Panobinostat

LBH589
EU Safety Risk Management Plan

Active substance (INN or common name):	Panobinostat
Product(s) concerned (brand name):	Farydak®
Document status:	Final
Version number:	7.1
Data lock point for this RMP	10-May-2024, LBH589B2207: 10-Aug-2011, LBH589DUS71: 04-Dec-2012, LBH589D2308: 10-Sep-2013, PM exposure: 10-May-2024
Date of final sign off	13-Nov-2024

Rationale for submitting an updated RMP: During the clinical development program and 9 years of intensive post-marketing monitoring, sufficient data was collected to better understand the risks. Sufficient time has passed since drug was the first introduced and relevant stakeholders gained experience with risk minimisation measures. Risks are appropriately managed. Accumulating data shows impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important. No further evaluation is planned as part of the PV plan and no significant new safety information is expected from the routine PV. The European Union (EU) Risk Management Plan (RMP) version 7.0 is prepared in line with GVP Module V rev2.

Summary of significant changes in this RMP: In this RMP, two important identified risks (Severe haemorrhage, Severe infections (including sepsis/pneumonia/reactivation of hepatitis B infection)) and three important potential risks (Developmental toxicity, Carcinogenicity/Second primary malignancy, Medication errors) have been removed in line with the GVP Module V rev2.

In addition to this, post marketing drug exposure information has been updated with the DLP of 10-May-2024 and the incidence and demographics of the population in the authorised indication has been updated.

Part	Major changes compared to RMP v 6.0
Part I	ATC code and chemical class of the agent have been updated.
Part II	**Module SI:** Updated the incidence and demographics of the population in the authorised indication **Module SII:** No major change. **Module SIII:** No change. **Module SIV:** No change. **Module SV:** Updated the section with post marketing exposure information up to 10-May-2024. **Module SVI**: No change. **Module SVII**: Following safety concerns details are removed: • Important identified risks - Severe haemorrhage, Severe infections (including sepsis/pneumonia/reactivation of hepatitis B infection). • Important potential risks - Developmental toxicity, Carcinogenicity/Second primary malignancy, Medication errors. **Module SVIII:** Updated the list of safety concerns as per module SVII
Part III	Updated the section based on the revised list of safety concerns as per module SVIII
Part IV	No change.
Part V	Updated the section based on the revised list of safety concerns as per module SVIII.
Part VI	Updated the section based on the revised list of safety concerns as per module SVIII.
Part VII	Removed targeted follow up checklist for the risks - Severe haemorrhage and Medication errors, removed patient compliance cards as additional risk minimisation measure in Annex 6 and updated Annex 8 with summary of changes.

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 6.0

Approved with procedure: Renewal of the Marketing Authorisation (EMEA/H/C/003725/R/0020)
Date of approval (date of the EC decision): 28.4.2020

QPPV: Darko Krnić

SIGNATURE:

The content of this RMP has been reviewed and approved by the marketing authorization's holder QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under Curve
AV	Atrioventricular
Hb	Hemoglobin
BTZ	Bortezomib
CDS	Core Data Sheet
CI	Confidence Interval
Cmax	Maximum Concentration
CR	Complete response
CrCl	Creatinine Clearance
CTCL	Cutaneous T Cell Lymphoma
CYP	Cytochrome P450
Cys-C	Cystatin-C
DDI	Drug-Drug Interactions
Dex	Dexamethasone
DMD	Defined Monthly Dose
DNA	Deoxyribonucleic Acid
DOR	Duration of response
DVT	Deep Vein Thrombosis
ECAS	European Cancer Anemia Survey
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EU	European union
HDAC	Histone Deacetylases
HDACi	Histone Deacetylase inhibitor
HHV	Human Herpes Virus
HIV	Human Immuno Deficiency Virus
HR	Hazard Ratio
IHD	Ischemic Heart Disease
IMiD	Immunomodulatory Drug
LLN	Lower Limit of Normal
LoQ	List of Questions
MedDRA	Medical Dictionary For Regulatory Activities
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRR	Minimal Response Rate
MTD	Maximum Tolerated Dose

NCI	National Cancer Institute
NCI-CTEP	National cancer Institute Cancer Therapy Evaluation Program
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporters
OS	Overall Survival
PAN	Panobinostat
PASS	Post-authorization Safety Study
PBO	Placebo
PD	Progressive Disease
PFS	Progression-Free Survival
P-gp	Permeability Glycoprotein
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTY	Patient Treatment Years
PV	Pharmacovigilance
QOW	Every Other Week
QW	Every Week
RM	Risk Management
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SEER	Surveillance Epidemiology and End Results
SmPC	Summary of product characteristics
T3	Triiodothyronine
T4	Tetraiodothyronine
TBL	Total bilirubin
TIW	Three Times a Week
TSH	Thyroid Stimulating Hormone
TTP	Time to progression
TTR	Time to treatment response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VTE	Venous thromboembolism

1. Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Panobinostat
Pharmacotherapeutic groups (ATC Code)	L01XH03
Marketing Authorization Holder	pharmaand GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	FARYDAK®
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Other antineoplastic agents, histone deacetylase (HDAC) inhibitors
	Summary of mode of action: Panobinostat inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyse the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Panobinostat shows more cytotoxicity towards tumour cells compared to normal cells.
	Important information about its composition: Panobinostat is a cinnamic acid hydroxamic acid-compound. 2-Hydroxypropanoic acid, compd. with 2(E)-N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide (1:1)
Hyperlink to the Product Information	[Proposed Product Information]
Indication(s) in the EEA	**Current:** 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.
	Proposed: Not applicable
Dosage in the EEA	**Current:** The recommended starting dose of panobinostat is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10 and 12, of a 21-day cycle. Patients should be treated initially for eight cycles. It is recommended that patients with clinical benefit continue the treatment for eight additional cycles. The total duration of treatment is up to 16 cycles (48 weeks). The recommended dose of bortezomib is 1.3 mg/m^2 given as an injection (Cycles 1 to 8: twice weekly, and Cycles 9 to 16: once weekly).

	The recommended dose of dexamethasone is 20 mg taken orally on a full stomach (Cycles 1 to 8: Day 1, 2, 4, 5, 8, 9, 11, 12; and Cycles 9 to 16: Day 1, 2, 8, 9).
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Hard gelatin capsules: 10 mg, 15 mg, 20 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2. Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1. Indication

Multiple myeloma

Multiple myeloma (MM) is a relatively uncommon cancer accounting for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies (SEER 2023, Siegel et al 2024).

