discontinuation of the study drug. This suggests that the majority of AEs in this study were manageable without discontinuation of the study drug.

The AEs (all Grades) leading to discontinuation of the study drug reported in ≥ 1% of patients in either treatment arm were (PAN+BTZ+Dex versus PBO+BTZ+Dex) diarrhoea (4.5% versus 1.6%), peripheral neuropathy (3.7% versus 1.9%), asthenia (2.9% versus 0%), fatigue (2.9% versus 2.9%), thrombocytopenia (1.6% versus 0.5%), pneumonia (1.3% versus 2.1%). AEs (all Grades) requiring dose adjustment or study drug interruption reported in ≥ 5% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were thrombocytopenia (31.0% versus 10.9%), diarrhoea (26.0% versus 9.0%), fatigue (16.3% versus 7.2%), peripheral neuropathy (12.6% versus 14.3%), pneumonia (10.5% versus 7.7%), neutropenia (10.2% versus 2.4%), anaemia (8.1% versus 4.5%), asthenia (8.1% versus 3.2%), pyrexia (7.9% versus 2.9%), neuralgia (7.9% versus 9.3%), upper respiratory tract infection (6.6% versus 4.2%), vomiting (6.0% versus 1.6%), peripheral sensory neuropathy (5.5% versus 5.3%), and herpes zoster (2.6% versus 5.8%).

On treatment deaths were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (7.9%, n = 30 versus 4.8%, n = 18, respectively). Furthermore, the incidence of on treatment deaths considered to be not related to disease progression was 6.8% (n = 26) in the PAN+BTZ+Dex arm and 3.2% (n = 12) in patients in the PBO+BTZ+Dex arm. Of the 26 deaths in the PBO+BTZ+Dex considered by investigators not to be related to disease progression, 10 (2.6%) were associated with infections (primarily lung) and occurred in association with neutropenia, leukopenia or lymphopenia, 5 (1.3%) were associated with haemorrhage, 3 (0.8%) were associated with myocardial infarction, 2 (0.5%) were associated with acute renal failure, and the remaining 6 were each due to various causes.

Serious adverse events (SAEs) regardless of the relationship with the study drug were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (59.8% versus 41.6% (all Grades) and 56.2% versus 37.4% (Grade 3/4), respectively). SAEs (all Grades) reported in ≥ 5% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were pneumonia (14.7% versus 10.6%), diarrhoea (11.3% versus 2.4%), and thrombocytopenia (7.3% versus 2.1%). SAEs (Grade 3/4) reported in ≥ 2% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were pneumonia (12.3% versus 9.5%), diarrhoea (9.2% versus 2.1%), thrombocytopenia (6.8% versus 2.1%), asthenia (2.9% versus 0.5%), anaemia (2.6% versus 0.5%), vomiting (2.6% versus 0.8%), fatigue (2.6% versus 0.5%), sepsis (2.4% versus 1.6%), septic shock (2.4% versus

0.5%), and orthostatic hypotension (2.4% versus 0.3%). Each of the most commonly reported SAEs (all Grades and Grade 3/4) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm.

Laboratory results for haematological parameters showed markedly higher Grade 3/4 events (newly occurring or worsening from baseline) relating to thrombocytopenia, leukopenia, neutropenia and lymphopenia in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. These results are consistent with the observed AE profiles in the two treatment arms.

Laboratory results for biochemical parameters abnormalities showed a consistent trend towards both higher frequency and greater severity in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. The number of electrolyte disturbances was high in patients in the PAN+BTZ+Dex arm, which probably reflects the high incidence of severe diarrhoea in patients in this arm. Newly occurring or worsening increased serum creatinine levels (any Grade) in the PAN+BTZ+Dex arm were approximately 2 fold higher than in the PBO+BTZ+Dex arm (41.4% versus 22.6%), and the majority of these events in both treatment arms were Grade 1/2 in severity. In the PAN+BTZ+Dex arm versus the PBO+BTZ+Dex arm, newly occurring or worsening increased ALT levels (all Grades) were reported in 31.1% versus 29.2% of patients, respectively, and the corresponding results for AST levels (all Grades) were 30.9% versus 38.4%, ALP (all Grades) 28.8% versus 19.7%, and total bilirubin (all Grades) 20.8% versus 12.8%.

Qualitative electrocardiogram (ECG) abnormalities occurred more frequently in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm (63.5% versus 42.2%). The three abnormalities of note were T wave changes, ST-segment depression, and sinus tachycardia all of which occurred more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. Tachyarrhythmias (CNAEs) were reported notably more commonly in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (12.1% versus 4.8%), and the majority of events were Grade 1/2 in severity. The most frequently occurring tachyarrhythmias (≥ 1%) in the PAN+BTZ+Dex arm versus PBO+BTZ+Dex (respectively) were atrial fibrillation (2.9% versus 1.3%), tachycardia (2.9% versus 1.1%), palpitations (2.6% versus 1.3%) and sinus tachycardia (2.4% versus 0.3%). Ventricular tachycardia was reported in 0.5% of patients in the PAN+BTZ+Dex arm and no patients in the PBO+BTZ+Dex arm.

QTcF prolongation detected by scheduled ECG monitoring, occurred more frequently in patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. However, no patients in the PAN+BTZ+Dex arm reported QTcF increases > 500 ms, while 2 (0.5%) patients in the PBO+BTZ+Dex arm reported QTcF increases > 500 ms. QT prolongation (CNAE) was reported in 10.5% of patients in the PAN+BTZ+Dex arm compared to 6.1% of patients in the PBO+BTZ+Dex arm, but most of these events were syncope (6.0% versus 2.4%, respectively). QT prolongation as an AE was reported in 1.8% of patients in the PAN+BTZ+Dex arm and 1.9% of patients in the PBO+BTZ+Dex arm. The sponsor commented that 30% of patients were reported to have received concomitant medications known to prolong the QTc interval during the study. There have been no reports of torsade de pointes associated with the oral formulation of panobinostat, while one patient treated with the IV formulation on consecutive days experience this life threatening arrhythmia.

First round benefit-risk assessment

First round assessment of benefits

In the pivotal study (Study D2308), the primary efficacy analysis was investigator assessment of PFS using mEMBT criteria. This analysis showed a statistically significant

3.9 month increase in median PFS for patients in the PAN+BTZ+Dex arm (n = 387) compared to patients in the PBO+BTZ+Dex arm (n = 381). The median PFS was 12.0 months (95% CI: 10.3, 12.9 months) in the PAN+BTZ+Dex arm and 8.1 months (95% CI: 7.6, 9.2 months) in the PBO+BTZ+Dex arm: HR = 0.63 (95% CI: 0.52, 0.76); p < 0.0001. The study was powered on an assumption that the difference in the median PFS between the two treatment arms would be 2.7 months.

In the primary analysis of the PFS (disease progression/relapse/death), disease progression was reported more frequently in the PBO+BTZ+Dex arm compared to the PAN+BTZ+Dex arm (60.6% versus 42.4%), while death was reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (5.3% versus 3.7%, respectively) as was relapse (5.2% versus 3.9%).

There are doubts about the validity of the primary PFS analysis due to the high censoring rate of patients in both arms who were not receiving on-going treatment (that is, 'dropouts'). In a PFS sensitivity analysis aimed at assessing the impact on the primary PFS analysis of missing data from patients who 'dropped out', the difference in median PFS between the PAN+BTZ+Dex arm and the PBO+BTZ+Dex arm was 1.8 months (9.46 months and 7.62 months, respectively); HR = 0.71 (95% CI: 0.61, 0.83); p < 0.0001. The observed PFS difference of 1.8 months in the sensitivity analysis (dropout) is considered to be of doubtful clinical significance, and is inconsistent with the PFS difference of 3.9 months from the primary PFS analysis. The results suggest that the missing data from the patients who 'dropped-out' might have biased the results of the primary PFS efficacy analysis towards the PAN+BTZ+Dex arm.

Furthermore, in a sensitivity analysis of PFS based on IRC assessment using mEMBT criteria the difference in median PFS between the PAN+BTZ+Dex arm and the PBO+BTZ+Dex arm was 2.3 months (10.0 months and 7.7 months, respectively); HR = 0.69 (95% CI: 0.58, 0.83); p < 0.0001. The observed PFS difference of 2.3 months is considered to be of doubtful clinical significance, and is inconsistent with the PFS difference of 3.9 months obtained from the primary analysis. In general, centralised IRC assessment of PFS is considered to be a more robust method of evaluation as it is potentially less subject to bias than assessment based on individual site-specific investigator review.

There are no data indicating that treatment with PAN+BTZ+Dex provides an overall survival benefit compared to treatment with PBO+BTZ+Dex. In the interim analysis based on immature data, OS was not statistically significantly different between the two treatment arms (HR = 0.87 (95% CI: 0.69, 1.10); p = 0.2856), with median OS in the PAN+BTZ+Dex and PBO+BTZ+Dex arms being 30.4 months and 33.6 months, respectively. Other key secondary efficacy endpoints assessed by the investigators (protocol specified) showed a numerical advantage for patients in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex (that is, ORR, nCR/CR rate, median TTR, median DOR, median TTP). However, there was no statistically significant difference between the two treatment arms in the ORR based on investigator assessment using mEMBT (60.7% (PAN+BTZ+Dex) versus 54.6% (PBO+BTZ+Dex); p = 0.0873). Patient reported outcomes did not demonstrate a quality of life benefit for patients in the PAN+BTZ+Dex arm compared to patients in the PBO+BTZ+Dex arm.

The limited efficacy data from the two uncontrolled, single arm, supportive studies suggest that treatment with PAN+BTZ+Dex might be associated with a treatment benefit (that is, ORR). However, in the absence of a controlled arm little evidentiary weight can be given to the efficacy results from these two studies.

In the USA, the FDA approved panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with MM who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. The prescribing information states that the indication is approved 'under accelerated approval based on

progression free survival' and that continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials'. The US prescribing information indicates that approval of panobinostat was based on 'efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median or 2 prior therapies as the benefit-risk appeared to be greater in this more heavily treated population than in the overall trial population'.

The sponsor is not seeking registration in the current submission of the indication approved by the FDA. Of note, a pre-specified subgroup analysis of PFS in the pivotal Study D2308 in 198 patients who had received prior treatment with IMiDs and BTZ showed that the HR was 0.53 (95% CI: 0.37, 0.76) in favour of PAN+BTZ+Dex over PBO+BTZ+Dex. The promising results in this heavily pre-treated subgroup of patients should be confirmed by an appropriately designed Phase III controlled study if the sponsor wishes to narrow the indication to this subgroup. There were a number of subgroup analyses of PFS in the pivotal study which consistently favoured the PAN+BTZ+Dex arm over the PBO+BTZ+Dex arm. However, it is considered that all subgroup analyses of PFS in the pivotal study are exploratory rather than confirmatory.

First round assessment of risks

- The risks of treatment with PAN+BTZ+Dex for the proposed indication are considered to be notably greater than the risks of treatment with PBO+BTZ+Dex. The major risks of PAN+BTZ+Dex treatment are myelosuppression (including severe thrombocytopaenia, anaemia, and neutropenia), severe diarrhoea, severe infections including sepsis, fatigue, haemorrhage, cardiac disorders (including ischaemic heart disease and tachyarrhythmias), hepatic dysfunction, and renal dysfunction. The following risks discussed for treatment with PAN+BTZ+Dex are based on the data from the pivotal study (Study D2308), unless otherwise stated.
- There were a total of 381 patients exposed to PAN+BTZ+DEX in the pivotal study (Study D2308). Therefore, based on the 'rule of threes' it is 95% certain that any AE event not reported in this patient population occurs less often than 3 in 351 patients (that is, with a incidence of less than 0.8%).
- It is of particular concern that patients aged ≥ 65 years had an increased risk of AEs associated with PAN+BTZ+Dex compared to patients aged < 65 years (48.1% versus 36.7%, respectively). Furthermore, AEs leading to treatment discontinuation were reported in 45.0% of patients aged ≥ 65 years in the PAN+BTZ+Dex arm compared to 25.6% of patients in the PBO+BTZ+Dex arm, while on treatment deaths were reported in 10.6% and 5.6% of patients, respectively. The poor safety profile of patients aged ≥ 65 years treated with PAN+BTZ+Dex is particularly significant as the average age of patients diagnosed with multiple myeloma in Australia in 2009 was 69.2 years,9 which is older than the mean age of the patients in the pivotal study (62.1 years (standard deviation (SD) = 9.38 years)).
- AEs (all Grades) were reported in 99.7% of all patients in both treatment arms. Most AEs in both treatment arms were Grade 3/4 in severity and were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (95.5% versus 82.5%, respectively). AEs (Grade 3/4) reported in ≥ 10% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were thrombocytopenia (57.0% versus 24.9%), diarrhoea (25.5% versus 8.0%), neutropenia (24.1% versus 8.0%), hypokalaemia (19.2% versus 6.4%), fatigue (17.1% versus 8.8%), anaemia (16.5% versus 15.9%), pneumonia (12.6% versus 10.3%), and lymphopenia (12.3% versus 7.4%). Each of the Grade 3/4 AEs reported in ≥ 10% of patients in either treatment arm occurred more frequently in the PAN+BTZ+Dex arm than in the

PBO+BTZ+Dex arm, with differences of ≥ 10% for thrombocytopaenia, neutropenia, lymphopenia, diarrhoea and hypokalaemia.

- The increased severity of thrombocytopaenia in patients in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm is reflected in the notably higher frequency of patients receiving platelet transfusions in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (33.3% versus 10.3%, respectively). In addition, based on the proportion of patients requiring red blood cell transfusions it can be inferred that anaemia was more severe in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (31.5% versus 21.8%, respectively). Furthermore, the higher incidence of infections and infestations (SOC) categorised as Grade 3/4 AEs in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm (31.2% versus 23.9%, respectively), is likely to be a reflection of the higher incidence of Grade 3/4 neutropenia in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (21.4% versus 8.0%, respectively). In addition, colony stimulating factors (granulocyte and granulocyte-macrophage) were used in 13.1% and 4.2% of patients in the PAN+BTZ+Dex and PBO+BTZ+Dex arms, respectively.
- AEs leading to discontinuation of the study drug (PAN/PBO) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (36.2% versus 20.4% (all Grades), 25.5% versus 13.3% (Grade 3/4)). AEs requiring dose interruption or temporary study drug interruption were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (88.7% versus 75.6% (all Grades) and 77.2% versus 52.0% (Grade 3/4), respectively). In both treatment arms, AEs requiring dose interruption or temporary study drug interruption occurred more frequently than AEs leading to discontinuation of the study drug. This suggests that the majority of AEs were manageable without discontinuation of the study drug.
- AEs (all Grades) leading to discontinuation of the study drug reported in ≥ 1% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex, respectively) were diarrhoea (4.5% versus 1.6%), peripheral neuropathy (3.7% versus 1.9%), asthenia (2.9% versus 0%), fatigue (2.9% versus 2.9%), thrombocytopenia (1.6% versus 0.5%), pneumonia (1.3% versus 2.1%). AEs (all Grades) requiring dose adjustment or temporary study drug interruption reported in ≥ 5% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex, respectively) were thrombocytopenia (31.0% versus 10.9%), diarrhoea (26.0% versus 9.0%), fatigue (16.3% versus 7.2%), peripheral neuropathy (12.6% versus 14.3%), pneumonia (10.5% versus 7.7%), neutropenia (10.2% versus 2.4%), anaemia (8.1% versus 4.5%), asthenia (8.1% versus 3.2%), pyrexia (7.9% versus 2.9%), neuralgia (7.9% versus 9.3%), upper respiratory tract infection (6.6% versus 4.2%), vomiting (6.0% versus 1.6%), peripheral sensory neuropathy (5.5% versus 5.3%), and herpes zoster (2.6% versus 5.8%).
- On treatment deaths were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (7.9%, n = 30 versus 4.8%, n = 18, respectively). Furthermore, the incidence of on treatment deaths considered not to be related to disease progression was 6.8% (n = 26) in the PAN+BTZ+Dex arm and 3.2% (n = 12) in patients in the PBO+BTZ+Dex arm. On treatment deaths considered to be related to the study drug by the investigator were reported in 11 (2.9%) patients in the PAN+BTZ+Dex arm and 7 (2.0%) patients in the PBO+BTZ+Dex arm. Of the 26 deaths in the PAN+BTZ+Dex arm considered to be not related to disease progression, 10 (2.6%) were associated with infections (primarily lung) and occurred in association with neutropenia, leukopenia or lymphopenia, 5 (1.3%) were associated with haemorrhage, 3 (0.8%) were associated with myocardial infarction, 2 (0.5%) were associated with acute renal failure, and the remaining 6 were each due to various causes (1 each for intentional overdose with unknown medicines, intestinal ischaemia, breathing

difficulty of unknown cause, cardiac arrest, pulmonary oedema, cerebrovascular accident (CVA) (lacunar infarction)). Of the 12 deaths in the PBO+BTZ+Dex arm considered to be not related to disease progression, 6 (1.6%) were associated with infections and infestations, 2 (0.5%) with cardiac arrest, 2 (0.5%) with pulmonary failure, and 1 each with pulmonary embolism and intracranial haemorrhage.

- SAEs occurring irrespective of the relationship with the study drug were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (59.8% versus 41.6% (all Grades) and 56.2% versus 37.4% (Grade 3/4) events, respectively). Nearly all SAEs in both treatment arms were Grade 3/4 events. SAEs (Grade 3/4) reported in ≥ 2% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were pneumonia (12.3% versus 9.5%), diarrhoea (9.2% versus 2.1%), thrombocytopenia (6.8% versus 2.1%), asthenia (2.9% versus 0.5%), anaemia (2.6% versus 0.5%), vomiting (2.6% versus 0.8%), fatigue (2.6% versus 0.5%), sepsis (2.4% versus 1.6%), septic shock (2.4% versus 0.5%), and orthostatic hypotension (2.4% versus 0.3%). Each of the most commonly reported SAEs (all Grades and Grade 3/4) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm.
- Haemorrhage was reported notably more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (all Grades, 20.7% versus 11.7%; Grade 3/4, 4.2% versus 2.4%). Haemorrhagic AEs (all Grades) reported in ≥ 1% of patients either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex, respectively) were epistaxis (5.0% versus 4.0%), haematoma (2.9% versus 1.1%), contusion (2.4% versus 2.6%), conjunctival haemorrhage (2.1% versus 0.5%), gastrointestinal haemorrhage (2.1% versus 1.6%), gingival bleeding (1.0% versus 1.1%), haematochezia (1.3% versus 0.5%), and haematuria (1.0% versus 0%). In the PAN+BTZ+Dex arm, all patients with any Grade haemorrhage also reported thrombocytopenia of any Grade within 30 days preceding the haemorrhage event, with 74.7% of patients reporting Grade 3/4 thrombocytopenia. In the pivotal study, 5 (1.3%) patients died due to haemorrhage in the PAN+BTZ+Dex arm compared to 1 (0.3%) patient in the PBO+BTZ+Dex arm.
- Laboratory results for haematological parameters showed markedly higher Grade 3/4 events (newly occurring or worsening from baseline) for thrombocytopenia, leukopenia, neutropenia and lymphopenia in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. These results are consistent with the observed haematological AE profiles in the two treatment arms.
- Laboratory results for abnormal biochemical parameters showed a consistent trend towards higher frequency and greater severity in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. The proportion of patients with electrolyte disturbances was high in the PAN+BTZ+Dex arm, which probably reflects the high incidence of severe diarrhoea in patients in this arm.
- Laboratory abnormalities for newly occurring or worsening increased serum creatinine levels (any Grade) in the PAN+BTZ+Dex arm were approximately 2 fold higher than in the PBO+BTZ+Dex arm (41.4% versus 22.6%), with the majority of these events in both treatment arms being Grade 1/2 in severity. The results suggest an increase in renal dysfunction in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm. However, 'renal and urinary disorders' (SOC) categorised as SAEs Grade 3/4 were reported in a similar proportion of patients in the PAN+BTZ+Dex and PBO+BTZ+Dex arms (3.1%, n = 12 versus 3.4%, n = 13, respectively), with acute renal failure (Grade 3/4) being reported in 1.8% (n = 7) and 1.9% (n = 7) of patients, respectively, and renal failure (Grade 3/4) being reported in 0.8% (n = 3) and 1.1% (n = 4) respectively. There were 2 deaths due to acute renal failure in the PAN+BTZ+Dex arm.

- In the PAN+BTZ+Dex arm versus the PBO+BTZ+Dex arm, laboratory results showed that newly occurring or worsening increased ALT levels (all Grades) were reported in 31.1% versus 29.2% of patients, respectively, and the corresponding results for AST levels (all Grades) were 30.9% versus 38.4%. The incidence of increased ALP (all Grades) levels was higher in patients in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm (28.8% versus 19.7%, respectively), as was the incidence of increased total bilirubin (all Grades) (20.8% versus 12.8%, respectively). The most frequently reported newly occurring liver enzyme abnormalities in the PAN+BTZ+Dex arm versus the PBO+BTZ+Dex arm were ALT or AST > 3 x upper limit of normal (ULN) (6.9% versus 4.8%), ALT or AST > 5 x ULN (2.4% versus 1.6%), ALP > 1.5 x ULN (13.4% versus 8.7%), ALP > 2 x ULN (8.5% versus 4.0%), TBL > 1 x ULN (20.6% versus 12.4%), TBL > 1.5 x ULN (6.6% versus 3.5%), and TBL > 2 x ULN (3.7% versus 0.5%). There was one patient in the PAN+BTZ+Dex arm who met Hy's law criteria for drug induced liver injury (DILI), but the result was confounded by other plausible explanations for the finding. Overall, the results suggest that treatment with PAN+BTZ+Dex is associated with liver dysfunction. However, 'hepato biliary disorders' (SOC) categorised as SAEs (Grade 3/4) were reported infrequently in patients in both the PAN+BTZ+Dex and PBO+BTZ+Dex treatment arms (0.3%, n = 3 versus 0.8%, n = 3, respectively), with one case of hepatic failure being reported in the PAN+BTZ+Dex arm.
- Qualitative ECG abnormalities occurred more frequently in the PAN+BTZ+Dex arm than in PBO+BTZ+Dex arm (63.5% versus 42.2%). In particular, T wave changes, ST-segment depression, and sinus tachycardia all occurred notably more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. Tachyarrhythmias (CNAEs) were reported notably more commonly in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (12.1% versus 4.8%), and the majority of events were Grade 1/2 in severity. The most frequently occurring tachyarrhythmias (≥ 1%) in the PAN+BTZ+Dex arm versus the PBO+BTZ+Dex arm were (respectively) atrial fibrillation (2.9% versus 1.3%), tachycardia (2.9% versus 1.1%), palpitations (2.6% versus 1.3%) and sinus tachycardia (2.4% versus 0.3%). Ventricular tachycardia was reported in 0.5% of patients in the PAN+BTZ+Dex arm and no patients in the PBO+BTZ+Dex arm.
- QTcF prolongation detected by protocol specified ECG monitoring occurred more frequently in patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. However, no patients in the PAN+BTZ+Dex arm reported QTcF increases > 500 ms, while 2 (0.5%) patients in the PBO+BTZ+Dex arm reported QTcF increases > 500 ms. QT prolongation (CNAE) was reported in 10.5% of patients in the PAN+BTZ+Dex arm compared to 6.1% of patients in the PBO+BTZ+Dex arm, but most of these events (identified by broad Standardised MedDRA[29] Query (SMQ) criteria) were syncope (6.0% versus 2.4%, respectively). QT prolongation as an AE was reported in 1.8% of patients in the PAN+BTZ+Dex arm and 1.9% of patients in the PBO+BTZ+Dex arm. The sponsor commented that 30% of patients were reported to have received concomitant medications known to prolong the QTc interval during the study. There have been no reports of torsade de pointes associated with the oral formulation of panobinostat, while one patient treated with the IV formulation at a dose level of 20 mg/m^2/day on two consecutive days experienced this life-threatening arrhythmia (Study A2101).

First round assessment of benefit-risk balance

The benefit-risk balance of PAN+BTZ+Dex, given the proposed usage, is unfavourable. It is considered that the efficacy data for PAN+BTZ+Dex has not unequivocally demonstrated a clinically meaningful PFS benefit compared to PBO+BTZ+Dex, while the safety data for

[29] MedDRA: Medical Dictionary for Regulatory Activities

PAN+BTZ+Dex showed that the risks of treatment with the combination are notably greater than those for PBO+BTZ+Dex. In addition, there are no data showing that treatment with PAN+BTZ+Dex increases overall survival compared to PBO+BTZ+Dex or is associated with an improvement in the quality of life.

First round recommendation regarding authorisation

It is recommended that the application to register panobinostat in combination with bortezomib and dexamethasone for the treatment of the treatment of patients with multiple myeloma, who have received at least 1 prior therapy be rejected. The reasons for this recommendation are as follows:

1. In the pivotal study (Study D2308), treatment with PAN+BTZ+Dex significantly prolonged the median PFS by 3.9 months compared with PBO+BTZ+Dex based on investigator assessment using mEMBT criteria (primary efficacy analysis). However, there are doubts about the validity of the results of this analysis due to the high rate of patient censoring in both treatment arms (46.5% (180/387) in the PAN+BTZ+Dex arm; 31.8% (121/381) in the PBO+BTZ+Dex arm. Of particular concern was the high rate of censoring of non ongoing patients (that is, dropouts) (37.5% (145/387) in the PAN+BTZ+Dex arm and 27.8% (106/381) in the PBO+BTZ+Dex arm). Such high rates of censoring in non ongoing patients raise doubts about the robustness of the primary analysis and the precision of the observed treatment effect.
2. In the pivotal Study D2308, PFS events were disease progression, relapse from CR and death. In the pivotal study (Study D2308), the increased median PFS of 3.9 months observed with PAN+BTZ+DEX compared with PBO+BTZ+Dex is being driven by a difference between the two treatment arms in disease progression (42.4% versus 60.6%, respectively). However, deaths contributed more frequently to PFS events in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex (5.2% versus 3.7%) as did relapse (5.2% versus 3.9%). Therefore, lower rates of disease progression in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm are off-set by worsening rates of death and disease relapse.
3. The results for two key sensitivity PFS analyses for the median difference in the PFS between the two treatment arms were inconsistent with the results for the primary PFS analysis (Study D2308). The difference in median PFS between the two treatment arms was 1.8 months in the 'dropout' sensitivity analysis, 2.3 months in the IRC assessment/mEMBT criteria sensitivity analysis and 3.9 months in the primary analysis (investigator/mEMBT criteria). While with the median PFS comparison for both sensitivity analyses statistically significantly favoured the PAN+BTZ+Dex arm relative to the PBO+BTZ+Dex arm, the difference in median PFS between the two treatment arms was less than 2.7 month for both analyses (that is, the difference used to power the pivotal study). Therefore, the PFS results for the two key sensitivity analyses are considered to be of doubtful clinical significance, given that it can be reasonably inferred from the power calculations that a treatment difference of 2.7 months is the minimum clinically meaningful difference applicable to the two treatment arms in the pivotal study.
4. There were no confirmatory data in the pivotal study (Study D2308) showing that PAN+BTZ+Dex confers an OS benefit compared to PBO+BTZ+Dex in the proposed patient population. The interim OS data were immature and showed no statistically significant difference between the two treatment arms in median OS survival. In addition, treatment with PAN+BTZ+Dex did not improve the quality of life compared with PBO+BTZ+Dex, based on patient reported outcomes.

5. In the pivotal study (Study D2308), the safety profile of the PAN+BTZ+Dex arm was notably inferior to the safety profile of the PBO+BTZ+Dex arm. Furthermore, the risks of treatment with PAN+BTZ+Dex increase with age. AEs leading to treatment discontinuation were reported in 29.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 45.0% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 16.6% and 25.6%, respectively. In addition, on treatment deaths were reported in 5.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 10.6% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 4.1% and 5.6%, respectively. The mean age of diagnosis of MM in patients in Australia based on 2009 data is 69.2 years. Therefore, it is likely that the majority of patients who would be eligible for treatment with PAN+BTZ+Dex in Australia would be older than 69 years. Consequently, on average Australian patients eligible for treatment with PAN+BTZ+Dex are likely to be at a notably greater risk of AEs, treatment discontinuation due to AEs, and on treatment death than the patients in this treatment arm in the pivotal study (mean age of 61.2 years).

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefit

- The benefit of treatment with panobinostat for the amended proposed indication is based on data from a pre-specified subgroup analysis in patients (n = 193) with relapsed and/or refractory MM previously treated with both BTZ and IMiDs. In this subgroup (Subset 1) all patients had been treated with BTZ and IMiD, and in addition 78% (73/94) of patients in the PAN+BTZ+Dex arm had received ≥ 2 lines of prior treatment compared to 75% (74/99) of patients in the PBO+BTZ+Dex arm.
- In the pre-specified subgroup (Subset 1), 94 patients were treated with PAN+BTZ+Dex and 99 patients were treated with PBO+BTZ+Dex. The primary analysis showed that median PFS (investigator assessed) was 10.6 months in the PAN+BTZ+Dex arm and 5.8 months in the PBO+BTZ+Dex arm (that is, difference of 4.8 months), with a HR of 0.52 (95% CI: 0.36, 0.76), nominal p value = 0.0005. The difference in median PFS of 4.8 months between the two treatment arms is considered to be clinically meaningful.
- In Subset 1, the OS was 28.0 months in the PAN+BTZ+Dex arm and 24.7 months in the PBO+BTZ+Dex arm (that is, difference of 3.3 months), with a HR of 0.92 (95% CI: 0.63, 1.35). However, no weight can be given to the trend towards greater OS in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex arm due to
  - the HR being statistically non-significant
  - confounding due to high rates of post treatment new MM therapies in both treatment arms, and
  - cross-over of the survival curves violating the assumption of proportionality for the hazard functions.

- However, death events were similar in the PAN+BTZ+Dex and PBO+BTZ+Dex treatment arms (5.3% (5/94) versus 5.1% (5/99)), suggesting that survival in the PAN+BTZ+Dex arm is at least no worse than in the PBO+BTZ+Dex arm.
- The pre-specified subgroup (Subset 1) included a non, pre-specified subgroup (Subset 2) of more heavily pre-treated patients (n = 147) who had received prior treatment with BTZ and IMiD and ≥ 2 lines of therapy (PAN+BTZ+Dex n = 73, PBO+BTZ+Dex n = 74). In Subset 2, PFS (investigator assessed) was longer in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (12.5 months versus 4.7 months; difference = 7.8 months), with a HR of 0.47 (95% CI: 0.31, 0.72), nominal p-value of 0.0003. The median OS in Subset 2 was 26.1 months in the PAN+BTZ+Dex and and 19.5 months in the PBO+BTZ+Dex (that is, difference of 6.6 months), with a statistically non-significant HR of 0.84 (95% CI: 0.55, 1.28). The sponsor states that the PFS results in Subset 2 support the PFS results in Subset 1.

Second round assessment of risk

- In general, the safety profile of PAN+BTZ+Dex in the subgroup of interest (Subset 1) was consistent with the safety profile of the regimen in the total population. In addition, the safety profiles of PAN+BTZ+Dex in Subsets 1 and 2 were similar. Of note, the risk of on treatment death in patients in the PAN+BTZ+Dex arm was lower in Subset 1 than in the total patient population, while the risk in patients in the PBO+BTZ+Dex arm was similar in the two patient populations. However, in both populations the risk of on treatment death was greater in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (7.9% versus 4.8% (total population) and 6.5% versus 5.1%, (Subset 1)). In Subset 2, the risk of on treatment death was similar in patients in the PAN+BTZ+Dex arm and the PBO+BTZ+Dex arm (6.9% versus 6.8%, respectively).
- Nearly all patients in the PAN+BTZ+Dex in the total population and in Subsets 1 and 2 experienced at least one Grade 3/4 AE (preferred term regardless of relationship to the study drug), and these events occurred approximately 15% to 16% more commonly in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm in the three patient populations. The majority of Grade 3/4 AEs (preferred term) in both treatment arms in all three patient populations were considered to be related to the study drug.
- Clinically notable Grade 3/4 AEs (regardless of relationship to the study drug) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm in Subset 1 (94.6% (87/97) versus 80.8% (80/99)) and Subset 2 (98.6% (71/72) versus 79.5% (58/73)).
- In both subsets, clinically notably Grade 3/4 AEs of greatest concern associated with PAN+BTZ+Dex compared to PBO+BTZ+Dex were thrombocytopenia, leukopenia, diarrhoea and asthenia/fatigue, with all events occurring in ≥ 10% more patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. In Subset 1, the most commonly reported clinically notable Grade 3/4 AEs occurring in ≥ 10% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were thrombocytopenia (66.3% versus 46.5%), leukopenia (39.1% versus 22.2%), diarrhoea (30.4% versus 13.1%), asthenia/fatigue (25.0% versus 12.1%), anaemia (20.7% versus 22.2%), pneumonia (18.5% versus 14.1%), and peripheral neuropathy (15.2% versus 9.1%). In Subset 2, the most commonly reported clinically notable Grade 3/4 AEs occurring in ≥ 10% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were thrombocytopenia (66.7% versus 43.8%), leukopenia (44.4% versus 19.2%), diarrhoea (33.3% versus 15.1%), asthenia/fatigue (26.4% versus 13.7%), anaemia (23.6% versus 23.3%), pneumonia (19.4% versus 16.4%), and peripheral neuropathy (16.7% versus 6.8%).

- Two AEs of particular interest are haemorrhage and sepsis. In Subset 1, Grade 3/4 clinically notable AEs of haemorrhage occurred in a similar proportion of patients in the PAN+BTZ+Dex and PBO+BTZ+Dex arms (3.3% versus 2.0%, respectively) as did Grade 3/4 clinically notable AEs of sepsis (4.3% versus 5.1%, respectively). In Subset 2, Grade 3/4 clinically notable AEs of haemorrhage occurred in a similar proportion of patients in the PAN+BTZ+Dex and PBO+BTZ+Dex arms (2.8% versus 2.7%, respectively), respectively), while Grade 3/4 clinically notable AEs of sepsis occurred less frequently in the PAN+BTZ+Dex arm than in PBO+BTZ+Dex arm (2.8% versus 6.8%, respectively).
- Preferred term SAEs (all Grades and regardless of relationship to the study drug) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm in the total population (59.8% (228/381) versus 41.6% (157/377)), Subset 1 (56.5% (52/92) versus 46.5% (46/99)), and Subset 2 (59.7% (43/72) versus 52.1% (38/73)). In Subset 1, SAEs reported in ≥ 5% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were pneumonia (15.2% versus 12.1%), thrombocytopenia (10.9% versus 6.1%), and diarrhoea (9.8% versus 4.0%). In Subset 2, SAEs reported in ≥ 5% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were pneumonia (13.9% versus 13.7%), thrombocytopenia (6.9% versus 2.7%), and diarrhoea (8.3% versus 5.5%).
- In each of the three patient populations, study drug discontinuation due to AEs was reported more frequently in patients in the PAN+BTZ+Dex treatment arm than in the PBO+BTZ+Dex arm (36.2% versus 20.4% (all patients); 31.5% versus 18.2% (Subset 1); 31.9% versus 17.8% (Subset 2)). Nearly all patients (approximately 90%) in the three patient populations underwent dose adjustments and/or treatment interruptions due to AEs. The results suggest that most AEs associated with PAN+BTZ+Dex can be managed with dose adjustment and/or treatment interruptions rather than treatment discontinuation.
- In both subsets, the most commonly reported AEs resulting in discontinuation of the study drug reported in ≥ 2% of patients in the PAN+BTZ+Dex arm were diarrhoea, asthenia, thrombocytopenia, and pneumonia. In Subset 1, AEs resulting in discontinuing of the study drug reported in ≥ 2% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were diarrhoea (4.2% versus 1.0%), asthenia (4.3% versus 0%), thrombocytopenia (2.2% versus 0%), and pneumonia (2.2% versus 0%). In Subset 2, AEs resulting in discontinuing of the study drug reported in ≥ 2% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were diarrhoea (5.6% versus 1.4%), asthenia (4.2% versus 0%), thrombocytopenia (2.8% versus 0%), and pneumonia (2.8% versus 0%).
- The changes in laboratory parameters (haematology and clinical chemistry) in both treatment arms were similar in both Subset 1 and Subset 2, as were the abnormal QTcF profiles.
- There were no safety analyses in special subgroups in Subsets 1 or 2. However, given the similar safety profiles in patients in both subsets and the overall population it can be reasonably inferred that safety in special subgroups will be similar in the three patient populations. Therefore, the conclusions in the first round clinical evaluation report relating to patients in special subgroups in the total safety population are considered to apply to patients in Subsets 1 and 2.
- The main safety concern in special subgroups relate to the increased toxicity of PAN+BTZ+Dex in elderly patients aged ≥ 65 years compared to patients aged < 65 years. AEs leading to treatment discontinuation were reported in 29.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 45.0% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 16.6% and

25.6%, respectively. In addition, on treatment deaths were reported in 5.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 10.6% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 4.1% and 5.6%, respectively.