Data from the US Surveillance, Epidemiology, and End Results (SEER) registry estimate 36,000 new cases of MM and 13,000 deaths from MM annually in the US. This correlates with an annual incidence of approximately 7 per 100,000 males and females per year (SEER 2023, Siegel et al 2024, Kyle et al 2004). A similar incidence has been reported in Canada, the South Thames area of the United Kingdom, and in Europe in general (Phekoo et al 2004, Sant et al 2010, Smith et al 2011, Tsang et al 2019). Worldwide, there are approximately 180,000 cases and 117,000 deaths per year attributed to MM (GLOBOCAN database).

The true incidence appears to be stable (SEER 2023, Kyle et al 2004, Turesson et al 2010). While some reports have suggested an increase in incidence over time, this likely reflects an increased use of routine laboratory testing, greater awareness of MM, and the enhanced availability and use of medical facilities, especially by older persons. A database from Olmsted County, Minnesota, has documented a stable incidence from the 1940s to the early 21st century (Kyle et al 2003).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and sex distribution – MM is largely a disease of older adults. The median age at diagnosis is 65 to 74 years; only 10 and 2 percent of patients are younger than 50 and 40 years, respectively (Kyle et al 2003, Bladé et al 1998). MM is also slightly more frequent in males than in females (approximately 1.4:1).

Variation with ethnicity – MM occurs in all races and all geographic locations (Cowan et al 2018). The incidence varies by ethnicity; the incidence in African Americans and Black populations is two to three times that in White populations in studies from the United States and United Kingdom (Kyle et al 2003, Waxman et al 2010, Shirley et al 2013, Giaquinto et al 2022). In contrast, the risk is lower in people from Japan and Mexico (Waxman et al 2010, Huang et al 2007). The aetiology of MM is not known, but various potential associations have been reported. Genetic, environmental, and infectious factors have been proposed as risk factors. Family clusters of myeloma have been reported suggesting a genetic predisposition to MM (Greenberg et al 2012). Some studies have reported an association of viral infections, including Human Immunodeficiency Virus (HIV) and hepatitis C, with MM (Becker 2011). Inconsistent results have been noted from studies evaluating diet and obesity with some reporting a decreased risk of myeloma with a high consumption of fruits and vegetables or increasing risk with increasing body weight (Becker 2011, Alexander et al 2007). Various chemical agents, including benzene and other organic solvents, and exposure to radiation have also been associated with MM (Becker 2011). There is some suggestion of an association with autoimmune disease. In a systematic review by McShane et al (2014), an autoimmune disorder was associated with an increased risk of MM (RR 1.13, 95% CI: 1.04, 1.22).

Pernicious anemia was associated with an increased risk of both monoclonal gammopathy of undetermined significance (RR 1.67; 95% CI: 1.21, 2.31) and MM (RR 1.50; 95% CI: 1.25, 1.80).

The main existing treatment options:

Relapsed/refractory disease

By expert consensus, relapsed MM refers to the circumstance where a patient treated to the point of maximal response experiences progressive disease (PD), whereas refractory MM refers to a clinical scenario in which a patient is either unresponsive to current therapy or progresses within 60 days of last treatment. Relapsed and refractory MM describes an individual who previously achieved at least a minimal response, experiences PD, receives salvage therapy, and is either unresponsive to salvage therapy or progresses within 60 days of last treatment. Relapsed and/or refractory patients typically receive salvage therapy until relapse or toxicity and then go onto the next salvage option. However, with each treatment failure and subsequent line of treatment, the clinical benefit typically decreases (Anderson et al 2008).

There are many treatment options for relapsed or refractory multiple myeloma. Most patients experience serial relapse and will be treated with most available agents at some point during their disease course. The choice of therapy at each relapse is informed by prior therapies used, response to these treatments, comorbidities, and disease aggressiveness (Dimopoulos et al 2021).

Treatments approved for multiple myeloma differ by country and patient population (initial treatment of multiple myeloma versus relapsed/refractory multiple myeloma). The treatment options approved in the EU include the following:

- Stem cell transplant (usually autologous but allogeneic is a later-line option)
- Chemotherapeutic agents (melphalan, vincristine, cyclophosphamide, etoposide, bendamustine, doxorubicin);
- Histone deacetylase inhibitors (panobinostat);
- Monoclonal antibodies (daratumumab, isatuximab, elotuzumab);
- Immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide);
- Proteasome inhibitors (bortezomib, ixazomib, carfilzomib);
- Nuclear export inhibitor (selinexor);
- Peptide-drug conjugate (melflufen);
- Antibody-drug conjugate (belantamab mafodotin);
- CAR-T products (idecabtagene vicleucel, ciltacabtagene autoleucel);
- Bispecific antibody (teclistamab, erlanatumab, talquetamab);
- Corticosteroids (dexamethasone, methylprednisone, prednisone).

Natural history of the indicated condition in the population, including mortality and morbidity:

While multiple myeloma (MM) is considered an incurable form of cancer, patient outcomes continue to improve in terms of both the duration and quality of life. With modern treatments, the median overall survival exceeds eight years, and varies from a few months in patients with ultra-high-risk features to more than 15 years in patients with lower risk features. In patients who are eligible for hematopoietic cell transplantation, median overall survival exceeds 12 years with standard risk myeloma and is over 6 years in high-risk myeloma (Joseph et al 2020, Cote et al 2022).

Several adverse events are known to contribute to the morbidity in patients with MM. Kyle et al (2003) reported anemia (hemoglobin [Hb] ≤ 12g/dL) in 73% of 1027 patients with newly diagnosed MM. According to the European Cancer Anemia Survey (ECAS), a large epidemiologic observational survey conducted in centers specializing in cancer care in 24 European countries, 69.2% of MM patients were anemic (Hb <8.0g/dl in 4.6%, Hb 8.0-9.9g/dl in 25.1%, Hb 10.0-11.9 in 39.5%) at the time of enrolment in ECAS (new diagnosis MM with no treatment – 13.3%, new diagnosis with treatment -14.6%, persistent or recurrent disease- 54.7%, remission – 17.4%) (Birgegard et al 2006). During the ECAS, 85.3% of MM patients were anemic at any time.

Infections are a significant cause of morbidity in patients with MM. MM itself as well as comorbidities and treatment-associated organ dysfunction (e.g., renal, respiratory, alimentary mucosal damage, multisystem-myeloma-associated deposition diseases) increase the risk of infection. Age-related decline in the physiological reserve of various organs and multiple relapses and salvage therapies resulting in cumulative immunosuppression may also contribute to a higher risk of infection (Nucci and Anaissie 2009). In a large population-based study in Sweden with data on over 9000 MM patients and over 30000 controls (matched on age, sex, and county), Blimark et al (2015) reported that MM patients had a 7-fold (hazard ratio (HR) = 7.1; 95% CI: 6.8, 7.4) risk of developing a bacterial infection and 10-fold increase in viral infections (HR = 10.0; 8.9–11.4) as compared to controls. The risk of bacterial and viral infection was highest during the first year after diagnosis; the risk was 11-fold (95% CI: 10.4, 12.7) higher for bacterial infection and 18-fold (HR=17.6, 95% CI: 13.1, 23.8) higher for viral infection compared to controls during the first year after diagnosis.