- Of particular note, the risks of the following AEs (all Grades) in patients treated with PAN+BTZ+Dex versus PBO+BTZ+Dex significantly increased with age (< 65 versus 65-74 versus 75-84 years): thrombocytopenia (67.9% versus 46.5% versus 77.8% versus 42.4% versus 85.3% versus 39.3%); diarrhoea (63.3% versus 40.1% versus 71.4% versus 45.5% versus 88.2% versus 35.7%); asthenia/fatigue (52.5% versus 35.0% versus 59.5% versus 47.0% versus 76.5% versus 53.6%); anaemia (40.3% versus 35.5% versus 46.9% versus 40.2% versus 64.7% versus 35.7%); and haemorrhage (16.7% versus 13.4% versus 26.2% versus 9.8% versus 26.5% versus 7.1%).
- The sponsor acknowledges the higher risk of toxicity in patients aged ≥ 65 years treated with PAN+BTZ+Dex, and identifies treatment with PAN in these elderly patients as an important risk. The sponsor states that the increased risk could be minimized with individualized assessment of elderly patients prior to treatment to determine an appropriate starting dose of each component of the triplet treatment regimen per recommendations for each drug. In addition, the sponsor states that close monitoring should be instituted with appropriate dose adjustment and prompt supportive care per established guidelines for elderly patients with MM.

Second round assessment of benefit-risk balance

- It is considered that the benefit-risk balance is unfavourable for panobinostat in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received bortezomib and an immunomodulatory agent (that is, the proposed indication). Overall, it is considered that the clinically meaningful benefit of improved PFS with PAN+BTZ+Dex in the proposed patient population is outweighed by the significant risks of treatment with the combination regimen, particularly in patients aged ≥ 65 years.
- The benefits of treatment with PAN+BTZ+Dex in the pre-specified subset analysis submitted to support the indication showed that the median PFS was 10.6 months in the PAN+BTZ+ Dex arm and 5.8 months in the PBO+BTZ+Dex arm (that is, difference of 4.8 months), with a HR of 0.52 (95% CI: 0.36, 0.76), nominal p value = 0.0005. However, there was no evidence from the OS analysis that the PAN+BTZ+Dex treatment regimen improved overall survival in the proposed patient population compared to the PBO+BTZ+Dex control regimen. In addition, on treatment deaths were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (6.5% versus 5.1%, respectively).
- The risk of experiencing clinically notable Grade 3/4 events was greater in patients in the proposed population (Subset 1) treated with PAN+BTZ+Dex than with PBO+BTZ+Dex (94.6% versus 80.8%, respectively). Clinically notably Grade 3/4 AEs of greatest concern associated with PAN+BTZ+Dex were thrombocytopenia, leukopenia, diarrhoea and asthenia/fatigue, with all of these events occurring in ≥ 10% more patients in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm.
- The risk of discontinuing treatment due to AEs was notably greater in patients in the proposed population (Subset 1) treated with PBO+BTZ+Dex than with PBO+BTZ+Dex (31.5% versus 18.2%). The most commonly reported AEs resulting in discontinuation of the study drug in ≥ 2% of patients in the PAN+BTZ+Dex arm (versus the PBO+BTZ+Dex arm) were diarrhoea (4.2% versus 1.0%), asthenia (4.3% versus 0%), thrombocytopenia (2.2% versus 0%), and pneumonia (2.2% versus 0%). AEs resulting in dose adjustment were reported in 90.2% of patients in the PAN+BTZ+Dex arm

compared to 73.7% of patients in the PBO+BTZ+Dex arm in the proposed population (Subset 1), suggesting that the majority of AEs can be managed with dose adjustment and/or interruption rather than treatment discontinuation.

- There are significant risks in elderly patients (aged ≥ 65 years) with MM treated with PAN+BTZ+Dex. There were no specific safety data in the proposed patient population (Subset 1) in patients aged ≥ 65 years. However, it is considered that the safety data in elderly patients from the total patient population are directly relevant to the proposed more heavily pre-treated population (Subset 1). Particular AEs of concern in the elderly population were thrombocytopaenia, diarrhoea, asthenia/fatigue, anaemia, and haemorrhage. Furthermore, AEs leading to treatment discontinuation were reported in 29.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 45.0% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 16.6% and 25.6%, respectively. In addition, on treatment deaths were reported in 5.9% of patients in the PAN+BTZ+Dex arm aged < 65 years and 10.6% of patients aged ≥ 65 years, with the corresponding results for patients in the PBO+BTZ+Dex arm being 4.1% and 5.6%, respectively.

Second round recommendation regarding authorisation

It is recommended that Farydak, in combination with bortezomib and dexamethasone, not be authorised for the treatment of adult patients with multiple myeloma who have received bortezomib and an immunomodulatory agent. The safety and efficacy of Farydak regimen for the proposed indication have not been established in a confirmatory Phase III study. The safety and efficacy data of the Farydak regimen for the proposed indication were limited to a pre-specified subgroup analysis in Study D2308. It is considered that the benefit-risk balance for the subgroup analysis is unfavourable for the reasons discussed above.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted EU-RMP (Version: 1.0, dated 9 April 2014) with an Australian Specific Annex (ASA) Version: 1.0, dated 9 April 2014 for evaluation.[30]

Summary of ongoing safety concerns

The sponsor's summary of ongoing safety concerns are outlined in Table 10 below.

[30] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 10: Summary of ongoing safety concerns

Category	Safety concern
Important identified risks	QTc prolongation Myelosuppression Severe haemorrhage Severe infection Hepatic dysfunction Renal dysfunction Diarrhoea
Important potential risks	Cardiac failure Ischaemic heart disease Tachyarrhythmias Venous thromboembolism Ischaemic colitis Hypothyroidism Reactivation of hepatitis B infection Interaction with strong CYP3A4 inhibitors Interaction with CYP2D6 substrates Interaction with strong CYP3A inducers Interaction with sensitive CYP3A4 substrates Interaction with warfarin Interaction with drugs that may prolong the QT interval
Missing Information	Pregnancy and breastfeeding Patients with cardiac diseases Patients with renal impairment Patients with hepatic impairment Off label use

Proposed pharmacovigilance activities

The sponsor proposes to apply routine pharmacovigilance activities, including the use of targeted questionnaires/checklists for the follow-up of the following adverse events: QTc prolongation, cardiac failure, ischemic heart disease, tachyarrhythmias and venous thromboembolism. The follow-up questionnaires were included as an annex to the EU-RMP.

In addition, the following clinical Study LBH589X2105 (as described in Table 11) to address the missing information of 'Patients with renal impairment' was ongoing at the time of dossier submission but has been completed since.

Table 11: Description of Study LBH589X2105

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
LBH589X2105 (Renal impairment study) A phase I, open-label, multi-center study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function interventional category 3	Potential effect of varying degrees of renal function on the PK and safety of panobinostat	Potential effect of varying degrees of renal function on the safety of panobinostat	Ongoing. PK core phase complete	18-Dec-2013 (Interim report [actual date]) Planned date Q1 2015 (Final report).

Reconciliation of issues outlined in the RMP report

Table 12 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 12: Reconciliation of issues outlined in the first round RMP evaluation report

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluator through the consolidated request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states: 'There were no safety considerations raised by the clinical evaluator that affects the RMP'. A number of issues were raised in the nonclinical and clinical evaluation reports and an assessment of the sponsor's response to these matters was undertaken.	It is reiterated that: · The important potential risk: 'tachyarrhythmia's' be reclassified as an important identified risk. · The important identified risk: 'fatigue/asthenia' be included as a new safety concern. · The safety concern: 'renal dysfunction' be retained as an important identified risk. · The important potential risk: 'degeneration of intestinal mucosa' be included as a new safety concern. · The important potential risk: 'Interaction with P-gp inhibitors or inducers' be included as a new safety concern. Any subsequent changes to the summary of the safety concerns and missing information for

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
		Farydak as specified in the ASA must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved. In addition consideration must be given to proposing appropriate pharmacovigilance and risk minimisation activities for any new ongoing safety concerns, to be reflected accordingly in the revised ASA.
It is brought to the Delegate's attention that the indication approved by the US FDA is a third line indication.	The sponsor states that a sub-group analysis as presented in the US PI is discussed in detail in the response to the CER.	If there is any subsequent change to the indications such detail must be reflected in a revised ASA.
Amendments to the table of ongoing safety concerns: Genotoxicity and effects on fertility have been observed in non-clinical studies as described in section 'nonclinical part of the safety specification'. It is recommended that these two adverse events be added as potential risks. Pharmacovigilance and risk minimisation activities should be assigned to these potential risks as appropriate.	The sponsor has stated that 'Developmental toxicity' and 'Reduced fertility in males' were added as important potential risks in the EU RMP, which will be provided to the TGA when finalised. In addition Carcinogenicity/Secondary Primary Malignancy was added in the EU RMP which will be provided to the TGA when finalised.	This is acceptable. Nevertheless until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.
The sponsor should provide an update as to whether this completed clinical trial LBH589X2105 will lead to any changes in the safety specifications of the RMP.	The sponsor states: 'Based on the results of this study, Novartis considers that the RMP safety specification does not require updating at this time. The final CSR for study LBH589X2105 is available upon request'.	This is acceptable.
It is recommended that the sponsor provides clarification as to whether any confirmatory clinical trials are ongoing, and if so, the pharmacovigilance section of the EU-RMP/ASA should be amended to include	The sponsor states: 'details of planned FDA post-market studies will be included in the next update of the ASA'.	This is acceptable. Nevertheless until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
these trials.		
Given that Farydak is the first HDAC inhibitor to be used for the treatment of multiple myeloma, and very limited post-marketing data is available for this indication, advice will be sought from ACSOM regarding the sufficiency of the proposed pharmacovigilance plan.	The sponsor states: 'Novartis supports the assessment of the Farydak pharmacovigilance plan of the RMP by ACSOM'.	The sponsor should address each issue raised in the ACSOM advice. Any subsequent changes to the pharmacovigilance and/or risk minimisation activities in Australia for Farydak must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved.
It is recommended that the sponsor provides the package insert containing the guidance table for review prior to approval. Furthermore, the sponsor should consider if this represents an additional risk minimisation activity, and should update the risk minimisation plan of the RMP accordingly.	The sponsor states: 'In the updated EU RMP a patient compliance card is included as an additional risk minimisation activity. Novartis Australia proposes to enhance patient compliance through the design of the blister pack. Proposed blister packs have Days 1 to 21 printed on the foil. Capsules are only available at the days corresponding to the proposed posology (that is Days 1, 3, 5, 8, 10, and 12). The blister pack provides a tool for patients/caregivers to remind them of the prescribed medication scheme. The objective of the Australian blister pack foil is the same as the EU patient compliance card, to prevent the occurrence of medication errors due to the complex posology scheme'.	It is unclear as to whether such a blister pack design is also used in the EU in conjunction with a patient compliance card rather than either or. The sponsor should clarify this matter and then identify and justify the differences between the risk minimisation activities in the EU (as detailed in the EU RMP) compared to those proposed for Australia in a revised ASA, as suggested in Section 3: 'Risk Minimisation Plan' of the ASA template (as found on the TGA website as of 4 May 2015).
The ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the	The sponsor states: 'An updated ASA, to be provided with an updated EU RMP, will be revised to include a table with details by safety concern of information included in	This is acceptable. Nevertheless until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
actual content and wording of the EU SmPC and the proposed Australian PI and consumer medicine information (CMI) for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive. In addition to the above described details the sponsor should also provide reference to the US PI, as it is noted that various details which are included in the approved US-PI are not proposed to be included in the Australian PI.	the Australia Product Information and EU SmPC and justification for any differences. Reference to the US PI is also provided within this table'.	
As Farydak is the first deacetylase inhibitor to be used for the treatment of multiple myeloma, and there is very limited market experience in the use of drugs in this class for this indication, and due to its toxicity profile, it is recommended that the sponsor implements a risk-mitigation strategy in Australia, similar to that employed in the US. Details regarding such an activity (materials, communication and distribution plan, target audience, timelines and all other relevant details) employed in Australia should be provided with the sponsor's response.	The sponsor states: 'Novartis agrees with this recommendation and has provided details below on a letter and educational material (Healthcare Professional (HCP) brochure and Patient booklet). The ASA will be updated accordingly to align with the information below and the educational materials adapted for Australia will be included'.	This is acceptable. Nevertheless until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
	In regard to the distribution of educational materials the sponsor states: 'The letter, HCP brochure and patient brochure are proposed to be mailed-out to potential prescribers (Haematologists/ Oncologists) upon private launch in Australia. Patients are expected to be treated by specialist HCP teams (for example Haematologists/ Oncologists, Oncology Nurses and Oncology pharmacists). Therefore, it is proposed prescribing physicians can make the HCP brochure available to other HCPs in their team'.	This proposal would appear to be in conflict with the ACSOM advice, which states that consideration to providing the letter plus factsheet direct to each healthcare provider (prescribers, nurses and pharmacists) as well as suitable information to Australian nursing societies and pharmacy associations, including: · the Clinical Oncology Society of Australia (COSA) the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) · the Cancer Nurses Society of Australia (CNSA) Haematology Society of Australia and New Zealand · the Australian and New Zealand Society of Blood Transfusion and the Australasian Society of Thrombosis and Haemostasis (HAA) · the Society of Hospital Pharmacists of Australia (SHPA) · the Pharmaceutical Society of Australia (PSA). The sponsor should address each issue raised in the ACSOM advice. Any subsequent changes to the pharmacovigilance and/or risk minimisation activities in Australia for Farydak must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved.
	'The HCP letter will include encouragement for prescribing physicians to distribute educational materials to other members of their HCP team at respective treatment centres. Educational materials for patients are to be distributed to via their prescriber'.	

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
	In regard to measuring the effectiveness of the Australian education program, the sponsor states: 'Novartis Australia believes that the results of these assessments are applicable to Australia, as the Australian education programme is based on the US REMS. The REMS prescriber and pharmacist survey has not yet been finalised, but can be provided to the TGA upon request after it has been agreed with the FDA. REMS assessments can also be provided to the TGA upon request'.	Given the apparent differences between the registration details approved in the USA and those proposed in Australia (for example indications), the sponsor's position is not considered acceptable. Consequently the sponsor should provide detail in a revised ASA about how and when the evaluation of the printed educational materials for healthcare providers (prescribers, nurses and pharmacists) will be undertaken in Australia and reported to the TGA before this application is approved.
	In regard to measuring the effectiveness of the Australian education program, the sponsor has made no mention as to how the effectiveness of the Australian education program for patients will be measured.	Consequently the sponsor should provide detail in a revised ASA about how and when the evaluation of the printed educational materials for patients will be undertaken in Australia and reported to the TGA before this application is approved.
Amendments to the PI, including: The data package is primarily based on one phase III trial during which PFS was assessed as the primary end point and OS was assessed as the secondary end point. It is noted that at the time of dossier submission the secondary end point of OS could not be conclusively assessed.	The sponsor has agreed to all the recommendations, except for the specified change. The sponsor appears to decline this recommendation stating that such information is located in the clinical trials section of the PI.	This recommendation to the Delegate remains outstanding.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
Consequently, it is recommended that a statement describing that OS benefit has not been conclusively proven, be included in a prominent fashion in the Australian-PI, preferably in the black box warning.		

New and outstanding recommendations from second round evaluation

Issues in relation to the RMP

The sponsor states: 'An updated EU RMP, and an updated Australian Specific Annex, will be provided to the TGA when available. Currently the EU RMP is still being finalised with EMA'. Until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.

The sponsor was asked to respond to safety considerations raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports, in the context of relevance to the RMP. A number of issues were raised in the nonclinical and clinical evaluation reports and an assessment of the sponsor's response to these matters was undertaken. Consequently it is reiterated that:

The important potential risk: 'tachyarrhythmias' be reclassified as an important identified risk.

- The important identified risk: 'fatigue/asthenia' be included as a new safety concern.
- The safety concern: 'renal dysfunction' be retained as an important identified risk.
- The important potential risk: 'degeneration of intestinal mucosa' be included as a new safety concern.
- The important potential risk: 'Interaction with P-glycoprotein (P-gp) inhibitors or inducers' be included as a new safety concern.

Any subsequent changes to the summary of the safety concerns and missing information for Farydak as specified in the ASA must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved. In addition consideration must be given to proposing appropriate pharmacovigilance and risk minimisation activities for any new ongoing safety concerns, to be reflected accordingly in the revised ASA.

It was brought to the Delegate's attention that the indication approved by the US FDA is a third line indication, as compared to second line therapy proposed for Australia. The sponsor states that a sub-group analysis as presented in the US PI is discussed in detail in the response to the CER. If there is any subsequent change to the indications such detail must be reflected in a revised ASA.