Bone pain occurs in about 60% of patients with MM at presentation (Hsu et al 2012). In a review of 1027 patients with newly diagnosed MM, bone pain was present at diagnosis in 58% of patients: mild in 29%, moderate in 20% and severe (grade 3 or 4) in 9% (Kyle et al 2003). Osteoporosis was a radiographic finding in 23% of patients. In another study on 108 patients with MM, 66% of patients had osteoporosis (Diamond et al 2011). It is generally believed that fractures are common in patients with MM as a result of lytic bone lesions, generalized bone loss, and/or elevated bone turnover from excessive cytokine production. In a population-based retrospective cohort study, 165 patients with myeloma diagnosed from 1945 to 2001 were followed for 537 person-years (Melton et al 2005). Among them, 134 patients experienced 463 fractures - 238 before and 225 after the diagnosis of MM. In the year before diagnosis of myeloma, 16 times (95% CI: 13, 19) more fractures were observed than expected in general population. The majority (57%) of these were pathologic fractures caused by lytic bone lesions, mainly in the vertebrae and ribs. When the pathologic fractures were excluded, there was still an excess of fractures in the year before diagnosis (standardized incidence rate 6.9; 95% CI: 5.0, 9.2). After the diagnosis of myeloma,

there was a 9-fold increase (95% CI: 7.2, 11) in overall fracture risk compared with expected rates. The relative risk of an axial fracture was 14 (95% CI: 11, 17) compared with 2.0 (95% CI: 1.2, 3.0) for all limb fractures combined. Sixty-nine percent of these fractures were pathologic while 11% were found incidentally on myeloma monitoring. When pathological and incidentally found fractures were excluded, subsequent fracture risk was elevated 3-fold, with a 2-fold increase in the risk of an osteoporotic fracture.

Multiple myeloma has been reported to be associated with an increased risk of thromboembolic disease. In a study of more than 4 million military veterans in the US, 2.4% of 6192 patients with MM developed deep vein thrombosis (DVT) with an incidence of 8.7 per 1000 person-years. There was a 9.2-fold increased risk of DVT compared to other patients in the database. In a population-based study from Sweden with over 18000 MM patients and over 70000 matched controls, the risk of venous thrombosis in MM patients was increased 7.5-fold after 1-year of follow-up, 4.6-fold after 5 years, and 4.1-fold after 10 years as compared to the controls. The corresponding results for arterial thrombosis were 1.9-, 1.5- and 1.5-fold increase, respectively (De Stefano et al 2014, Kristinsson et al 2010). As reviewed by De Stefano et al (2014), the incidence of venous thromboembolism (VTE) in MM is estimated as 8 to 22 per 1000 person-years. Risk factors can be patient related (advanced age, other risk factors shared with the general population), disease related, and treatment related. Disease-related risk factors can derive from the monoclonal component (rarely hyperviscosity or inhibition of natural anticoagulants), or hypercoagulability sustained by inflammatory cytokines (increased von Willebrand factor, factor VIII, fibrinogen levels, decreased protein S levels, acquired activated protein C resistance). The 1% to 2% baseline of incident VTE associated with conventional therapies as melphalan and prednisone is at least doubled by the use of doxorubicin or other chemotherapeutic agents. The VTE rate associated with thalidomide or lenalidomide as monotherapy is similar, whereas combination with high-dose dexamethasone or multiple chemotherapeutic agents induces a multiplicative effect on the VTE rate up to 25%.

Renal impairment occurs commonly in patients with MM. Serum creatinine over 2 mg/dl is a criterion for symptomatic myeloma requiring therapy (International Myeloma Working Group 2003). Renal impairment is reported in 15% to 40% of patients with myeloma depending on the definition used, with 30% to 40% of patients having a serum creatinine above the upper limit of normal (ULN), according to a review by Dimopoulos et al (2010). Renal impairment can also evolve over time, and an estimated 25% to 50% of patients are affected during the course of their disease (Dimopoulos et al 2010). Eleutherakis-Papaiakovou et al (2007) evaluated 756 newly diagnosed symptomatic patients with MM and found that renal failure (serum creatinine ≥ 2 mg/dl) occurred in 21% of patients at the time of diagnosis. In another study by Kyle et al (2003), 19% of 1020 patients with newly diagnosed MM had serum creatinine ≥ 2 mg/dl. Knudsen et al (2000) studied renal failure in 775 MM patients diagnosed between 1984-86 and 1990-92 in the Nordic countries. At the time of diagnosis, renal failure (defined as plasma creatinine >130 mol/L) was noted in 29% of patients. During the first year after diagnosis 58%, achieved normalization of p-creatinine, and this was achieved mainly during the first 3 months. In a study by Terpos et al (2009), among 157 newly-diagnosed patients with MM, serum Cystatin-C (Cys-C) was increased in MM patients compared to healthy controls. Ninety patients (57.3%) with MM had higher Cys-C levels than the upper normal limit of 0.95 mg/L, with 37 (23.5%) having elevated serum creatinine (>1.4 mg/dL for men and >1.2 mg/dL for women), and 21 (13.3%) had serum creatinine of ≥ 2 mg/dL. In terms of creatinine clearance (CrCl), 97 patients (61.7%) had a CrCl lower than

80 mL/min/1.73 m2 (the lower normal limit), and 24 (15.2%) had CrCl values below 30 mL/min/1.73 m2.

Important co-morbidities:

Several comorbidities have been reported in patients with MM. As multiple myeloma occurs in older patients, comorbidities associated with aging are known to occur. In a Danish study, among over 2000 patients with newly diagnosed symptomatic MM identified in the Danish National Multiple Myeloma Registry during 2005-2012, 40.9% of multiple myeloma patients had at least one comorbidity in the Charlson Comorbidity Index. These included myocardial infarction (MI) (5.4%), congestive heart failure (5.8%), peripheral vascular disease (3.7%), cerebrovascular disease (7.3%), dementia (0.8%), chronic pulmonary disease (6.7%), connective tissue disease (3.3%), and ulcer disease (4.1%), mild liver disease (0.8%), moderate and severe liver disease (0.1%), diabetes mellitus (3.2%), diabetes mellitus with chronic complications (3.3%), hemiplegia (0.3%), moderate and severe renal disease (6.0%), any tumor (10.2%), leukemia (0.4%), lymphoma (1.0%), and metastatic solid tumor (1.9%) (Gregersen et al 2017). Kleber et al (2011) reported pain (57%), diminished Karnofsky Performance Status (30%), cardiac (20%), lung (18%) and liver disease (16%), hypertension (16%), diabetes (10%), renal impairment (10%) and additional malignancies (6%) as common comorbidities in MM patients.

3. Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat dose toxicity The respective findings of the single and repeat dose toxicity studies are described below under individual toxicity findings.	The relevance of these toxicity findings is detailed in below rows under individual toxicity findings.
Haematologic Changes Haematological effects included decreases in red cell parameters and white blood cell counts (lymphocytes, neutrophils, eosinophils, monocytes and basophils). Reductions in red blood cell parameters and haemoglobin were accompanied by marginally increased reticulocytes counts at high doses in rats (75 mg/kg) and dogs (1 mg/kg). Platelet counts were decreased in rat. In mouse models, thrombocytopenia observed during treatment with panobinostat seems to be due to a platelet production or release defect rather than myeloablation or direct platelet destruction. In contrast to chemotherapy-induced thrombocytopenia, there is little or no cytotoxicity on the megakaryocyte and the thrombocytopenias are rapidly responsive after treatment interruption (often with a rebound effect in mice) (Bishton et al 2011, Giver et al 2011). Dose and time-dependent decreases in bone marrow cellularity were present and characterized by a shift to immaturity/maturation arrest of myelopoiesis following oral administration in both rats (75 mg/kg) and dogs (1 mg/kg). In rats, bone marrow consisted of mild to marked decreases in the proportion of late-stage granulocytic series and mature cells accompanied by a decrease in erythroid cellularity. Pharmacologically mediated depletion of leukocytes in the bone marrow and lymphoid tissue was considered severe enough to compromise host-defense response. Decreases in haematology parameters were accompanied by histopathological findings of lymphoid atrophy and/or depletion in the thymus, lymph nodes and spleen following oral and intravenous administration in rats (≥ 30 mg/kg and ≥ 1 mg/kg, respectively) and dogs (≥ 0.5 mg/kg and ≥ 0.6 mg/kg, respectively).	
Gastrointestinal Tract In dogs, high oral or intravenous doses caused diarrhoea and necrosis of the epithelium in the small intestine. Other changes included atrophy of gastric glands, with accompanying increased fibrous tissue within the lamina propria noted in the cardiac and/or pyloric regions of the stomach in dogs at doses ≥ 0.15 mg/kg. Incidence and severity of the changes did not strictly correlate with dose. At the high dose (1.5 mg/kg), minimal focal dilatation of intestinal crypts, generally containing necrotic debris or inflammatory cells, was present in the small intestinal mucosa.	In clinical trials, GI side effects are the most commonly reported AEs and include nausea, diarrhoea, and vomiting. Diarrhoea has been characterized in CTs and confirmed in Post Marketing Setting. The risk is properly and effectively communicated through the SmPC. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the ongoing study or routine PV. Prevention and management of severe diarrhoea is fully integrated in clinical practice.
Thyroid Thyroid was identified as a target organ for panobinostat based upon observations of thyroid weight changes,	Safety information is available in the public domain, incl. independent reviews (Brioli et al 2017, Moore et al 2019, Tzogani et al 2018) for hypothyroidism. In clinical trials of oral PANO a trend towards elevated TSH and

Key Safety findings (from non-clinical studies)	Relevance to human usage
epithelial hypertrophy and cytoplasmic vacuolation in a 2-week oral study in rats at 10 mg/kg; decreased follicular colloid seen in 4-week oral study in dogs at ≥ 0.15 mg/kg, follicular cell vacuolation in the 4-week oral study in rats at ≥ 10 mg/kg and follicular cell hypertrophy in a 4 week intravenous study in dogs at all doses (≥ 0.06 mg/kg). An additional finding was a single follicular adenoma in one high dose male rat which had been administered 75 mg/kg for 26-weeks followed by a four-week recovery period. This finding is a common observation in Han Wistar rats in 104-week studies; however, it is atypical for this age group. Thyroid hormone changes were present in 13-week oral studies in rat and dog and included decreases in triiodothyronine (T3) at doses ≥ 10 mg/kg in the rat and at a dose of 1.5→1.0 mg/kg in the dog. Decreases in tetraiodothyronine (T4) and Thyroid Stimulating Hormone (TSH) were seen in the rat at 100 mg/kg. In an oral 4-week study in rats panobinostat produced minimal and often transient increases in TSH, decreases in T3 and T4 which were not accompanied by organ weight or microscopic changes in the thyroid, pituitary or liver. This finding may be attributed to the pharmacology of the compound since histone deacetylases (HDACs) are involved in T3 negative feedback of pituitary secretion of TSH (Sasaki et al 1999). Given their small magnitude and transient nature, these variations are not considered to be toxicological significant since sustained increases in TSH are required to induce thyroid tumours in rodents. In the thyroid panobinostat also induces expression of genes involved in cell cycle arrest, differentiation, apoptosis and DNA repair, consistent with its pharmacologic mode of action. The lack of significant and sustained increases in TSH combined with the cytostatic/cytotoxic effects of panobinostat in the thyroid suggests that the adenoma seen in the 26-week study was unlikely to be due to panobinostat.	decreased circulating T4 levels was observed with no associated clinical manifestation of thyroid dysfunction. No additional information was obtained in post marketing phase to further characterize this risk. The risk of hypothyroidism is adequately communicated through the SmPC. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the ongoing study or routine PV.
Bone In rats, hyperostosis (localized increase in immature bone) of the femoral cavity was seen at 100 mg/kg in the 13-week oral study. The hyperostosis was accompanied by clinical chemistry findings of increased calcium and phosphate, suggesting an effect on bone metabolism. No adverse bone effects were observed in the 26-week oral study in rats, or in the 39-week oral study in dogs. The no observed adverse effect level (NOAEL) for hyperostosis is 75 mg/kg/day (AUC0-24h of 555 and 662 ng·hr/ml, and maximum concentration (Cmax) of 129 and 279 for males and females respectively). These effects are also likely to be pharmacologically mediated since histone DACi have been shown to promote osteoblast maturation in vitro (Schroeder and Westendorf 2005), accelerate osteogenesis (Lee et al 2006), and suppress osteoclastogenesis and bone destruction in rats (Nakamura et al 2005). Given the lack of similar effects in dogs or in rat following chronic administration (26 weeks) the finding is likely to be species specific and age-related.	No evidence supports pre-clinical findings relevance to the human use.
Fertility	Based on this data the male fertility could be

Key Safety findings (from non-clinical studies)	Relevance to human usage
No impaired fertility was observed in male rat when panobinostat was administered orally 3 times a week (Days 1, 3 and 5) for 4 weeks at doses of 10, 30 and 100 mg/kg. However, when compared to humans, rats have a huge excess of sperm in their ejaculate. In the rat, sperm production can decrease by up to 90% without any effect on fertility (either pregnancy rate or litter size). Given this, it is best to rely on testes weights, testicular sperm counts and histopathology of the testes and epididymis in the male fertility or subchronic and chronic toxicity studies when trying to predict potential effects on fertility in men. Also, when there are species-specific differences in bioavailability and exposure emphasis on effects on male reproductive organs should be placed on species with greater exposure and bioavailability (dog in this case). In this regard male reproductive effects were observed in the testis, epididymis and prostate in 4- and 13-week repeated dose oral toxicity studies in the dog (doses of 1.5 mg/kg and 1.5→1.0 mg/kg, approximately 0.74 and 0.44 times the expected clinical exposure based upon Area Under Curve [AUC] for a 20 mg dose) and were not reversible following a 4-week recovery period. Effects on the female reproductive system were seen at higher doses in the dose-escalation study in dogs (Study 0270176) and in the 13-week (Study 0680019) and 26-week (Study 0680134) oral studies in rats. In the dog, atretic follicles in the ovary and uterine atrophy were seen at non-tolerated oral doses of 10 mg/kg. In the rat, treatment with panobinostat was associated with an increased frequency of females in oestrus. This findings are likely to be pharmacologically mediated since luteinizing hormone receptor gene promoter activity can be substantially up-regulated in cultured JAR cells (a human placental carcinoma cell line) in the presence of the histone DACi Trichostatin A or sodium butyrate (Zhang and Dufau 2003) and vorinostat has been shown to increase the number of corpora lutea in female rats (Wise et al 2008). In an oral gavage fertility and early embryonic development study in the rat (Study 0670759), the oestrus cycles and the mean number of days to mating was unaffected by treatment. The mating index, fertility index and the conception rates did not show toxicologically significant differences.	compromised and this issue has been appropriately addressed in SmPC in Section 4.6 and Section 5.3. Panobinostat is indicated in a life-threatening indication (treatment of adult patients with relapsed and/or refractory multiple myeloma), therefore the risk of reduced fertility in males will not affect the physician´s and patient´s decision to initiate treatment with panobinostat in this life-threatening disease. In other words, “reduced fertility in males” does not affect the benefit-risk of the product, and therefore does not qualify as an important risk.
Developmental toxicity Based on animal data, the likelihood that panobinostat increases the risk of foetal death and developmental skeletal abnormalities are predicted to be high. Reproductive studies were performed in pregnant rats at oral doses 0.24 to 24 times the recommended human dose (adjusted for body surface area). Panobinostat caused embryo-foetal-lethality, increases in skeletal variations and anomalies (extra vertebrae, extra ribs, and increases in minor skeletal variations) at doses that also produced decreases in foetal body weight and maternal toxicity. The NOAELs in pregnant rats for these findings was 10 mg/kg/day (0.15 times the expected human exposure for a 40 mg oral dose based on AUC). When tested in pregnant rabbits at doses approximately 0.48 to 38 times the recommended human dose	Women of childbearing potential should have a pregnancy test prior to the initiation of treatment with panobinostat and should be advised to use highly effective contraception methods while they are receiving panobinostat, and for up to three months after the last dose of panobinostat. Pregnant women should not be administered panobinostat unless the perceived benefits to the mother outweigh the potential risks to the foetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be counselled regarding the potential hazard to the foetus. It is not known whether panobinostat is excreted in human milk, but many drugs are. Due to the genotoxic potential of panobinostat and its cytostatic/cytotoxic

Key Safety findings (from non-clinical studies)	Relevance to human usage
(adjusted for body surface area) panobinostat caused embryo-foetal-lethality, increases in skeletal anomalies (similar to that seen in rats) at doses that also produced decreases in foetal body weight and maternal toxicity. The NOAELs for these findings in pregnant rabbits was 10 mg/kg/day (0.21 times the expected human exposure based on AUC).	mode of action and subsequent potential for serious adverse drug reactions (ADRs) in nursing infants, breast feeding is not recommended while taking panobinostat. Breast feeding will continue to be monitored as a potential risk under developmental toxicity.
Genotoxicity Panobinostat has a clear genotoxic potential in bacterial and eukaryotic systems (mutagenic and end reduplication inducing effects). AMES and COMET assays revealed a signal for bacterial mutagenicity and DNA damaging potential in mammalian cells, respectively. In the Ames test a clear dose dependent and reproducible mutagenic response was obtained. In the chromosome aberration test with human peripheral blood lymphocytes, a strong increase in the frequencies of polyploidy cells (predominantly end reduplication) was found in the presence and in the absence of S9.	Physicians and patients are advised of the potential for genotoxicity by including the findings in SmPC.
Carcinogenicity Based on positive signals for genotoxicity and mutagenicity panobinostat is assumed to have carcinogenic potential; therefore, no carcinogenicity studies are planned.	Physicians and patients are advised of the potential for carcinogenicity by including the findings in SmPC.
Safety Pharmacology/QTc prolongation In vitro studies in HEK cells and in vivo cardiovascular studies in dogs suggested a risk of QTc prolongation in man. Panobinostat was assessed in two ether-à-go-go-Related Gene channel patch-clamp assays (Study 0280136 and Study 0870294) and the estimated IC50 values were approximately 3.9 µM and 3.5 µM. One of its many trace metabolites (BJB432; [Study 087294]) had an estimated IC50 value of 1.6 µM. In an intravenous safety pharmacology screening study in dogs conducted at 1 and 3 mg/kg, prolongation of QTc was seen at both doses from 6 to 20 hours post-dose (Study 0110024). The study was repeated using lower doses (0.06, 0.2, and 0.6 mg/kg) and very slight treatment-related increases in QTc interval were seen at doses ≥ 0.2 mg/kg (Study 0210083). To support the current clinical oral dosing regimen (weekly on days 1, 3 and 5), a repeat oral dose telemetry study was conducted in dogs at a dose of 1.5 mg/kg (Study 0680202). Based on these data, the NOAEL for effects on the QTc interval following oral administration using the above clinical dosing regimen is <1.5 mg/kg, whereas the NOAEL following intravenous administration is 0.06 mg/kg in dogs. Treatment-related increases in the QTc interval were seen at 1.5 mg/kg through 24 hours and became more evident over time (i.e. following the second and third dose). The magnitude of QTc prolongation is dose-related and maximal increases in QTc were seen after Time of Maximum concentration (Tmax)/Cmax. The average exposures attained following an oral dose of 1.5 mg/kg and an intravenous dose of 0.2 mg/kg (Cmax 77 and 20 ng/mL, respectively; AUC 230 and 31 ng/mL, respectively) are comparable to those attained in	Extensive ECG monitoring, particularly QTcF intervals, from clinical trials over years, established the QTc prolongation potential of panobinostat which appears to be well characterize and is supported in post-marketing phase. The risk is properly and effectively communicated through the SmPC and literature (Spence et al 2016). No further evaluation is planned as part of the PV plan and no significant safety information is expected from the ongoing study or routine PV.