It was recommended that the sponsor provide the package insert containing the guidance table to help patients be compliant with the dosing schedule for review prior to approval. Furthermore, the sponsor was asked to consider if this represents an additional risk minimisation activity, and should update the risk minimisation plan of the RMP accordingly. The sponsor states: 'In the updated EU RMP a patient compliance card is included as an additional risk minimisation activity. The sponsor proposes to enhance

patient compliance through the design of the blister pack. Proposed blister packs have Days 1 to 21 printed on the foil. Capsules are only available at the days corresponding to the proposed posology (that is, Days 1, 3, 5, 8, 10, and 12). The blister pack provides a tool for patients/caregivers to remind them of the prescribed medication scheme. The objective of the Australian blister pack foil is the same as the EU patient compliance card, to prevent the occurrence of medication errors due to the complex posology scheme'. However, it is unclear as to whether such a blister pack design is also used in the EU in conjunction with a patient compliance card rather than either or. The sponsor should clarify this matter and then identify and justify the differences between the risk minimisation activities in the EU (as detailed in the EU RMP) compared to those proposed for Australia in a revised ASA, as suggested in Section 3: 'Risk Minimisation Plan' of the ASA template (as found on the TGA website as of 4 May 2015).

As Farydak is the first deacetylase inhibitor to be used for the treatment of multiple myeloma, and there is very limited market experience in the use of drugs in this class for this indication, and due to its toxicity profile, it was recommended that the sponsor implements a risk-mitigation strategy in Australia, similar to that employed in the US. Details regarding such an activity (materials, communication and distribution plan, target audience, timelines and all other relevant details) employed in Australia should be provided. The sponsor states: 'Novartis agrees with this recommendation and has provided details below on a letter and educational material (Healthcare Professional (HCP) brochure and Patient booklet). The ASA will be updated accordingly to align with the information below and the educational materials adapted for Australia will be included'. However, in regard to the distribution of educational materials the sponsor states:

The letter, HCP brochure and patient brochure are proposed to be mailed-out to potential prescribers (Haematologists/ Oncologists) upon private launch in Australia. Patients are expected to be treated by specialist HCP teams (for example Haematologists/ Oncologists, Oncology Nurses and Oncology pharmacists). Therefore, it is proposed prescribing physicians can make the Healthcare Professional brochure available to other HCPs in their team. The HCP letter will include encouragement for prescribing physicians to distribute educational materials to other members of their HCP team at respective treatment centres. Educational materials for patients are to be distributed to via their prescriber.

This proposal would appear to be in conflict with the ACSOM advice (see below), which states that consideration to providing the letter plus factsheet direct to each healthcare provider (prescribers, nurses and pharmacists) as well as suitable information to Australian nursing societies and pharmacy associations, including:

- the Clinical Oncology Society of Australia (COSA)
- the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG)
- the Cancer Nurses Society of Australia (CNSA)
- Haematology Society of Australia and New Zealand, the Australian and New Zealand Society of Blood Transfusion and the Australasian Society of Thrombosis and Haemostasis (HAA)
- the Society of Hospital Pharmacists of Australia (SHPA)
- the Pharmaceutical Society of Australia (PSA).

In regard to measuring the effectiveness of the Australian education program:

- The sponsor states: '[the sponsor] 'believes that the results of these assessments are applicable to Australia, as the Australian education programme is based on the US REMS. The REMS prescriber and pharmacist survey has not yet been finalised, but can be provided to the TGA upon request after it has been agreed with the FDA. REMS

assessments can also be provided to the TGA upon request'. Given the apparent differences between the registration details approved in the USA and those proposed in Australia (for example indications), the sponsor's position is not considered acceptable. Consequently the sponsor should provide detail in a revised ASA about how and when the evaluation of the printed educational materials for healthcare providers (prescribers, nurses and pharmacists) will be undertaken in Australia and reported to the TGA before this application is approved.

- The sponsor has made no mention as to how the effectiveness of the Australian education program for patients will be measured. Consequently the sponsor should provide detail in a revised ASA about how and when the evaluation of the printed educational materials for patients will be undertaken in Australia and reported to the TGA before this application is approved.

The data package is primarily based on one Phase III trial during which progression free survival (PFS) was assessed as the primary end point and overall survival (OS) was assessed as the secondary end point. It was noted that at the time of dossier submission the secondary end point of OS could not be conclusively assessed. Consequently, it was recommended that a statement describing that overall survival benefit has not been conclusively proven, be included in a prominent fashion in the Australian-PI, preferably in the black box warning. The sponsor appears to decline this recommendation stating that such information is located in the Clinical Trials section of the PI. Consequently this recommendation to the Delegate remains outstanding.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The sponsor should address each issue raised in the ACSOM advice. Any subsequent changes to the pharmacovigilance and/or risk minimisation activities in Australia for Farydak must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved.

The ratified advice regarding Farydak from the 28th meeting of the ACSOM

1. ***Can the committee comment on the adequacy of the proposed pharmacovigilance activities to monitor the risks associated with Farydak? If not considered adequate, can the committee advise which additional activities might be required?***

The pharmacovigilance activities proposed by the sponsor consisted of routine activities and also the provision of clinical trial reports, 'investigation' of adverse events from clinical trials or spontaneously reported and targeted questionnaires/checklists sent to those who report serious adverse events.

The committee noted the limited experience in the use of panobinostat in multiple myeloma patients, who are in general older and have much comorbidity that can add to the complexity of the assessment of adverse events. Experience in the use of panobinostat in combination with bortezomib and dexamethasone is small: pooled patient data included only 21 patients with exposure to panobinostat for greater than 12 months. The committee also noted the extension in median overall survival in the panobinostat group was numerically higher but did not differ statistically from that in the control group, also noting that the interim data are not yet mature with a large proportion of censored patients.

Noting the limitations on the available data, the committee advised that the proposed pharmacovigilance activities were not adequate for a treatment with the toxicity profile of panobinostat and no proven benefit in terms of overall survival. The committee acknowledged the limited treatment options in the target population, alongside the

importance of treatments in any population displaying evidence of appropriate efficacy and safety.

Specific suggestions to improve the pharmacovigilance plan included: that the plan should include a list of current or planned studies with expected reporting dates; formal observational studies to evaluate the large number of potential risks; a patient registry to collect information, with rigorous attention to adverse events and to identify the subgroup of patients in whom the use of panobinostat is most beneficial; development of case report forms and measures of quality of life.

2. Can the committee comment on the adequacy of the proposed risk minimisation activities, in particular for the risks of severe diarrhoea and cardiac toxicities?

Study D2308 had shown that patients receiving panobinostat had double the incidence of adverse events and double the rate of withdrawal of consent to the trial, compared to the control group.

The committee noted that diarrhoea was a very common adverse event (see extract from the European Union (EU) RMP Table 13 below). Thrombocytopenia, fatigue, nausea, neutropenia, decreased appetite, hypokalaemia (sic), vomiting, asthenia and leukopenia were also occurring at higher rates in the treatment group compared to the control group.

Table 13: Adverse events observed in at least ≥ 10% of multiple myeloma patients in the Phase III trial

	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
AEs by preferred term	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Diarrhoea	260 (68.2)	97 (25.5)	157 (41.6)	30 (8.0)
Thrombocytopenia	246 (64.6)	217 (57.0)	154 (40.8)	94 (24.9)

Overall, the committee was concerned about the balance between safety and efficacy, given the small number of patients exposed to panobinostat, limited data and the toxicity of the drug. In this context, the proposed risk minimisation plan of reliance on routine activities was considered insufficient.

The committee identified the need for a greater emphasis on education for health practitioners, including nurses and pharmacists. Some of the REMS communication activities mandated by the US FDA will be readily available to Australian healthcare providers, for example journal articles, displays at scientific meetings and the dedicated website. Many Australian haematologists/oncologists are members of the American Society of Clinical Oncology (ASCO) and/or American Society of Hematology (ASH) and so should receive direct notifications from these professional organisations. However, a number of frontline staff involved with the medication (for example nurses and pharmacists) would not necessarily have access to these materials. Consideration should be given to providing a letter plus factsheet direct to each healthcare provider as well as suitable information to Australian nursing societies and pharmacy associations, including:

- the Clinical Oncology Society of Australia (COSA)
- the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG)
- the Cancer Nurses Society of Australia (CNSA)
- Haematology Society of Australia and New Zealand, the Australian and New Zealand Society of Blood Transfusion and the Australasian Society of Thrombosis and Haemostasis (HAA)

- the Society of Hospital Pharmacists of Australia (SHPA)
- the Pharmaceutical Society of Australia (PSA).

Improvements to the PI were suggested. The risk of ischemic heart disease should be mentioned in the PI. Nine (2%) patients receiving panobinostat developed severe (grade 3/4) ischemic heart disease, compared to one (0.3%) patient in the control group. Given this observation, ischemic heart disease may be more properly described in the safety summary as an important identified risk rather than as an important potential risk.

The committee noted that there was evidence supporting greater prominence of other adverse events in the PI of: ischemic colitis, including that it is unknown if this is reversible upon discontinuation of the drug; cerebral haemorrhage; hypokalaemia, arrhythmia and QTc prolongation, as well as the importance of coherently linking these events with the dehydration and electrolyte disturbances caused by diarrhoea.

Inclusion in the PI of dosing modification details in a tabular format, similar to that included in the US prescribing information, would assist healthcare providers.

Consideration should be given to a boxed warning in the PI, to highlight the fatal and severe toxicities of panobinostat.

Patients could be provided with a wallet card indicating that they are receiving panobinostat and are at risk of haemorrhage, cardiac ischemia, arrhythmia, and diarrhoea with electrolyte disturbances.

The CMI should be improved to be relevant to this patient population. For example, the phrase 'even if you feel well' was misleading for this population of seriously ill patients who are unlikely to ever 'feel well' while receiving this treatment. Medical terminology should be used within a CMI only if it is appropriate (for example the side effect of 'fungal infection (aspergillosis)' was overly technical for patients).

Other

The committee noted that in Study D2308 the progression free survival of the control group (bortezomib and dexamethasone) was 8.1 months, compared to 12.0 months for the panobinostat treatment group. In comparison, Lonial et al.;[31] had recently published a study of patients with relapsed or refractory multiple myeloma that recorded a progression free survival period of 14.9 months for the control group (lenalidomide and dexamethasone) and 19.4 months for the group treated with elotuzumab. Although differences in control group treatments need to be borne in mind, this raised the possibility of the treatment populations, including the control group, in D2308 being atypical in some way. It also suggested additional caution in interpreting the results, given the survival in the treated group in Study D2308.

In general discussion reflecting on the indication approved by the US FDA, it was noted that Australian legislation does not include an 'accelerated approval' pathway comparable to the USA. In Australia, a decision about an application is made based on the available data.

Proposed wording for conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

[31] Lonial S et al 2015 Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *NEJM* 2015; Published Online: doi: 10.1056/NEJMoa1505654

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Multiple myeloma (MM) is characterised by the neoplastic proliferation of clonal plasma cells in the bone marrow and extramedullary sites, which usually produce a monoclonal immunoglobulin. This often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. Other clinical characteristics include hypercalcaemia, renal impairment, anaemia and an increased risk of infections.

Despite the much improved survival outcome since the introduction of novel therapeutic agents including the immunomodulatory drugs (IMiDs) and proteasome inhibitors, multiple myeloma (MM) remains an incurable disease. However, the expansion of effective treatment options over the last two decades, has converted what was once a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long term control, often for 7 years or more. However, almost all patients will relapse after an initial response.

Various definitions for relapsed and refractory disease exist; however, new definitions have recently appeared in the literature, primarily by the International Myeloma Working Group.

- Relapsed Disease: Relapsed myeloma is defined as previously treated myeloma, which after a period of being off-therapy, requires salvage therapy but does not meet criteria for 'primary refractory' or 'relapsed-and-refractory' categories, as outlined below.
- Refractory Disease: Refractory myeloma is defined as disease that is non-responsive while on therapy or progresses within 60 days of last therapy.
- Relapsed and refractory myeloma is defined as relapse of disease in patients who achieve Minimal Response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy.
- Primary refractory myeloma refers to refractory disease in patients who have never achieved an minimal response (MR) with any therapy, and includes 2 sub-categories:
  - Patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression.
  - Primary refractory Progressive Disease (PD).

Treatment options for patients with relapsed or refractory MM include hematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include a risk stratification of myeloma (that is, high, intermediate or standard risk disease), prior treatments used, and the duration of response to these treatments.

For those not eligible for HCT, salvage treatment regimens include those based upon thalidomide, lenalidomide, pomalidomide or bortezomib which are used variously in combination with dexamethasone or cytotoxic agents, or treatment regimens with the alkylating agents, melphalan or cyclophosphamide. Additional options include novel agents available through clinical trial participation.

Panobinostat belongs to a novel class of compounds called deacetylase (HDAC) inhibitors. It inhibits a broad range of HDACs and targets epigenetic changes via gene expression modulation and inhibition of protein metabolism. Panobinostat has been shown to act synergistically with bortezomib through the simultaneous inhibition of the proteasome and aggresome pathways, resulting in cytotoxicity.[1]

Background to the application

The sponsor initially sought registration for a broader population of myeloma patients who had received > 1 prior therapy. However, following the clinical evaluator's unfavourable first round report on the benefit-risk profile in the broader population within the trial, the sponsor sought to restrict the indication to those who had received prior bortezomib and an immunomodulatory agent and provided 2 subgroup analyses in support of this: one prespecified (Subset 1) and a second subset (Subset 2) of more heavily pre-treated patients within that subgroup (not prespecified, but representing a group with very limited remaining treatment options). This usage, too, was considered unfavourable by the clinical evaluator and following receipt of the second round clinical evaluation report, the sponsor restricted the indication further to those more heavily pretreated subgroup (Subset 2) on the grounds that these patients with relapsed and/or refractory myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent, have fewer treatment options and that this is therefore an area of unmet need. In Australia, pomalidomide was approved for the same population in 2014 but otherwise this group of patients has very few approved treatment options other than clinical trial participation if available.

Thus, the focus of this overview is on this final indication for Subset 2 rather than the trial population as a whole for an assessment of efficacy, while the safety data from all patients with myeloma who have received the proposed regimen is considered relevant to inform prescribers and patients of the risks. At the request of the Delegate a stop clock was put in place to allow submission and evaluation of the final survival analysis for the pivotal Study D2308, including a tabulated summary of deaths within 8 months of first dose. Subgroup OS analyses in the patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent were also provided. This was the post authorization efficacy study required by the EMA (see below).

The proposed wording of the indication is identical to that approved by the EMA, and similar to that granted accelerated approval (subject to verification and description of clinical benefit in confirmatory trials) by the FDA.

Overseas regulatory history

The EMA granted marketing authorisation on 11 September 2015 for the following indication:

Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

The condition of registration was submission of the updated overall survival from the pivotal Study D2308 as stated below:

> Description Post-authorisation efficacy study (PAES): The Applicant shall submit the final survival analysis for Study D2308, including a tabulated summary of deaths within 8 months of first dose. Subgroup OS analyses in the patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent shall also be provided. Due date November 2015

These data were provided to the TGA on 3 December 2015.

FDA:

The Oncology Drugs Advisory Committee to the FDA voted 5 to 2 against recommending the accelerated approval of panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with MM who have received at least one prior therapy. In essence, the majority of committee appear to have concluded that the benefits of the panobinostat combination did not outweigh the risks for the proposed patient population.

On February 23, 2015, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the following indication:

Farydak, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The indication was approved under accelerated approval procedures based on progression free survival in a pre-specified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent during the pivotal Phase III trial (PANOMARA-1). The approved indication was more restrictive than that being originally sought. The FDA commented that 'an improvement in survival or disease-related symptoms has not yet been established for Farydak. The company is now required to conduct confirmatory trials to describe and verify the clinical benefit of Farydak' (FDA News Release 23 February 2015).

The following are required to fulfil the post-marketing requirements for the accelerated approval:

Conduct a multicentre, randomized, placebo controlled Phase III trial comparing panobinostat in combination with subcutaneous bortezomib and dexamethasone 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 the interim analysis of the trial described in PMR 2181-1. Eligible patients will have previously treated multiple myeloma, 1 to 3 prior lines of therapy, prior immunomodulatory agent exposure (either thalidomide, lenalidomide, or pomalidomide), and measurable disease. The primary objective is to compare the progression free survival (PFS) in both treatment arms by investigator assessment (Ref: Farydak FDA approval letter).

This study is planned to start late 2017/early 2018 with dose selection based upon the interim analysis of the Phase II study described above. The study design of a phase III will be discussed with FDA once the Phase II data from planned interim analyses becomes available.

Comment: Submission of the CSRs for the above Phase II and III trials (and any other post marketing trials subsequently specified) for evaluation as a Category 1 application are a condition of registration.

In Canada, an application was planned for submission in August 2015.

Quality

The quality evaluator had the following comments: 'One impurity limit is currently being negotiated. Subject to resolution of this issue, registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.'

For the evaluation of the drug substance and drug product, absorption, clinical trial formulations, bioequivalence of strengths aspects please see Section III Quality findings above.

Nonclinical

The nonclinical evaluator had the following comments.

There are no objections on nonclinical grounds to registration of panobinostat for the treatment of patients with myeloma subject to risk minimisation strategies being in place.

For details of the nonclinical summary and conclusions please see Section IV: Nonclinical findings, above.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 12 clinical pharmacology studies including pharmacokinetic and/or pharmacodynamic data.
- 1 population pharmacokinetic study.
- 1 population pharmacokinetic/pharmacodynamic study (exposure/platelet count).
- 1 pivotal Phase III efficacy and safety study.
- 2 supportive, uncontrolled, single arm Phase Ib and Phase II clinical efficacy and safety studies.
- 6 other Phase II clinical efficacy and safety studies assessing various panobinostat dosing regimens for various solid tumour and haematological malignancy indications.
- 4 reports detailing the analytical methods used to measure panobinostat and its metabolites in human plasma and bortezomib in human plasma.
- 14 reports involving human biomaterials aimed at the in vitro identification of enzymes relevant to the hepatic metabolism of panobinostat and protein transporters relevant to potential drug-drug interactions.
- 2 subgroup analyses submitted with the sponsor's response
- Literature references.