Key Safety findings (from non-clinical studies)	Relevance to human usage
the clinic at 20 mg using three times weekly treatment regimen (Cmax = 27 ng/mL and AUC = 240 ng/mL). The findings appear to be consistent with those of other DAC inhibitors (Strevel et al 2007).	
Drug-drug interactions (DDI) CYP3A4 (Cytochrome P450 3A4) was found to be the main enzyme involved in the in vitro oxidative metabolism of panobinostat (70-98%) in human liver microsomes with possible minor contributions by CYP2D6 and CYP2C19 (3.5- and 13-fold lower than the CYP3A4 contribution, respectively). There is a potential that inhibitors of CYP3A4 may affect the hepatic oxidative clearance of panobinostat clinically, but the magnitude of interactions would be dependent upon the contributions of other panobinostat clearance pathways in humans. In a clinical DDI study evaluating the effect of ketoconazole on the panobinostat metabolism (Summary of Clinical Pharmacology, Study LBH589B2110), the results suggest that fraction metabolized through CYP3A is approximately 40% of total human metabolism. Panobinostat showed little or no inhibition of CYP enzymes, CYP1A2, CYP2C8, CYP2C9, and CYP2E1, when tested at concentrations of up to 100 µM. Based upon the maximum panobinostat plasma concentrations observed at a therapeutically relevant oral dose of 20 mg, it is unlikely that panobinostat would act as an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2E1, CYP3A4/5, or CYP2C19 by a reversible inhibition mechanism. However, it is possible that panobinostat could act as an in vivo inhibitor of CYP2D6. Panobinostat (0.01 to 1 µM) was not an in vitro inducer of CYP1A1/2, CYP2B6, CYP2C8/9/19, or CYP3A mRNA or activity in primary human hepatocytes. In addition, panobinostat was not an inducer of UGT1A1, ABCB1 (permeability glycoprotein (P-gp)) or ABCC2 (MRP2) mRNAs. The flux of panobinostat across confluent Caco-2 cell monolayers was investigated both in the presence and absence of transport protein-selective inhibitors in order to assess the in vitro permeability of panobinostat and its potential for transporter interactions. Due to the high permeability of panobinostat and likely saturation of transporters at commonly administered oral doses of panobinostat, it is not expected that P-glycoprotein (P-gp) would affect absorption of panobinostat from the intestinal tract. It is also unlikely that panobinostat would affect the distribution of co-medications that are substrates for P-gp or breast cancer resistant protein (BCRP). The potential of panobinostat to inhibit the organic anion transporting polypeptide (OATP) uptake transporters, OATP1B1 and OATP1B3, the organic anion transporters (OAT) OAT1 and OAT3, and the organic cation transporters (OCT) OCT1 and OCT) were evaluated in vitro. No clinical DDI with respect to OATP1B1/3, OAT3, OCT1, or OCT2 inhibition is expected.	Available data in post marketing phase is limited. The risk is properly and effectively communicated through the SmPC. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the ongoing study or routine PV.

Conclusions:

- Important identified risks from non-clinical studies, which have been confirmed by clinical data, include: Severe haemorrhage and Severe infections (including sepsis/pneumonia/reactivation of hepatitis B infection) are proposed to be removed. Details are provided in Section 8.2.
- Important potential risks from pre-clinical safety studies: Developmental toxicity and Carcinogenicity are proposed to be removed. Details are provided in Section 8.2.
- There is no missing information identified from pre-clinical studies.

4. Part II Safety specification Module SIII Clinical trial exposure

4.1. Part II Module SIII Clinical trial exposure

The panobinostat clinical development program in MM focuses on panobinostat in combination with bortezomib and dexamethasone (PAN+BTZ+Dex), and includes a large, double-blind, well-controlled Phase III study, one supportive Phase II study, safety and preliminary efficacy data from the dose expansion phase of a Phase Ib study (Table 4-1):

Table 4-1 Overview of key studies in the panobinostat clinical development program

Study No. (abbreviated)	Phase	Population	Study status	Patients (N)
Study LBH589B2207 (Study B2207)	Ib	Relapsed or relapsed and refractory Including BTZ refractory patients	Completed	15 (dose expansion)
Study LBH589DUS71 (Study DUS71)	II	Relapsed and refractory Selectively BTZ refractory patients	Completed	55
Study LBH589D2308 (Study D2308)	III	Relapsed or relapsed and refractory Excluding BTZ refractory patients	Completed	768

A randomized, double-blind, placebo (PBO) controlled design was employed for Study D2308 in patients with relapsed or relapsed and refractory MM. In the control arm, placebo was given on top of standard of care (bortezomib and dexamethasone), and was therefore ethical to use in this line of treatment. Cross-over of patients between the treatment arms was not allowed.

The dose-expansion phase of Study B2207 and the supportive Study DUS71 were designed as single-arm studies to determine the maximum tolerated dose (MTD) and preliminary activity and to confirm the clinical activity of the selected dose of panobinostat in patients with relapsed or relapsed and refractory MM (Study B2207) and relapsed and bortezomib-refractory patients (Study DUS71). Key study design features of all the three studies are provided in Table 4-2.

Table 4-2 Study design features of studies included in the submission

Studies	Study B2207	Study DUS71	Study D2308
Phase	Ib	II	III
Design	Dose escalation/Dose expansion	Open-label single arm	Double-blind, randomized (1:1)
Study objectives	MTD/safety and prelim. efficacy of the dose and modified schedule as concluded from the dose-escalation phase in patients with relapsed or relapsed and refractory MM	Efficacy/safety in patients with relapsed and BTZ-refractory MM who had received at least 2 prior lines of therapy including IMiD	Efficacy/safety in patients with MM having had 1 to 3 lines of prior therapy or relapsed and refractory MM who were not refractory to BTZ and who had received at least 1 prior line of therapy
Enrollment period	2007-2010	2010-2011	2009-2012
Sample size	N=62 (N=15 in dose expansion phase)	N=55	N=768 n=387 in PAN+BTZ+Dex n=381 in PBO+BTZ+Dex
Study status	Completed	Completed	Completed
Eligibility on response to last prior treatment	Any ≥ 1 prior line of therapy	Relapsed and refractory to BTZ ≥ 2 prior lines of therapy	Relapsed and not primary refractory to BTZ ≥ 1 ≤ 3 prior lines of therapy
Dosing schedule [1]			
PAN [2]	20 mg tiw; 2 weeks on and 1 week off		

Studies	Study B2207	Study DUS71	Study D2308
BTZ	Bolus iv, 1.3 mg/m^2 biw, 2 weeks on and 1 week off		
Dex	20 mg oral on D1 and after each BTZ injection four times a week		
Dexamethasone	+ (optional in dose escalation phase)	+	+
Treatment duration	8 cycles (24 weeks), thereafter until unacceptable toxicity or progression	Max. of 48 weeks Patients with a clinical benefit can continue until unacceptable toxicity or progression	Max. of 48 weeks Patients with clinical benefit will continue up through Week 48
Response criteria	IMWG	mEBMT (IMWG exploratory)	mEBMT (IMWG exploratory)
Primary EP	MTD	ORR	PFS
Secondary EPs	Safety, ORR, PK	MRR, TTR, TTP, PFS, OS, DOR, safety, PRO (neurotoxicity)	OS (key), TTP, ORR, nCR/CR, DOR, TTR, MRR, PK, safety, PRO

[1] Dose expansion phase only in Study B2207

[2] Weekly regimen in the dose expansion phase of Study B2207

BTZ, bortezomib; PAN, panobinostat; Dex, dexamethasone; ORR, overall response rate; MRR, minimal response rate; PFS, progression free survival; TTP, time to progression; TTR, time to treatment response; PK, pharmacokinetics; DOR, duration of response; PRO, patient reported outcomes; nCR, near complete response; CR, complete response; EBMT, European Society for Blood and Marrow Transplantation; mEBMT; modified EBMT; IMWG, International Myeloma Working Group; tiw, three times a week; biw, twice a week; IMiD, immunomodulatory drug; FU, Follow-Up

These three studies form the foundation for the efficacy analyses and are central to the safety analyses as they were specifically conducted in the indication being sought.

In addition, data from six completed studies (Studies B2201, B2202, B2203, B2211, B2101 and B2102) which evaluated panobinostat as a single agent in patients with other haematological malignancies and solid tumours provide additional information on the general safety profile at the relevant dose of 20 mg.

The combination of bortezomib and panobinostat has been shown to be synergistic in *in-vitro* and *in-vivo* models of MM (Ocio et al 2010), resulting in a synergistic inhibition of the unfolded protein response pathways (aggresome, proteasome) which are particularly relevant to MM.

Since the activation of the aggresome pathway is one escape mechanism involved in the resistance to proteasome inhibition, these effects may be related to the dual inhibition of the proteasome and aggresome pathways. Targeting both pathways induces greater accumulation of polyubiquitinated proteins, resulting in increased cellular stress and apoptosis. Therefore, combining bortezomib with a DAC inhibitor represents an attractive strategy for the treatment of patients with MM.

The dose and schedule of panobinostat (20 mg panobinostat, 2 weeks on / 1 week off) used in Study D2308 was selected based on the following rationale and clinical experience in the Phase I/II program.

Single-agent oral panobinostat was first tested in patients with MM in dose-escalation Phase I Study B2102 and in the Phase II Study B2203 in MM. These studies showed tumour responses in cutaneous T-cell lymphoma (CTCL), Hodgkin's Lymphoma, Acute Myeloid Leukaemia, myelofibrosis and MM patients at doses of ≥ 20 mg used in various schedules. In addition, these single-agent studies suggested that sustained histone acetylation was achieved in peripheral blood mononuclear cells up to one week after dosing at doses ≥ 20 mg.

The Phase Ib dose-finding Study B2207 was initiated for the combination of panobinostat with bortezomib in patients with relapsed or relapsed and refractory MM, following at least one prior line of therapy. This study determined a Maximum Tolerated Dose (MTD) of 20 mg panobinostat tiw in combination with 1.3 mg/m^2 bortezomib:

- Doses of 10 mg to 30 mg panobinostat (tiw, until progression) in combination with 1.0 or 1.3 mg/m^2 BTZ iv (on days 1, 4, 8 and 11 of a 21-days cycle) were tested.
- The MTD was defined as the highest dose level of panobinostat in combination with bortezomib in the specified dosing schedule that met the overdose control criteria based on dose limiting toxicities observed in Cycle 1 and additional safety information.
- Based on 15 evaluable patients, the MTD was declared at 20 mg panobinostat tiw and 1.3 mg/m^2 bortezomib.
- Dose limiting toxicities were reported in 3/15 patients (20%) in the MTD cohort.
- Thrombocytopenia as a dose limiting toxicity (≥ grade 3) was reported by 1/15 patient (6.7%) in the MTD cohort compared to more than 15% in the cohorts with higher doses of panobinostat. Of note, four patients in the MTD cohort (23.5%) received more than 12 months of therapy.
- In the dose-escalation phase of the study, overall response rates were highest in the cohorts using a dose of bortezomib of 1.3 mg/m^2 and a dose of panobinostat ≥ 20 mg, ranging from 52.9% to 57.1%.

The dosing schedule of 2 weeks on/ 1 week off was introduced into the dose expansion phase of Study B2207 to manage thrombocytopenia and to allow for accelerated platelet recovery (Lin et al 2009).

Due to the evolution of medical practice since Study B2207 had started and due to newly available pre-clinical data (Ocio et al 2010), dexamethasone was added optionally to the treatment schedule of patients who had worsening disease or suboptimal response in the dose escalation phase, and mandatory to the treatment schedule of all patients in the dose expansion phase of Study B2207. Twenty milligrams of dexamethasone was chosen based on evidence showing that for patients who had worsening disease/suboptimal response whilst receiving bortezomib alone, the addition of 20 mg of dexamethasone was associated with improved responses (Jagannath et al 2006). Dexamethasone administered "upfront" showed to be highly efficacious in patients with relapsed/refractory MM (Davies et al 2007, Corso et al 2009). Administration of dexamethasone was started in Cycle 2 of the expansion phase to allow for analysis of panobinostat and bortezomib pharmacokinetic (PK) in the absence (Cycle 1) and presence (Cycle 2) of the drug.

The backbone regimen of intravenous bortezomib with a dose of 1.3 mg/m^2 administered on days 1, 4, 8, 15 of 21-days treatment cycles was the standard approved regimen used in 2009 when the D2308 and DUS71 studies were initiated.