Publications:

Moreau P, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011; 12: 431-440.

Bringhen S, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010; 116: 4745-4753.

Launach, J, et al 'Panobinostat for the treatment of multiple myeloma' Clinical Cancer Research September 11, 2015; DOI: 10.1158/1078-0432.CCR-15-0530.

Guidance

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

EMA/CHMP/205/95 Rev 4 Guideline on the evaluation anticancer medicinal products in man[32]

EMA/CPMP/EWP/2330/99 Points to consider on application with1. Meta-analyses; 2. One pivotal study.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for the registration not be approved for the sponsor's first two proposed indications but as the final indication was proposed following completion of the second round clinical evaluation report, this has not been considered specifically by the clinical evaluator. The final OS analysis for the pivotal Study D2308 dated 23 November 2015 and received on 3 December 2015 has been reviewed by Delegate but not by the clinical evaluator.

Paediatric data

The submission did not include paediatric data. This is appropriate given the median age of onset is 70 years for myeloma.

Pharmacokinetics/Pharmacodynamics

Summary of PK data

Due to the genotoxic nature of panobinostat in nonclinical studies and the extensive program prior to use in myeloma, the PK studies were carried out in patients with malignancies other than myeloma. The majority of PK characterisation was done as a single agent, with only limited information in combination with bortezomib and dexamethasone.

Absorption and excretion

Absorption of a single 20 mg dose of panobinostat is rapid (median t_{max} of 2 hours) and almost complete, with at least 87% of the total dose being recovered in urine and faeces and less than 3.5% being excreted in the faeces as unchanged drug. The median recovery in the faeces was 47.8% (range: 44.4%, 77.4%) and median recovery in the urine was 41.3% (range: 28.6%, 51.2%). These were almost entirely metabolites, suggesting oral absorption is nearly complete.

No formal absolute bioavailability studies were conducted, with the value of 28% (95% CI: 25%, 32%) calculated from pooled and pop PK data, suggesting extensive first pass metabolism. The terminal half-life has been estimated to be 37 hours based on the Pop PK studies. The effect of multiple dosing on AUC_{inf}, t ½, Cl/F and Vz/F) cannot be reliably interpreted as the sampling for the PK estimation was done only up to 48 hours after dosing. There was wide inter individual variation (50 to 100%) in exposure (C_{max} and AUC) both across dose levels and after multiple dosing. No data on intra individual variability was available.

Comment: There should be a low threshold for dose reduction where toxicity is observed as it may be due to idiosyncratic differences in metabolism of the drug, hepatic impairment or drug interactions. This issue would have been clarified by intra subject variation PK measurements, and this deficiency has resulted in clinically relevant information being unavailable for prescribers.

[32] During the time of this submission a revision of this Guideline was underway and the new version is EMA/CHMP/205/95 Rev 4

Oral absorption was delayed by food, as was AUC_{inf} especially high fat food and there appeared to lower rates of AEs of nausea and vomiting when taken with food. The clinical evaluator noted that the C_{max}, t_{max} and AUC_{inf} values in a crossover food effect study all lay outside the bioequivalent 0.8 to 1.25 interval; it is possible that the reduction in AEs reflects lower exposure. The PI contains appropriate advice to take panobinostat with food, although this could be strengthened by the actual administration; any reduction in AEs are likely to offset the minor decrease in exposure through likely improved compliance, and fewer dose interruptions or reductions.

The physicochemical data showed that the aqueous solubility of panobinostat was pH dependent, but the sponsor states that the drug would be completely soluble at the maximum proposed dose of 20 mg over the physiological pH range in the upper gastrointestinal tract. This was studied by modelling rather than a clinical study, but given solubility was not affected across the pH range of 1 to 8, no clinical study is deemed necessary.

Distribution

Panobinostat is 89.6% protein bound, not affected by renal or hepatic impairment, and has a large V_d (9464 L), indicating extensive tissue distribution.

Metabolism

Panobinostat is extensively metabolised, with 30 to 47% undergoing CYP-mediated oxidative metabolism, predominantly CYP3A4 (approximately 40% of total clearance) and to a much lesser extent CYP2D6 and CYP2C19. No metabolites have been deemed pharmacologically active in inhibiting histone deacetylation activity.

Thus CYP3A4 inhibitors and inducers may affect the hepatic oxidative clearance of panobinostat, but the magnitude of interactions would be dependent on the contributions of other panobinostat clearance pathways. The PK interaction between panobinostat and ketoconazole (a potent inhibitor of CYP3A4) suggest that the contribution of CYP3A4 to the total human clearance of panobinostat clearance is approximately 40%. The effect of rifampin (a clinical CYP3A inducer) on the clearance of panobinostat (20 mg, single dose) was modelled using the Simcyp time based model to predict the induction effect (Study R0600943-01). It was reported that a 67% reduction in panobinostat AUC is predicted when the drug is administered with rifampicin 600 mg QD, based on simulated results using a steady state model.

Pharmacokinetics in the target population

Dose proportionality

While single dose PK of panobinostat based on the C_{max} and AUC_{inf} were approximately dose proportional over the dose range 10 mg to 30 mg, multiple dose PK of panobinostat based on the C_{max} and $AUC_{(0\text{-}48h)}$ were less than dose proportional over the dose range 10 mg to 30 mg. The inter subject PK of panobinostat are extremely variable with CV% for most PK parameters ranging from 60% to 100%.

Pharmacokinetic interactions

Pharmacokinetic interactions demonstrated in human studies

Hepatic impairment

Those with Child-Pugh classified mild or moderate hepatic impairment, had median panobinostat $AUC_{0\text{-}inf}$ values approximately 51% and 56%, respectively, above, that of the normal group. From the population PK model, mild or moderate hepatic impairment was associated with a 42% or 92% increase respectively. In the hepatic impairment study there were no patients studied with severe hepatic impairment, and once again, the CV% associated with the geometric mean of the AUC_{inf} was large, ranging from 44% to 72%.

Comment: The PI includes the clinical evaluator's recommended lower starting dose (or dose reduction if it develops on treatment to) 15 mg or 10 mg in patients with mild or moderate hepatic impairment, respectively. Patients with severe hepatic impairment should not be treated with panobinostat.

Renal impairment

The study in those with mild moderate or severe renal impairment did not suggest a dose reduction was required.

Other parameters

Age, gender, body surface area did not have a significant impact on the PK for panobinostat to warrant any dose adjustments.

PK interactions

CYP3A4 inhibition by ketoconazole

Co-administration with ketoconazole increased the C_{max} and the AUC_{inf} of panobinostat by 62% and 78%, respectively. The 90% CI for the geometric mean ratio (GMR) of both the C_{max} and the AUC_{inf} for panobinostat were outside the interval of 0.8 to 1.25, suggesting that there is a significant PK DDI between panobinostat and ketoconazole when co-administered. The C_{max} and AUC_{inf} values for panobinostat when co-administered with ketoconazole were highly variable, with the respective CV% being 80% and 52%. The results suggest that the starting dose of panobinostat should be reduced when co-administered with strong CYP3A4 inhibitors.

Comment: Co-administration with strong inhibitors should be avoided, but if clinically indicated, the dose of panobinostat should be reduced. The PI and CMI need to include Seville orange products in the list of foods to be avoided.

CYP3A4 induction by other drugs

No clinical studies were provided to assess the effect of co-administration with a CYP3A4 inducer. A simulation based on in vitro modelling of the effect of rifampicin predicted that the panobinostat AUC would decrease by 67% which would suggest that co-administration with strong inducers should be avoided.

CYP2D6 inhibition

Drug interaction studies with dextromethorphan indicate panobinostat is a weak inhibitor of CYP2D6 (that is, DM AUC increase ≥ 1.25 but < 2 fold for combination DM plus panobinostat compared to DM alone). However, the C_{max} and $AUC_{(0\text{-}48h)}$ values for DM following administration of dextromethorphan in combination with panobinostat were extremely variable (that is, CV 121% for C_{max} and 153% for $AUC_{(0\text{-}48h)}$), which suggests that panobinostat should be administered with caution in combination with drugs which are CYP2D6 substrates. Furthermore, the results suggest that co-administration of panobinostat with sensitive CYP2D6 substrates and CYP2D6 substrates with a narrow therapeutic window should be avoided. The PI contains appropriate information.

Panobinostat was not considered likely to have other significant drug interactions based on the in vitro studies. It was not reported to be likely to have a clinically relevant drug interaction with respect to OATP1B1/3, OAT3, OCT1, or OCT2 inhibition at the proposed dose level.

PK in combination with bortezomib, dexamethasone

In the 12 Japanese patients studied, adding panobinostat to bortezomib increased the AUC of the latter drug. The AUC of panobinostat in this study increased between the first and second cycle, most likely due to accumulation of that drug.

In Study B2207 (dose expansion phase), the AUC of both panobinostat was 20% lower following the addition of dexamethasone, a mild CY3A4 inducer. Both PAN and BTZ are metabolised by CYP3A4 (40% and 25%, respectively). Overall, the addition of Dex to PAN+BTZ combination is unlikely to result in clinically significant reduced exposure to either PAN or BTZ.

In the pivotal Phase III Study D2308, exposure to PAN increased by approximately 67% (C_{max}) and 56% ($AUC_{(0\text{-}48h)}$) following multiple dose treatment with PAN+BTZ+Dex compared to single dose administration of this regimen. The results suggest that PAN accumulates following multiple dosing. In this study, exposure to BTZ in the PAN+BTZ+Dex arm was greater than in the PBO+BTZ+Dex arm ($AUC_{(0\text{-}24h)}$ approximately 32% greater, C_{max} approximately 21% greater). The increased exposure to BTZ in the presence of PAN might be due to competition between the two drugs for binding sites on CYP3A4 (given that the two drugs are metabolised by this enzyme), resulting in decreased metabolism of BTZ.

Delegate Comment:

> These PK parameters are complex due to accumulation, wide CV, and opposing effects of drug interactions. Given these are all part of the regimen, close monitoring for toxicities and reduction in the dose of the panobinostat is recommended in the PI.

Target of CYP3A4 metabolism

No clinical or in vitro study was submitted to examine the effect on CYP3A4, but a model suggests there would be inhibition of the metabolism of other CYP3A4 substrates. This requires confirmation and submission of this study is a condition of registration, should this drug be approved. Of relevance to the proposed usage, the exposure to bortezomib increased with the addition of panobinostat, which may reflect competitive inhibition for the CYP3A4 enzyme.

Pharmacodynamic effects

Population pharmacokinetic modelling of thrombocytopenia, QTc prolongation and exposure-response relationship were presented, largely drawn from the development program for Hodgkin's lymphoma, and reflect different dosing. The clinical evaluator noted the wide inter-individual variation in PK parameters.

Delegate comment:

> There has been a long development program across a range of malignancies, and the dose modification/interruption is described in the PI. A high degree of vigilance is required for this AE given the risk of bleeding and the SAEs observed.

The sponsor indicated in the response to questions that no QTc study was possible in healthy subjects due to the genotoxicity but that ECG monitoring had been carried out and that while QTc prolongation was noted, it was generally mild to moderate, and the risk did not increase over time. The clinical evaluator noted that QTc prolongation is a class effect of HDACi, and therefore caution is warranted, especially if used concomitantly with other medications know to affect the QT interval, or in those with baseline QT prolongation. It is noteworthy that one of the metabolites in the nonclinical studies caused QT prolongation in addition to panobinostat itself.

The exposure response relationship between panobinostat $AUC_{(0\text{-}24h)}$ and efficacy (best overall response) showed a positive relationship for PAN 20 mg + BTZ 1.3 mg/m^2 and suggested a synergistic effect when Dex 20 mg was added to the regimen.

Dose selection

The Phase Ib Study B2207 was a dose finding study for the panobinostat and bortezomib combination, and as dexamethasone was added in the second stage of the study at the investigator's discretion it was not considered in the initial dose selection. The MTD was declared to be PAN 20 mg + BTZ 1.3 mg/m^2, based on 15 evaluable patients in Cohorts III plus VI (without dexamethasone). The key dose limiting toxicity was thrombocytopenia and the dosing schedule of 2 weeks on, 1 week off (similar to that of BTZ) was introduced into the dose expansion phase of in order to manage thrombocytopenia and to allow for accelerated platelet recovery. Other AEs included vomiting, aesthenia, tumour lysis syndrome.

The regimen of 2 weeks on, 1 week off was to allow for recovery of the platelet count.

Delegate comment:

1. the PK studies indicate a lower AUC of panobinostat when dexamethasone is used and this may improve the tolerability of the regimen.
2. Bortezomib was administered intravenously in this study. It is known and recommended that sc administration is better tolerated. The PI does not specify that the intravenous route be used which is appropriate.

Efficacy

Table 14: Study designs and key endpoints taken from Table 1 and 2, summary of clinical efficacy

	Study D2308	Study DUS71	Study B2207 Dose escalation phase	Study B2207 Dose expansion phase
Study design features	Phase III	Phase II	Phase Ib	Phase Ib
	Confirmatory	Proof of concept	Dose escalation	Dose expansion
	Placebo-controlled	Uncontrolled	Uncontrolled	Uncontrolled
Population	Relapsed or relapsed-and-refractory, excluding BTZ-refractory	Relapsed and refractory, selectively including BTZ-refractory	Relapsed or relapsed-and-refractory, including BTZ-refractory	Relapsed or relapsed-and-refractory, including BTZ-refractory
FPFV	21-Dec-2009	22-Jun-2010	18-Oct-2007	N/A
Database-lock / Type of analysis	29-Nov-2013 Final PFS and interim OS analysis	28-Jun-2013 Primary analysis	10-Aug-2011 Primary analysis	10-Aug-2011 Primary analysis
Study status	Ongoing[1]	Ongoing[2]	Completed	Ongoing[3]
Primary efficacy endpoint	PFS based on mEBMT criteria	ORR based on mEBMT criteria	MTD of PAN in combination with BTZ	N/A
Secondary efficacy endpoints	OS (key secondary), ORR, MRR, TTR, DOR, TTP, all based on mEBMT criteria, PRO	Rate of MR or better (≥ MR), TTR; DOR, PFS, TTP, all based on mEBMT criteria, OS, PRO	Preliminary efficacy (ORR based on IMWG criteria)	ORR based on IMWG criteria
Exploratory efficacy endpoints	VGPR and sCR based on updated IMWG criteria	VGPR based on updated IMWG criteria	Rate of minor response based on the updated IMWG criteria	Rate of minor response based on the updated IMWG criteria

Source: SCE (CTD 2.7.3), Table 1-2. DOR: Duration of response, IMWG: International Myeloma Working Group, mEBMT: modified European Group for Blood and Marrow Transplantation, MR: minimal response, MRR: minimal response rate, MTD: maximum tolerable dose; ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PRO: patient reported outcomes, RR: response rate, sCR: stringent complete response, TTP: time to progression, TTR: time to response, VGPR: very good partial response

[1] Study D2308: At the time of the data cut-off on 10 September 2013, 58 patients were being followed for disease progression and 416 patients were being followed for survival.

[2] Study DUS71: At the time of the data cut-off on 04 December 2012, 2 patients were on-going and 21 patients were being followed for survival.

[3] Study B2207: At the time of the data cut-off on 10 August 2011, 8 patients were on-going treatment.

Pivotal study

The pivotal efficacy Study, D2308 (PANORAMA-1) is described in detail in the Attachment 2. Briefly, it was a multinational, multicentre, randomised, double blind, placebo controlled Phase III study of panobinostat (PAN) in combination with intravenous bortezomib (BTZ) and dexamethasone (Dex) in patients with:

- Relapsed MM having received 1 to 3 prior lines of therapy; or
- Patients with relapsed-and-refractory MM who were not refractory to prior therapy with BTZ.

Patients were stratified according to the number of prior lines of therapy (1 versus 2 versus 3) and prior bortezomib use. While no crossover was allowed as part of the study design, there was extensive treatment switching to other options upon progression.

758 patients with a median age of 63 (range: 28 to 84) were enrolled; of these, 126 patients were aged ≥ 65 to < 75 years and 34 patients aged ≥ 75 years.

Delegate comments:

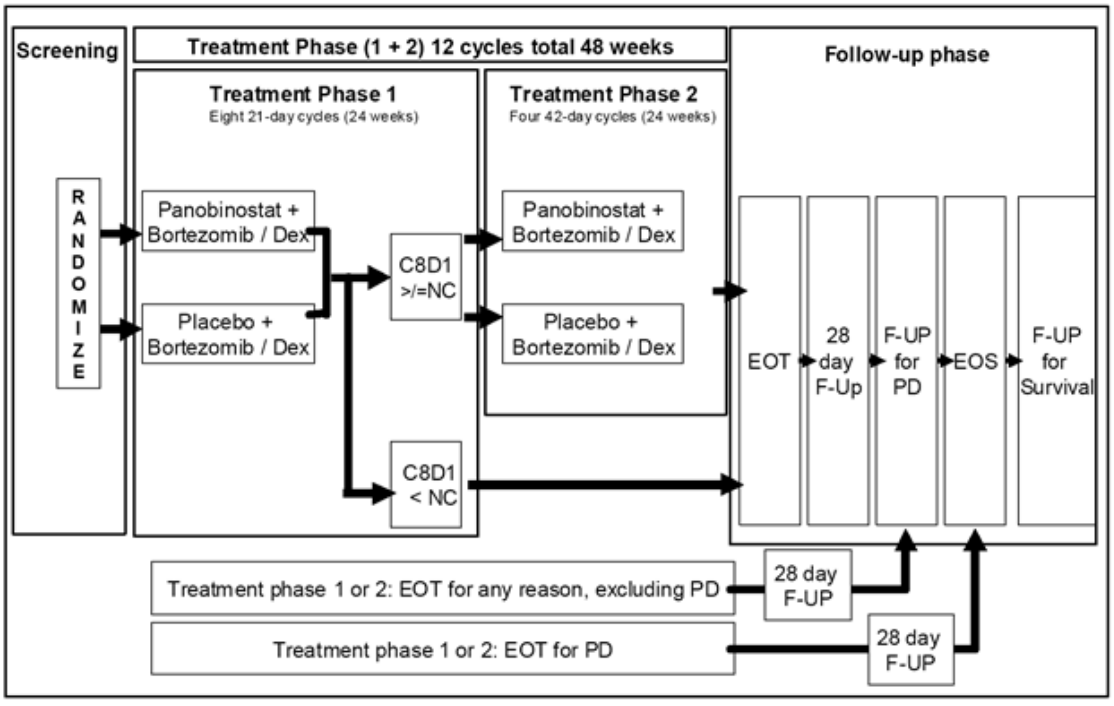
1. The median age is not representative of the general myeloma population in Australia, and is a source of bias limiting generalizability of the findings. The age of those in the trial, and in particular those in the heavily pre-treated subgroup where there was a positive benefit-risk equation, needs to be stated clearly in the PI.
2. There was no stratification by, and there was missing information on cytogenetic risk (13.3% PAN+BTZ+DEX; 18.5% PBO+BTZ+DEX). 20%of the treatment and 10% of the control arm had high risk disease: 17p13 deletion, t(4;14)(t14;16). The limited risk stratification is a deficiency as this might have permitted more accurate identification of individuals likely to benefit, especially given the mechanism of action of panobinostat and that bortezomib therapy has been shown to be effective in those with the intermediate risk profile. This is particularly important in an application where the benefit risk equation is marginal and toxicities significant.
3. Intravenous bortezomib is associated with increased GI and neurological toxicity compared with the now used subcutaneous route (this was established after this trial was designed). Once weekly bortezomib has also been shown to be as efficacious. Post marketing clinical trials to reassess the safety and efficacy of the proposed combination in light of these findings are being conducted as a post marketing requirement (see above and conditions of registration).

The primary objective was to compare progression free survival (PFS) in patients treated with panobinostat (PAN) in combination with bortezomib (BTZ) and dexamethasone (Dex) with patients treated with placebo (PBO) in combination with BTZ and Dex.

The key secondary objective was to compare overall survival (OS) between the two treatment arms.

Additional secondary efficacy, secondary safety, and exploratory objectives are summarised in Section 7.2.1.2 of Attachment 2.

Figure 3: Study D2308; study design and planned conduct



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

Dose: panobinostat 20 mg on Days 1, 3,5,8,10,12 of a 21 day cycle, with bortezomib 1.3 mg/m^2 via injection, dexamethasone 20 mg as per schedule below (Figure 4). Patients should be treated initially for 8 cycles, with those deriving a clinical benefit continuing for a further 8 cycles up to maximum duration of 16 cycles.

Figure 4: Dosing schedule

Cycles 1-8 (3 week cycles)	Week 1 Days							Week 2 Days							Week 3
FARYDAK	1		3		5			8		10		12			Rest
Bortezomib	1			4				8			11				Rest
Dexamethasone	1	2		4	5			8	9		11	12			Rest

Cycles 9-16 (3 week cycles)	Week 1 Days							Week 2 Days							Week 3
FARYDAK	1		3		5			8		10		12			Rest
Bortezomib	1							8							Rest
Dexamethasone	1	2						8	9						Rest

Following the clinical evaluator's recommendation against approval of the sponsor's two initially proposed indications, the sponsor revised the proposed indication to be a subgroup of a pre-specified subgroup that is those who had received at least two prior treatments including bortezomib and IMiDs. This group will be discussed in the overview. The safety data from all patients with myeloma receiving the proposed regimen will be used to inform regarding safety.

The sponsor presented data in the response to questions for two subsets of patients identified in the pivotal Phase III study (Study D2308) in patients with relapsed or relapsed and refractory MM, in order to identify patients who have a better benefit-risk profile compared with the overall study population. It is acknowledged that Subset 2 in particular, have few treatment options. Subset 1 was pre-specified in the statistical analysis plan (SAP) and included patients with prior treatment with BTZ and IMiDs. It consisted of a total of 193 patients, including 94 patients in the PAN+BTZ+DEX arm and 99 patients in the PBO+BTZ+DEX arm, and represented 25% of the total study population of 768 patients. The patients in the subgroup of interest were identified from information relating to use of prior BTZ and IMiDs captured in the electronic case report form (eCRF). The sponsor stated in its post-first round response that its proposal to amend the indication is based on the pre-specified subgroup (that is, Subset 1). However, when this was not supported by the clinical evaluator in the second round report, the sponsor further restricted this to Subset 2 (who form part of Subset 1, were not pre-specified in the SAP and are more heavily pre-treated).

Of the 193 patients in Subset 1, 147 patients referred to as Subset 2 had received both BTZ and an IMiD plus at least 2 lines of prior therapy (n = 73 in PAN+BTZ+Dex arm and n = 74 in PBO+BTZ+Dex arm). Subset 2 included a more heavily pre-treated, non pre-specified, sub-population of Subset 1, and represented 19% of the total study population of 768 patients.

Delegate comment:

> Subset 2 is a non-prespecified subgroup of Subset 1. Therefore, the statistics can only be descriptive. Few conclusions can be drawn about differences between the two groups due to the relatively small numbers of patients in each arm.

The key baseline disease characteristics of the two subsets and the overall study population are summarised below in Table 15. The baseline demographic characteristics

of Subsets 1 and 2 are summarised in Table 16, and Table 17, respectively of the CER and were balanced.

Table 15: Key baseline characteristics, Study D2308, full analysis set

	Subset 1 Prior BTZ and IMID (N=193)		Subset 2 Prior BTZ and IMID ≥ 2 therapy lines (N=147)		Overall study population (N=768)	
	PAN N= 94	PBO N=99	PAN N= 73	PBO N=74	PAN N= 387	PBO N=381
Prior lines median (range)	2 (1, 4)	2 (1, 3)	3 (2,4)	3 (2,3)	1 (1, 4)	1 (1,3)
≥2 lines of prior therapy, %	78	75	100	100	49	48
Prior ASCT, %	72	70	74	64	56	59
Relapsed and refractory, %	49	54	47	58	35	37
Myeloma ISS Stage I, %	43	35	42	34	40	40
Renal impairment, %	63	64	64	65	68	65
Age [years] median (range)	60 (28, 79)	61 (32, 77)	61 (33-79)	61 (32-77)	63 (28, 84)	63 (32, 83)

Table 16: Study D2308; Demographics Subset 1, FAS

	PAN+BTZ+Dex (N=94)	PBO+BTZ+Dex (N=99)	All (N=193)
Age [years]			
n	94	99	193
Mean	59.3	60.6	60.0
SD	10.06	9.46	9.75
Median	59.5	61.0	60.0
Minimum	28	32	28
Maximum	79	77	79
Age category [years] - n (%)			
<65	65 (69.1)	61 (61.6)	126 (65.3)
>=65	29 (30.9)	38 (38.4)	67 (34.7)
Sex - n (%)			
Male	52 (55.3)	49 (49.5)	101 (52.3)
Female	42 (44.7)	50 (50.5)	92 (47.7)
Race - n (%)[1]			
Caucasian	59 (62.8)	63 (63.6)	122 (63.2)
Black	1 (1.1)	5 (5.1)	6 (3.1)
Asian	34 (36.2)	29 (29.3)	63 (32.6)
Native American	0 (0.0)	0 (0.0)	0 (0.0)
Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (2.0)	2 (1.0)
Ethnicity - n (%)			
Hispanic/Latino	5 (5.3)	10 (10.1)	15 (7.8)
Chinese	14 (14.9)	15 (15.2)	29 (15.0)
Indian (Indian subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	1 (1.1)	3 (3.0)	4 (2.1)
Mixed ethnicity	1 (1.1)	3 (3.0)	4 (2.1)
Other	73 (77.7)	68 (68.7)	141 (73.1)
ECOG performance status [2] - n(%)			
0	56 (59.6)	38 (38.4)	94 (48.7)
1	35 (37.2)	53 (53.5)	88 (45.6)
2	3 (3.2)	4 (4.0)	7 (3.6)
>2	0 (0.0)	1 (1.0)	1 (0.5)
Missing	0 (0.0)	3 (3.0)	3 (1.6)
Body Weight [kg]			
n	94	99	193
Mean	72.26	73.07	72.68
SD	17.847	16.764	17.260
Median	72.20	72.00	72.00
Minimum	39.8	42.0	39.8
Maximum	144.0	123.5	144.0
Body Height [cm]			
n	92	98	190
Mean	164.49	164.70	164.60
SD	11.764	10.204	10.958
Median	162.00	163.90	163.00
Minimum	135.0	143.0	135.0
Maximum	193.0	185.0	193.0
Body surface area [m^2]			
n	92	98	190
Mean	1.82	1.84	1.83
SD	0.269	0.259	0.264
Median	1.80	1.80	1.80
Minimum	1.3	1.3	1.3
Maximum	2.7	2.5	2.7

Source: s31 Response, App 1, Table TGA7-4.23
[1] Categories for race and ethnicity displayed in case of >2% for any treatment group. Otherwise, patients are counted in the "other" category
[2] ECOG: 0=Fully active, able to carry out normal activity without restriction 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work; 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3=Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours; 4=Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
The subgroup was based on prior anti-neoplastic therapies collected in eCRF.

Table 17: Study D2308; Demographics Subset 2, FAS

	PAN+BTZ+Dex (N=73)	PBO+BTZ+Dex (N=74)	All (N=147)
Age [years]			
n	73	74	147
Mean	60.3	60.4	60.4
SD	10.34	9.87	10.07
Median	61.0	60.5	61.0
Minimum	33	32	32
Maximum	79	77	79
Age category [years] - n (%)			
<65	46 (63.0)	45 (60.8)	91 (61.9)
>=65	27 (37.0)	29 (39.2)	56 (38.1)
Sex - n (%)			
Male	41 (56.2)	33 (44.6)	74 (50.3)
Female	32 (43.8)	41 (55.4)	73 (49.7)
Race - n (%)[1]			
Caucasian	48 (65.8)	49 (66.2)	97 (66.0)
Black	1 (1.4)	3 (4.1)	4 (2.7)
Asian	24 (32.9)	21 (28.4)	45 (30.6)
Native American	0 (0.0)	0 (0.0)	0 (0.0)
Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.4)	1 (0.7)
Ethnicity - n (%)			
Hispanic/Latino	5 (6.8)	9 (12.2)	14 (9.5)
Chinese	9 (12.3)	10 (13.5)	19 (12.9)
Indian (Indian subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	1 (1.4)	2 (2.7)	3 (2.0)
Mixed ethnicity	1 (1.4)	2 (2.7)	3 (2.0)
Other	57 (78.1)	51 (68.9)	108 (73.5)
ECOG performance status [2] - n(%)			
0	41 (56.2)	26 (35.1)	67 (45.6)
1	30 (41.1)	41 (55.4)	71 (48.3)
2	2 (2.7)	3 (4.1)	5 (3.4)
>2	0 (0.0)	1 (1.4)	1 (0.7)
Missing	0 (0.0)	3 (4.1)	3 (2.0)
Body Weight [kg]			
n	73	74	147
Mean	72.69	73.04	72.87
SD	18.223	16.608	17.370
Median	72.00	72.50	72.00
Minimum	44.0	43.5	43.5
Maximum	144.0	120.0	144.0
Body Height [cm]			
n	71	73	144
Mean	164.23	164.00	164.11
SD	11.690	9.484	10.592
Median	162.00	163.00	163.00
Minimum	135.0	143.0	135.0
Maximum	193.0	185.0	193.0
Body surface area [m^2]			
n	71	73	144
Mean	1.83	1.83	1.83
SD	0.273	0.255	0.263
Median	1.80	1.80	1.80
Minimum	1.3	1.3	1.3
Maximum	2.7	2.5	2.7

Source: s31 Response, App 1, Table TGA7-4.24
[1] Categories for race and ethnicity displayed in case of >2% for any treatment group. Otherwise, patients are counted in the "other" category
[2] ECOG: 0=Fully active, able to carry out normal activity without restriction 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work; 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3=Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours; 4=Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
The subgroup was based on prior anti-neoplastic therapies collected in eCRF.

The baseline characteristics were generally balanced apart from the placebo group in Subsets 2 having more patients who were relapsed and refractory (78% versus 64%) which would favour a treatment effect. The patients in both subsets had more advanced disease than patients in the overall study population, as evidenced by the higher median number of prior lines of therapy, the higher proportion of patients with prior autologous stem cell transplantation (ASCT), and the higher proportion of patients with relapsed and refractory MM. In Subset 2, the median number of prior lines of therapy was 3 in both treatment arms, with a range of from 2 to 4 lines in the PAN+BTZ+Dex arm and 2 to 3 lines in the PBO+BTZ+Dex arm. These patients were younger than in the overall study population, with the median age of patients in the two treatment arms in the two subsets being approximately 2 to 3 years younger than patients in the overall study population.

Delegate comments:

1. The median age of those recruited into this study was already below the median age at diagnosis for myeloma in Australia (69 years), potentially reflecting a bias and an increased ability to tolerate robust treatments. The median age of these more heavily pre-treated patients is 2 to 3 years younger again and that there were no patients over the age of 80; this is highly relevant information when selecting patients who might benefit, and needs to be communicated in the PI to inform prescribers.
2. Common to all patients was prior exposure to bortezomib and IMiDS, hence the proposed indication to restrict usage to such patients. The further restriction to those with ≥ 2 prior treatments identifies a population with few remaining treatment options and an area of unmet need.

The characteristics of prior lines of anti-neoplastic therapy reported in ≥ 20% of patients for single agents, and for combinations of interest are summarised below in Table 18. Combinations include at least 2 drugs, but combinations with any additional 3rd drug are included in the row.

Table 18: Key baseline characteristics Subsets 1 and 2, Study D2308, full analysis set

	Subset 1 (n=193)		Subset 2 (n=147)	
	PAN+BTZ+Dex (n=94)	PBO+BTZ+Dex (n=99)	PAN+BTZ+Dex (n=73)	PBO+BTZ+Dex (n=74)
Number of prior lines of antineoplastic therapy				
Mean ± SD	2.2 ± 0.81	2.2 ± 0.81	2.6 ± 0.52	2.6 ± 0.50
Median (range)	2.0 (1, 4)	2.0 (1, 3)	3.0 (2, 4)	3.0 (2, 3)
Number 0, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number 1, n (%)	21 (22.3%)	25 (25.3%)	0 (0.0%)	0 (0.0%)
Number 2, n (%)	32 (34.0%)	31 (31.3%)	32 (43.8%)	31 (41.9%)
Number 3, n (%)	40 (42.6%)	43 (43.4%)	40 (54.8%)	43 (58.1%)
Number > 3, n (%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)

The most commonly reported last prior lines of antineoplastic medication for drugs with ≥ 10% of patients were bortezomib (alone or in combination), lenalidomide, thalidomide, melphalan, cyclophosphamide and dexamethasone summarised in Table 19).

Table 19: Key baseline characteristics Subsets 1 and 2, study D2308, full analysis set

	Subset 1 (n=193)		Subset 2 (n=147)	
	PAN+BTZ+Dex (n=94)	PBO+BTZ+Dex (n=99)	PAN+BTZ+Dex (n=73)	PBO+BTZ+Dex (n=74)
Bortezomib	68 (72.3%)	63 (63.3%)	47 (64.4%)	38 (51.4%)
Lenalidomide	28 (29.8%)	38 (38.4%)	22 (30.1%)	30 (40.5%)
Thalidomide	39 (41.5%)	28 (28.3%)	24 (32.9%)	9 (12.1%)
Melphalan	35 (37.2%)	35 (35.4%)	20 (27.4%)	12 (16.2%)
Combined BTZ + Len	11 (11.7%)	11 (11.1%)	5 (6.8%)	3 (4.1%)
Combined BTZ + IMiDs	42 (44.7%)	31 (31.3%)	21 (28.8%)	6 (8.1%)
Combined BTZ + Dex	59 (62.8%)	53 (53.5%)	39 (53.4%)	33 (44.6%)
Cyclophosphamide	29 (30.9%)	21 (21.2%)	18 (24.7%)	13 (17.6%)
Dexamethasone	78 (83.0%)	22 (77.8%)	58 (79.5%)	67 (77.0%)
Other	24 (25.5%)	28 (28.3%)	15 (20.5%)	18 (24.3%)

Patient disposition

The disposition of patients was similar in Subset 1 (patients with prior BTZ and IMiD) and Subset 2 (patients with prior BTZ and IMiD and ≥ 2 prior lines of antineoplastic therapy) (see Table 20).

Table 20: Patient disposition Subsets 1 and 2, Study D2308, full analysis set

	Subset 1 (n=193)		Subset 2 (n=147)	
	PAN+BTZ+Dex (n=94)	PBO+BTZ+Dex (n=99)	PAN+BTZ+Dex (n=73)	PBO+BTZ+Dex (n=74)
Treated / Untreated	93 (98.9%) / 1 (1.1%)	98 (99.0%) / 1 (1.0%)	72 (98.6%) / 1 (1.4%)	73 (98.6%) / 1 (1.4%)
Ongoing / Discontinued	0 (0.0) / 93 (98.9%)	0 (0.0%) / 98 (99.0%)	0 (0.0%) / 72 (98.6%)	0 (0.0%) / 73 (98.6%)
Entering treatment phase 2	39 (41.5%)	41 (41.4%)	31 (42.5%)	26 (35.1%)
Primary reason for discontinuation				
Abnormal test procedure	0 (0.0%)	2 (2.0%)	0 (0.0%)	1 (1.4%)
Administrative problems	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.4%)
Adverse event (s)	28 (29.8%)	13 (13.1%)	21 (28.8%)	9 (12.2%)
Death	4 (4.3%)	5 (5.1%)	4 (5.5%)	5 (6.8%)
Disease progression	28 (29.8%)	56 (56.6%)	19 (26.0%)	44 (59.5%)
New cancer therapy	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (1.4%)
Protocol deviation	2 (2.1%)	1 (1.0%)	2 (2.7%)	1 (1.4%)
Withdrawn consent	7 (7.4%)	6 (6.1%)	6 (8.2%)	3 (4.1%)
Treatment completed PP	23 (24.5%)	13 (13.1%)	20 (27.4%)	8 (10.8%)
Post-treatment evaluation - being followed-up				
Yes/No	6 (6.5%) / 87 (93.5%)	2 (2.0%) / 96 (98.0%)	4 (5.6%) / 68 (98.4%)	2 (2.7%) / 71 (97.3%)
Primary reason for study evaluation completion				
Death	6 (6.4%)	5 (5.1%)	5 (6.8%)	5 (6.8%)
Disease progression	59 (62.8%)	76 (76.8%)	46 (63.0%)	56 (75.7%)
New cancer therapy	5 (5.3%)	5 (5.1%)	4 (5.5%)	3 (4.1%)
Withdrawn consent	18 (19.1%)	11 (11.1%)	14 (9.2%)	8 (10.8%)

Delegate comment:

In both subsets, at the cut-off date for the analysis all randomised and treated patients had discontinued treatment. In general, the results were consistent between the subsets, with more patients discontinuing treatment due to disease progression in the control arms; and while more stopped due to adverse events in the experimental arm, this did not appear to be sufficient to offset the numbers experiencing improvement in disease control in the treatment arm. 27.4% of patients in Subset 2 were able to complete the experimental treatment as per protocol compared with 10.8% in the control arm, suggesting that this is a potentially tolerable therapy; this could be further improved with careful patient selection (younger, fitter etcetera) in those who are otherwise coming to the end of their treatment options.

Efficacy results

Primary efficacy endpoint; progression free survival (PFS)

In the Phase III Study D2308, the primary endpoint was PFS as assessed by the investigator. The PFS results for Subset 2 are summarised below in Table 21: the median PFS for the PAN+BTZ+Dex arm and the PBO+BTZ+Dex arm was 7.8 months (HR: 0.47 (95% CI: 0.31, 0.72), nominal p = 0.0003).

Delegate comment: median PFS was improved by 7.8 months in Subset 2 which is statistically and clinically significant in this heavily pre-treated population. There is uncertainty when calculating median PFS for the panobinostat/BTZ/Dex arms when 40% of patients' outcomes are unaccounted for.

The increase in PFS has to be considered in light of the impact of the toxicity and withdrawals as demonstrated by the shorter median duration of treatment. Overall, this indicates that while there appears to be activity against myeloma when panobinostat is used in combination with BTZ and Dex, it is not well tolerated. The FDA have stipulated conduct of trials using bortezomib administered subcutaneously to assess whether this improves tolerability and safety.

Table 21: PFS in Subset 2; Study D2308, FAS

b. Subset 2 - patients with prior BTZ and IMiD and ≥ 2 lines of therapy

	PAN+BTZ+Dex N=73	PBO+BTZ+Dex N=74	HR [95% CI] PAN+BTZ+Dex/ PBO+BTZ+Dex [1]
No. of PFS events - n (%)	44(60.3%)	54(73.0%)	0.47[0.31, 0.72]
- Disease progression	37(50.7%)	49(66.2%)	
- Relapse from CR	3(4.1%)	0(0.0%)	
- Death	4(5.5%)	5(6.8%)	
No. of censored	29(39.7%)	20(27.0%)	
Kaplan-Meier estimates [95% CI] (months) at:			
25th percentile probability	5.32[2.83, 7.26]	3.09[1.87, 3.71]	
75th percentile probability	16.07[13.83,18.96]	7.75[6.24,12.65]	
Median PFS (months) [95% CI]	12.48[7.26,14.03]	4.70[3.71, 6.05]	

Source: s31 Response, Appendix 1, Tables TGA7-4.17 and TGA7-4.18

[1] Hazard ratio (HR) is obtained from the stratified Cox model

[2] 2-sided p-value is obtained from the stratified log rank-test.

The sponsor also provided an analysis of the 'treatment free interval' (TFI), defined as the time from end of treatment until disease progression or relapse. No 95% confidence intervals were provided, and little can be inferred from this. The clinical evaluator noted that this apparent increase TFI in the treatment arm of the whole population was not associated with greater benefits in patient-reported outcomes.

Other efficacy endpoint results

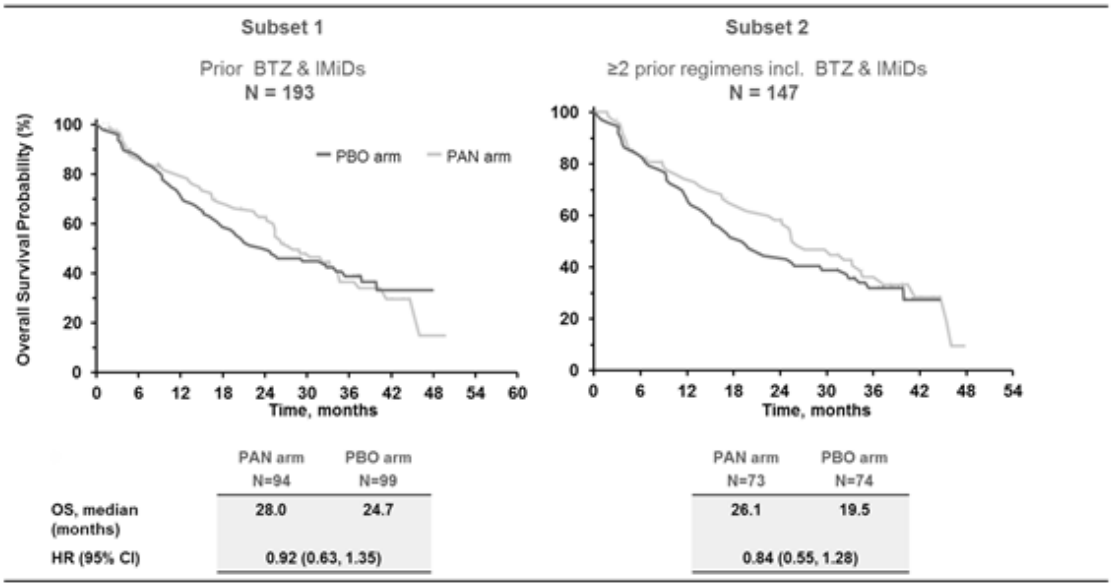
Overall survival second interim analysis

The results of the second interim OS analyses (only 359 out of 415 prespecified events had occurred in the trial as a whole), the median duration of OS in both subsets were not statistically significant. In Subset 1, the number of OS events in the PAN+BTZ+Dex arm was 56.4% (53/94) compared to 58.6% (58/99) in the PBO+BTZ+Dex arm, while in Subset 2 the corresponding values were 58.9% (43/73) and 66.2% (49/74).

Delegate comment:

The significant patient censoring make interpretation of median OS difficult.

Figure 5: Overall survival by treatment group (2nd interim analysis); study group D2308, FAS



	PAN arm N=94	PBO arm N=99	PAN arm N=73	PBO arm N=74
OS, median (months)	28.0	24.7	26.1	19.5
HR (95% CI)	0.92 (0.63, 1.35)		0.84 (0.55, 1.28)	

In an OS landmark analysis by response (CR/nCR versus PR) indicated not surprisingly that OS was improved in those establishing a deeper response, but this could not be confirmed in Subset 2 because of low patient numbers.

Final OS analysis; submitted 3 December 2015 to TGA (reviewed by Delegate)

The final OS analysis (full analysis set (FAS)) was performed when 415 events had occurred (prespecified critical two sided alpha level for statistical significance for 415 OS events set to 0.0475). In the overall population the median OS was not statistically significant (HR 0.94; 95% CI:0.78, 1.14; p = 0.54). A small improvement in median OS was not statistically significant: 25,5 months (95% CI: 19.6, 34.3) versus 19.5(95% CI: 14.1, 32.5).

Delegate comment:

The Delegate does not consider the data provided support the sponsor's conclusions; given the high rate of censoring, outcomes and further treatment for nearly one third of the population are not accounted for (31.5% patients were censored). The reasons for withdrawal amongst those who are censored are not available. The sponsor proposes that treatment switching might explain the non-significant OS results, and notes a higher proportion of patients in the placebo arm commenced further therapies. However, the Delegate notes that fewer patients commenced treatment following cessation of panobinostat than the placebo and it cannot be excluded that these heavily pre-treated patients were no longer as fit for treatment after panobinostat, particularly if discontinued due to an AE. 30.4% did not commence further treatment following discontinuation of panobinostat due to an AE, and the critical comparative information of how many patients in the placebo arm went on to further treatment after an AE is not provided.

In Subset 2, 31.5% of patients were censored from the final analysis. Numerical median OS rates (no HR or p value provided) were similar to the earlier interim analysis in favour of panobinostat: 25.5 months (95%CI: 19.6, 34.3) versus 19.5 months (95%CI: 14.1, 32.5) but little can be concluded from these data given the non-significant OS in the overall population.

Subset 2 Overall Response Rate (ORR); modified EBMT criteria per investigator assessment

The ORR (CR+nCR+PR) was 58.9% (43 out of 73) in the PAN+BTZ+Dex arm and 39.2% (29 out of 74) in the PBO+BTZ+Dex arm; nominal p-value = 0.01703. The nCR+CR rate was 21.9% (16 out of 73) in the PAN+BTZ+Dex arm and 8.1% (6 out of 74) in the PBO+BTZ+Dex arm; nominal p-value = 0.02296.

Delegate comment:

These results, particularly the CR/nCR indicate that panobinostat has activity in myeloma, even when heavily pre-treated.

Other efficacy studies

Study DUS71 was an open label, Phase II, single arm study in patients with relapsed and refractory MM that was refractory to bortezomib treated with the regimen proposed here for registration. All had received at least 2 prior lines of therapy including an IMiD, with a median of 4 prior treatments.

Delegate comment:

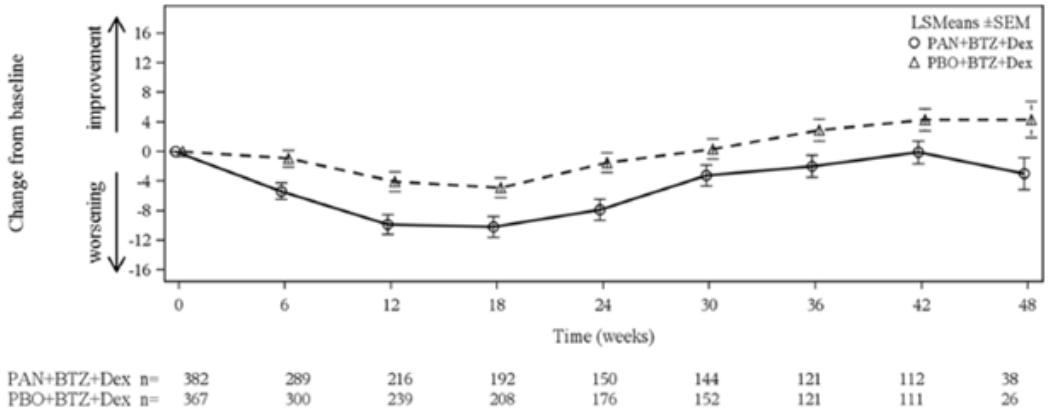
These patients included a very heavily pre-treated subgroup (29% had received 6 to 8 lines prior therapy), and support that there is some modest activity even in this bortezomib refractory population.

Quality of life

Quality of life was assessed using the EORTC QLQ-C30 Global Health Status/ quality of life (QoL) score, where a change from baseline > 5 is defined as a minimally important change.

As can be seen from the graph of the responses for the whole population, the addition of panobinostat to bortezomib and dexamethasone was associated with a clinically meaningful and inferior quality of life (Figure 6). It is not clear whether cessation of treatment restored quality of life. This is particularly important as the treatment duration was shorter for the panobinostat arm, but the PFS longer. It would be important to determine, given the increased frequency of discontinuations in this arm due to adverse events or withdrawal of consent, whether the delay in clinical progression was accompanied by a recovery and/or overall improvement in quality of life. This is all the more important as there is no demonstrable increase in OS.

Figure 6: EORTC QoL score



Safety data

451 patients from the pivotal and supportive studies were exposed to PAN+BTZ+Dex at doses relevant to the proposed indication, including 381 (84.4%) patients from the pivotal

Study D2308, 55 (12.2%) patients from the supportive Study DUS71, and 15 (3.3%) from the dose expansion phase of supportive Study B2207.

StudyD2308

381 patients in the PAN+BTZ+Dex arm and 377 patients in the PBO+BTZ+Dex arm received at least 1 dose of study drug

The median duration of exposure to study treatment was 5.0 months for the PAN+BTZ+Dex arm (152 days (range: 3, 411 days)) compared with 6.1 months for the PBO+BTZ+Dex arm (187 days (range: 3, 443 days)). Consistent with this longer duration of treatment (that is higher AEs and discontinuations in the treatment arm), and the tendency to reduce the panobinostat, the dose intensity was higher in the control arm for each of the drugs than the treatment arm.

Delegate Comment:

This would indicate lower tolerance of the treatment arm but increased disease activity of the treatment arm as there is still an improvement in disease control rate despite a shorter treatment window.

Platelet transfusions were more common in the active treatment arm (33% versus 10.3%)

Adverse events

Adverse events were frequent in both arms but more severe, including deaths, in the treatment arm (see Table 22).

Table 22: Study D2308; Summary of patients with at least one adverse event in any category; safety set

Category of AE	PAN+BTZ+Dex N=381 n (%)	PBO+BTZ+Dex N=377 n (%)
On-treatment death [1]	30 (7.9)	18 (4.8)
Adverse events (AEs)	380 (99.7)	376 (99.7)
AEs of grade 3-4	364 (95.5)	310 (82.2)
AEs of grade 3-4 suspected to be related to study drug	293 (76.9)	193 (51.2)
Serious adverse events	228 (59.8)	157 (41.6)
AEs causing study treatment discontinuation	138 (36.2)	77 (20.4)
AEs causing study treatment discontinuation suspected to be related to study drug	90 (23.6)	45 (11.9)
Clinically notable adverse events (CNAE) [2]	371 (97.4)	357 (94.7)
CNAEs suspected to be related to study drug	316 (82.9)	251 (66.6)
AEs leading to dose adjustment or temporarily dose interruption	338 (88.7)	285 (75.6)
AEs requiring additional therapy	370 (97.1)	347 (92.0)

Source: CSR, Table 12-4. AEs occurring more than 28 days after the discontinuation of study treatment are not summarised. The categories are not mutually exclusive.
[1] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarised.
[2] Clinically notable adverse events (CNAEs) are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.

The most frequently reported AEs (all grades) reported in ≥ 30% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) in descending order of frequency in the 'PAN' arm were diarrhoea (68.2% versus 41.6%), thrombocytopenia (64.6% versus 40.8%), anaemia (41.5% versus 33.4%), fatigue (41.2% versus 29.2%), nausea (36.2% versus 20.7%), peripheral neuropathy (30.7% versus 35.3%), and constipation (26.8% versus 32.6%).

The most frequently reported AEs grade 3/4 reported in ≥ 10% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) in descending order of frequency in the 'PAN' arm were thrombocytopenia (57.0% versus 24.9%), diarrhoea (25.5% versus 8.0%), neutropenia (24.1% versus 8.0%), hypokalaemia (19.2% versus 6.4%), fatigue

(17.1% versus 8.8%), anaemia (16.5% versus 15.9%), pneumonia (12.6% versus 10.3%), and lymphopenia (12.3% versus 7.4%).

Treatment related adverse events (adverse drug reactions)

The majority of AEs reported in the study were suspected to be related to study treatment and were reported more frequently in patients in the PAN+BTZ+Dex arm (90.6% versus 75.3%), as were AEs grade 3/4 (76.9% versus 51.2%).

AEs (all grades)suspected of being related to the study drug (PAN or PBO) reported in ≥ 10% and in descending order of frequency in the 'PAN' arm were diarrhoea (50.9% versus 25.2%), thrombocytopenia (50.7% versus 28.6%), fatigue (31.0% versus 21.8%), anaemia (25.5% versus 15.9%), nausea (23.4% versus 12.2%), neutropenia (21.8% versus 7.2%), vomiting (16.3% versus 6.1%), decreased appetite (15.7% versus 6.9%), peripheral neuropathy (13.9% versus 16.2%), asthenia (13.1% versus 6.4%), constipation (12.1% versus 13.8%), hypokalaemia (10.8% versus 2.9%), leukopaenia (10.5% versus 5.6%), and lymphopaenia (10.0% versus 5.6%). The only AE (all grades) suspected to be related to the study reported in ≥ 10% of patients in either of the two treatment arms and more commonly in the 'PBO' than in the 'PAN' arm were peripheral neuropathy and constipation.

AEs (grade 3/4) reported in ≥ 10% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) and in descending order of frequency in the 'PAN' arm were thrombocytopenia (43.6% versus 17.8%), diarrhoea (18.9% versus 6.1%), neutropenia (16.5% versus 4.8%), and fatigue (14.7% versus 7.7%).

On-treatment deaths

On-treatment deaths were reported more frequently in the PAN+BTZ+Dex arm (7.9%, n = 30 versus 4.8%, n = 18, respectively). Deaths due to disease progression were reported in 4 (1.0%) patients in the PAN+BTZ+Dex arm and 6 (1.6%) patients in the PBO+BTZ+Dex arm, and deaths due to causes other than disease progression were reported in 26 (6.8%) and 12 (3.2%) patients, respectively. On treatment deaths are summarised in Table 23.

Table 23: Study D2308; on treatment deaths by SOC and preferred term; safety set

	PAN+BTZ+Dex N=381 n (%)	PBO+BTZ+Dex N=377 n (%)
Deaths by SOC and PT		
Total number of deaths	30 (7.9)	18 (4.8)
-due to study indication	4 (1.0)	6 (1.6)
-due to other causes	26 (6.8)	12 (3.2)
Cardiac disorders		
Total	4 (1.0)	3 (0.8)
Myocardial infarction	2 (0.5)	0
Cardiac arrest	1 (0.3)	1 (0.3)
Myocardial ischaemia	1 (0.3)	0
Cardio-respiratory arrest	0	1 (0.3)
Cardiopulmonary failure	0	1 (0.3)
Gastrointestinal disorders		
Total	2 (0.5)	0
Gastrointestinal haemorrhage	1 (0.3)	0
Intestinal ischaemia	1 (0.3)	0
General disorders and administration site conditions		
Total	1 (0.3)	0
Death	1 (0.3)	0
Infections and infestations		
Total	7 (1.8)	5 (1.3)
Septic shock	3 (0.8)	0
Bronchopneumonia	1 (0.3)	0
Lung infection	1 (0.3)	0
Pneumonia	1 (0.3)	3 (0.8)
Pulmonary tuberculosis	1 (0.3)	0
Necrotising fasciitis	0	1 (0.3)
Neutropenic sepsis	0	1 (0.3)
Injury, poisoning and procedural complications		
Total	1 (0.3)	0
Toxicity to various agents	1 (0.3)	0
Nervous system disorders		
Total	2 (0.5)	2 (0.5)
Cerebral haemorrhage	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Brain injury	0	1 (0.3)
Haemorrhage intracranial	0	1 (0.3)
Renal and urinary disorders		
Total	2 (0.5)	0
Renal failure acute	2 (0.5)	0
Respiratory, thoracic and mediastinal disorders		
Total	6 (1.6)	2 (0.5)
Respiratory failure	2 (0.5)	0
Acute respiratory failure	1 (0.3)	1 (0.3)
Lung disorder	1 (0.3)	0
Pulmonary haemorrhage	1 (0.3)	0
Pulmonary oedema	1 (0.3)	0
Pulmonary embolism	0	1 (0.3)
Vascular disorders		
Total	1 (0.3)	0
Shock haemorrhagic	1 (0.3)	0

On-treatment deaths occurred up to 28 days after the discontinuation of study treatment.

Deaths defined by preferred term reported in ≥ 2 patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) were:

- septic shock (n = 3, 0.8% versus n = 0)
- myocardial infarction (n = 2, 0.5% versus 0)
- acute renal failure (n = 2, 0.5% versus 0)
- respiratory failure (n = 2, 0.5% versus n = 0),
- pneumonia (n = 1, 0.3% versus n = 3, 0.8%).

Overall, 11 (2.9%) of the 30 the on treatment deaths in patients in the PAN+BTZ+Dex arm were suspected to be related to panobinostat per the investigator, and 7 (2.0%) of the 18 on-treatment deaths in patients in the PBO+BTZ+Dex arm were suspected to be related to placebo per the investigator.

The sponsor undertook a medical review of the 26 on treatment deaths in patients in the PAN+BTZ+Dex arm associated with AEs (regardless of causality) that had not been classified by investigators as being due to disease progression. The medical review attributed some of the deaths to disease progression. The results of this review are outlined below.

Delegate comment:

The attribution of causality is difficult in a population where the majority are elderly, likely to have comorbidities as well an advanced malignancy which predisposes to infection. Nonetheless, it is clear that there was an increased risk of death associated with the treatment. The main treatment related causes of death appear to be cardiac, infection and renal.

Post treatment deaths

Post treatment deaths (that is, deaths occurring more than 28 days after last exposure to the study drug) were common but attribution in this population with progressing disease is difficult.

Deaths within the first 8 months of treatment

The EMA requested this information be provided together with the final OS analysis and this was provided to the TGA on 3 December 2015.

FAS (this information from the whole population is considered important to inform re risks of treatment)

The data presented indicate a greater number of deaths in the treatment arm (48 versus 43) with 28 versus 17 of these occurring while on treatment. Given the median duration of exposure to study treatment was 5.0 months for the PAN+BTZ+Dex arm (152 days (range: 3, 411 days)) compared with 6.1 months for the PBO+BTZ+Dex arm (187 days (range: 3, 443 days)), this higher rate cannot be attributed to a longer exposure period. Indeed, the earlier discontinuation indicates the risk of toxicity.

The risk of death from progression was similar in the overall population (4 in the treatment arm, 5 in the placebo) but on-treatment deaths were higher in the treatment arm once progression had been removed (24 versus 12). This indicates harm from the treatment, which is not offset by benefit in reducing death from progression. When looking at the causes, multiple different terms are used to report similar events; however, a clear pattern emerges: an increase absolute numbers of death due to myocardial toxicity, haemorrhage, infection, renal injury. The reporting term 'death' should be avoided and is an inadequate, uninformative reporting term for a clinical trial.

Delegate comment:

The increase in risk of death related to treatment in the broader, earlier stage population justifies restriction of the indication to those with few remaining treatment

options although the Boxed Warning needs to be strengthened to indicate the 4 adverse events listed currently also mentions that fatalities have occurred.

Subset 2

The on treatment deaths were much smaller in number and equal between the arms (all 5 in each arm, with two due to progressive disease in the placebo arm while all 5 deaths in the panobinostat arm were attributed to 'other' that is potentially related to treatment), consistent with this being a subgroup but generally followed the same pattern (cardiac, haemorrhage, renal failure and infection). The same causes of death as observed in the FAS were seen, with 2 more seen in the panobinostat arm; the numbers in the placebo group indicate that such events are seen with the advanced stage of this disease as well as the age group being treated (although the median age in this group was lower than the median age of onset of myeloma in Australia). In the post treatment phase, 4 fewer deaths were seen in the panobinostat arm due to progressive disease.

Delegate comment:

The currently proposed Boxed Warning in the PI does not adequately capture the risks posed by these adverse events and needs to state these events have been associated with fatal outcomes; this is seen in the increase in deaths in the broader population, mirrored by those in the smaller subset should be communicated clearly in both the PI and CMI.

The introduction section of the Clinical Trials section needs to state that the median age of this subset of patients and that no patients over 80 were treated with panobinostat in this group.

Serious adverse events

SAEs (all grades) reported more commonly in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (59.8% versus 41.6%, respectively) as were SAEs (Grade 3/4) (56.2% versus 41.6%). The most frequently occurring SAEs (all grades) were pneumonia (14.7% versus 10.6%), diarrhoea (11.3% versus 2.4%), and thrombocytopenia (7.3% versus 2.1%).

SAEs (all grades) suspected to be related to the study drug (that is, PAN or PBO) were reported more frequently in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm (34.9% versus 15.1%), as were SAEs (Grade 3/4) suspected to be related to the study drug (31.8% versus 14.3%). SAEs (all grades) suspected to be related to the study drug reported in ≥ 5% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) in descending order of frequency in the 'PAN' arm were pneumonia (8.1% versus 3.4%), diarrhoea (7.9% versus 1.6%) and thrombocytopenia (5.8% versus 1.6%). SAEs (grade 3/4) suspected to be related to the study drug reported in ≥ 5% of patients in either treatment arm (PAN+BTZ+Dex versus PBO+BTZ+Dex) in descending order of frequency in the 'PAN' arm were pneumonia (7.1% versus 3.2%), diarrhoea (5.8% versus 1.3%), thrombocytopenia (5.2% versus 1.6%), vomiting (2.4% versus 0.8%), and fatigue (2.4% versus 0.3%).

Discontinuation due to adverse events

AEs (all grades) leading to discontinuation of the study drug (that is, PAN or PBO) were more in patients in the PAN+BTZ+Dex arm (36.2% versus 20.4%, respectively), with Grade 3/4 25.5%, versus 13.3%. Leading causes of discontinuation (PAN+BTZ+Dex versus PBO+BTZ+Dex) were, diarrhoea (4.5% versus 1.6%), peripheral neuropathy (3.7% versus 1.9%), asthenia (2.9% versus 0%), fatigue (2.9% versus 2.9%), thrombocytopenia (1.6% versus 0.5%), and pneumonia (1.3% versus 2.1%).

Delegate comment:

This would seem to be an underestimate as there were many patients who withdrew consent, which would seem most likely to be related to an adverse event but may not have been captured.

Adverse events of special interest

In the panobinostat development program the following were identified, and the rates in pivotal trial are in brackets (treatment versus control arm):

- *myelosuppression/ thrombocytopenia (63.3% versus 28.1%)
- myelosuppression/leukopaenia (38.6% versus 18.6%)
- *diarrhoea (25.5% versus 8.0%)
- asthenia/fatigue (23.9% versus 11.9%)
- myelosuppression/anaemia (18.6% versus 18.6%)
- peripheral neuropathy (17.6% versus 14.6%)
- infection/sepsis (6.6% versus 3.7%)
- QT prolongation (5.2% versus 2.9%)
- renal dysfunction (5.0% versus 4.5%).

The asterisked risks of these are covered by a boxed warning in the PI and CMI. In addition, this also includes a warning about the risk of cardiac ischaemic events, severe arrhythmias and ECG changes. The remainder of the adverse events are familiar to specialist haematologists and would be monitored routinely and managed accordingly.

Laboratory tests; haematology and clinical laboratory tests

There were extensive new abnormalities which emerged on treatment which require close, regular monitoring; currently this is not adequately covered in the PI as there is no mention of liver function test monitoring; this needs to be added to the Dosage and Administration section (see PI changes). The single case reported to satisfy Hy's Law was attributed to concurrent anti-TB medications.

Electrocardiograph/Cardiovascular

ECG changes were more common in the treatment arm and are clearly discussed in the PI. These included most commonly, tachyarrhythmias, T wave changes, ST segment depression. While there was QTc prolongation reported, it seldom exceeded 60 ms, there were no patients reported with > 500 ms prolongation; the sponsor reports that the risk did not appear to increase with increased exposure. The PI contains appropriate advice to avoid the use with other medicines that might prolong the QT interval and to monitor closely.

There were increased reports in the pivotal trial of cardiac AEs in the treatment arm, many of which were ischaemic, and there were 4 deaths from cardiac causes compared with 3 in the placebo arm. The sponsor notes the increased baseline cardiac comorbidities in the treatment arm and argues against it being established that panobinostat increases cardiac risk. This would appear to be reasonable and should be a focus for routine pharmacovigilance.

Safety in the elderly

This is important given the median age at diagnosis for myeloma is 69. Of note, the median age of all patients enrolled in Study D2308 was 6 years younger than that, and younger again (62) with no patients > 80 years enrolled in subgroup identified where the benefit-risk equation could be considered potentially positive.

Delegate comment:

This may reflect clinician judgment or bias in considering enrolment and likely tolerability but this was also observed in the Phase II study. MM median age of diagnosis is 70, with 37% < 65 years yet this trial had 58% < 65 and median age 62. This raises questions about generalisability of findings especially safety, tolerability for the broader MM population, as the regimen is clearly not as well tolerated in the older population. The submitted data relating to the overall patient population in Study D2308 indicates that the safety profile of PAN+BTZ+Dex is significantly inferior in patients aged ≥ 65 years compared with patients aged < 65 years. This is stated in the PI.

Table 24: Study D2308; Adverse events leading to discontinuation and on treatment death by age

	Study D2308			
	PAN+BTZ+Dex		PBO+BTZ+Dex	
	<65 year N=221	≥ 65 year N=160	<65 year N=217	≥ 65 year N=160
AEs leading to discontinuation	66 (29.9%)	72 (45.0%)	36 (16.6%)	41 (25.6%)
On-treatment death	13 (5.9%)	17 (10.6%)	9 (4.1%)	9 (5.6%)
On-treatment death (non-progressive disease)	12 (5.4%)	14 (8.8%)	6 (2.8%)	6 (3.8%)

Risk-benefit analysis

Benefit risk

The Delegate is in agreement with the clinical evaluator that the benefit-risk for the two indications proposed during the evaluation period was negative, due to the adverse safety profile, and the absence of demonstrated statistically significant overall survival advantage to support the marginal gain in PFS (undermined by the high rate of patient censoring) and to offset the adverse effect on quality of life. Due this unfavourable safety profile, the sponsor identified a prespecified subgroup where a 7.8 month improvement in PFS was clearly demonstrated. The indication was further restricted to the majority within this group who were more heavily pre-treated, and therefore have few remaining options. However, the Delegate considers the patients in the Subset 2 are a group for whom there are currently very limited treatment options; as such, the risks of treatment may be considered acceptable by a fully informed patient given the data demonstrate the potential benefit of an increase in disease control with panobinostat (as described by the PFS and ORR). Registration is therefore considered for this restricted population on the grounds of unmet need. There is no overall survival benefit demonstrated with treatment; the absence of a detrimental effect on quality of life may be a sampling bias, missing the assessment of the large number who withdrew from the study; given the lack of treatment alternatives, this would seem most likely to be due to unacceptability of the treatment. This population had a median age of 57 and there were no patients over the age of 80 in the group. This should be stated in the introduction section of the clinical trials section (of the PI) which identifies this subgroup.

In the data submitted on3 December 2015 (final OS analysis, and report of deaths within the first 8 months of treatment) fatalities were observed while on treatment that could be related to the adverse events identified in the Boxed Warning. This needs to be made clearer: fatalities occurring from diarrhoea, infection and haemorrhage need to be stated clearly, and a separation of the myelosuppression from the thrombocytopenia and clarification of the associated risks and fatalities presented. The PI requires these to ensure prescribers are fully aware of the risks, and of the need for close monitoring, and

the CMI should also reflect these risks, conveyed in appropriate language. A Boxed Warning should be included in the CMI to match that in the PI.

Panobinostat has an unfavourable safety profile, which would be improved somewhat with close monitoring. With the suggested changes, the PI and CMI would inform prescribers and patients respectively, of the risks and benefits of treatment, and it is appropriate that clinicians and such patients to be able to choose whether this is a reasonable treatment option. It is noted that post marketing commitments with the FDA may provide data to support a better posology, and once this study is completed, it should be submitted for evaluation.

Proposed action

The Delegate had no reason to say, at this time, that the application for the following indication should not be approved for the amended indication, restricting prescribing to specialists with expertise in the management of haematological malignancies. The reason for this is to avoid repeat prescriptions for this oral medication being provided to patients without appropriate monitoring and assessment.

> *'Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.*
>
> *Treatment with Farydak should be initiated and monitored by a specialist physician with expertise in managing haematological malignancies.'*

Risk management plan

The Office of Product Review (of the TGA) had not yet received an updated RMP with ASA and at the time of preparing the overview, this was an outstanding issue.

It is considered that the sponsor's response to the TGA questions had not yet adequately addressed all of the issues identified in the RMP evaluation report. A number of recommendations for the RMP were provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the Office of Product Review.

The Delegate considers that renal dysfunction; asthenia/fatigue should be included as an important identified risk in the RMP.

The opinion of the Advisory Committee for the Safety of Medicines (ASCOM) was sought on 10 July 2015.

Data Deficiencies/Limitations

The pivotal study used twice weekly intravenously administered bortezomib, rather than the once weekly dosing, subcutaneous route of administration; the latter has been shown to cause less GI toxicity and peripheral neuropathy, with no apparent loss of efficacy. Accordingly, the FDA have requested a re-assessment of the optimal dosing strategy for panobinostat, and route of administration for the combination of panobinostat, bortezomib and dexamethasone.

Conditions of registration

The following are proposed as conditions of registration:

1. Implementation of the EU-RMP Version EU-RMP (Version: 1.0, dated 9 April 2014) with an Australian Specific Annex (ASA) Version: 1.0, dated 9 April 2014 and any updates as required by the TGA.

2. Any promotional material should include the Boxed Warning in addition to the Indication.
3. Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion.
    a. which was designed to evaluate the potential clinical effects of co-administration of panobinostat and midazolam in a clinical drug interaction study.
    b. The Phase III study (including any interim analyses) as post-marketing requirement for the FDA:
        i. Conduct a multicentre, randomised, placebo controlled Phase III trial comparing panobinostat in combination with subcutaneous bortezomib and dexamethasone 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 the interim analysis of the trial described in PMR 2181-1. 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 is to compare the progression free survival (PFS) in both treatment arms by investigator assessment (Ref: Farydak FDA approval letter).

            This study is planned to start end 2017/early 2018 with dose selection based upon the interim analysis of the Phase II study described above. The study design of a phase III will be discussed with FDA once the Phase II data from planned interim analyses becomes available.

Request for ACPM advice

The advice of the ACPM was not sought as the Delegate had no specific questions to ask, and the prior decisions by the EMA and FDA and analysis of their reports, and with the perspective provided by the SAG-O.

Response from sponsor

In response to the Delegate's Overview dated 22 February 2016, Novartis welcomes the Delegate's recommendation to approve Farydak for:

> *Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.*
>
> *Treatment with Farydak should be initiated and monitored by a specialist physician with expertise in managing haematological malignancies*

The sponsor has carried out the requested changes to the Australian PI including the black box warning discussed with the Delegate

The sponsor accepts the conditions of registration 1, 2 and 3b. As discussed on the 25 February 2016 registration condition 3a (midazolam DDI study) is no longer required based on the updated simulation report DMPK R1400354-1 (submitted to TGA in response to questions). The sponsor understands the RMP request regarding asthenia/fatigue and renal dysfunction was adequately addressed in the response to the second round RMP Evaluation Report/ACSOM.

Advisory Committee Considerations[33]

The Delegate did not refer this application to the Advisory Committee on Prescription Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of (full ARTG name of drug) for (dosage and administration), indicated for:

> *Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.*
>
> *Treatment with Farydak should be initiated and monitored by a specialist physician with expertise in managing haematological malignancies.*

Specific conditions of registration applying to these goods

1. Any promotional material should include the Boxed Warning in addition to the Indication
2. Submission of the following clinical trial(s) as Category 1 submissions for evaluation within 6 months of completion, the planned Phase III study (including any interim analyses) as post-marketing requirement for the FDA:

   Conduct a multicentre, randomized, placebo controlled Phase III trial comparing panobinostat in combination with subcutaneous bortezomib and dexamethasone with subcutaneous bortezomib und dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The panobinostat dose selection will be hosed upon the interim on analysis of the trial described in PMR 2181-1. 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 is to compare the progression free survival (PFS) in both treatment arms by investigators assessment (Ref: Farydak FDA Approval letter).
3. The Farydak RMP (Version 5, dated 3 November 2014, data lock point 20 May 2014) with Australian Specific Annex (Version I, dated 5 November 2015) and any future updates, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Farydak approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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