Exposure data from patients with relapsed or relapsed and refractory MM is reported from the Phase III Study D2308 (n=381) and the two supportive studies DUS71 (n=55) and B2207 (n=15). The clinical trial exposure is presented in the tables below. The exposure data is presented by study treatment, and then by individual drugs in the combination. In these tables, the study treatment refers to any component of the combination treatment, i.e. either panobinostat (PAN), or placebo, or bortezomib (BTZ) or dexamethasone (Dex) and study drug refers to panobinostat or placebo.

The duration of exposure to study treatment is the time interval from the first dose of any component to the last dose of any component of the combination treatment.

The median duration of exposure to study treatment was relatively lower in PAN+BTZ+Dex treated patients (in the randomized blinded trial, D2308) as compared to patients in the PBO+BTZ+Dex arm (152 vs. 187 days, respectively). More patients in both the treatment arms were exposed to the study treatment between 9 to12 months (Table 4-3). Per protocol design for the Phase III study D2308, the duration of treatment in the study was fixed to 48 weeks in total.

Table 4-3 Clinical trial exposure to study treatment by duration of exposure

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
Exposure categories (months) - n (%)			
<1	45 (10.0)	37 (9.7)	30 (8.0)
≥ 1 and <3	101 (22.4)	84 (22.0)	69 (18.3)
≥ 3 and <6	110 (24.4)	90 (23.6)	87 (23.1)
≥ 6 and <9	54 (12.0)	45 (11.8)	62 (16.4)
≥ 9 and <12	120 (26.6)	108 (28.3)	122 (32.4)
≥ 12	21 (4.7)	17 (4.5)	7 (1.9)
Duration of exposure (days)			
N	451	381	377
Mean	181.5	183.5	195.0
SD	127.29	125.75	118.33
Median	152.0	152.0	187.0
25 – 75 percentiles	68.0 - 327.0	68.0 - 327.0	86.0 - 327.0
Minimum	2	3	3
Maximum	735	411	443
Patient-month	2689.9	2297.0	2415.1

- A patient is counted only once in each category.
- Duration of exposure (days) = [(Last dosing date of any study treatment component – date of first administration of any study treatment component) + 1]
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- "n" is the number of patients.

Source: EU RMP v4.0 Annex 12-Table 4-1.1

Similarly, the duration of exposure to study drug (panobinostat) was lower (median: 152 days) than placebo (median: 187 days) in D2308 (Table 4-4).

Table 4-4 Clinical trial exposure to panobinostat by duration

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
Exposure categories (months) - n (%)			
<1	47 (10.4)	39 (10.2)	33 (8.8)
≥ 1 and <3	100 (22.2)	83 (21.8)	68 (18.0)
≥ 3 and <6	109 (24.2)	89 (23.4)	85 (22.5)
≥ 6 and <9	55 (12.2)	45 (11.8)	63 (16.7)
≥ 9 and <12	120 (26.6)	108 (28.3)	121 (32.1)

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
≥ 12	20 (4.4)	17 (4.5)	7 (1.9)
Duration of exposure (days)			
N	451	381	377
Mean	180.7	182.8	193.8
SD	127.79	126.34	118.78
Median	151.0	152.0	187.0
25 – 75 percentiles	68.0 - 327.0	68.0 - 327.0	82.0 - 327.0
Minimum	1	3	3
Maximum	735	411	443
Patient-month	2678.1	2288.2	2400.6

- A patient is counted only once in each category.
- Duration of exposure (days) = [[(date of last dosing of PAN/PBO) – (date of first administration of PAN/PBO) + 1]]
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- "n" is the number of patients.

Source: EU RMP v4.0 Annex 12-Table 4-1.2

Consistently, the duration of exposure to bortezomib or dexamethasone in the PAN+BTZ+Dex arm was lower than that in the PBO+BTZ+Dex arm in D2308 (Table 4-5 and Table 4-6).

Table 4-5 Clinical trial exposure to bortezomib by duration

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
Exposure categories (months) - n (%)			
<1	50 (11.1)	40 (10.5)	30 (8.0)
≥ 1 and <3	108 (23.9)	93 (24.4)	79 (21.0)
≥ 3 and <6	118 (26.2)	93 (24.4)	88 (23.3)
≥ 6 and <9	47 (10.4)	40 (10.5)	61 (16.2)
≥ 9 and <12	113 (25.1)	103 (27.0)	113 (30.0)
≥ 12	15 (3.3)	12 (3.1)	6 (1.6)
Duration of exposure (days)			
N	451	381	377
Mean	170.4	172.3	185.4
SD	124.24	123.04	116.11
Median	137.0	137.0	172.0
25 – 75 percentiles	67.0 - 317.0	67.0 - 323.0	75.0 - 323.0
Minimum	1	1	1
Maximum	735	407	439
Patient-month	2524.9	2157.1	2296.3

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377

- A patient is counted only once in each category.
- Duration of exposure (days) = [(last dosing date of BTZ) – (date of first administration of BTZ) + 1]
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- "n" is the number of patients.

Source: EU RMP v4.0 Annex 12-Table 4-1.3

Table 4-6 Clinical trial exposure to dexamethasone by duration

	Pooled data	Randomized blinded trial	
	PAN+BTZ+Dex N=451	PAN+BTZ+Dex N=381	PBO+BTZ+Dex N=377
Exposure categories (months) - n (%)			
<1	54 (12.0)	43 (11.3)	34 (9.0)
≥ 1 and <3	102 (22.6)	86 (22.6)	70 (18.6)
≥ 3 and <6	110 (24.4)	90 (23.6)	86 (22.8)
≥ 6 and <9	53 (11.8)	43 (11.3)	65 (17.2)
≥ 9 and <12	112 (24.8)	103 (27.0)	116 (30.8)
≥ 12	20 (4.4)	16 (4.2)	6 (1.6)
Duration of exposure (days)			
N	451	381	377
Mean	173.3	175.9	188.9
SD	126.03	124.61	116.73
Median	138.0	139.0	180.0
25 – 75 percentiles	65.0 - 324.0	66.0 - 324.0	78.0 - 324.0
Minimum	2	2	2
Maximum	735	408	440
Patient-month	2567.7	2202.2	2339.9

- A patient is counted only once in each category.
- Duration of exposure (days) = [(last dosing date of Dex) – (date of first administration of Dex) + 1]
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- "n" is the number of patients.

Source: EU RMP v4.0 Annex 12-Table 4-1.4

Exposure by age and gender

Exposure to study treatment by age was comparable in both the treatment arms (majority of the population was below 75 years of age); and predominantly in the age group of 55−65 years. Gender difference was not remarkable between the two treatment arms as well. (Table 4-7).

Similar trend was observed for exposure to study drug (panobinostat), BTZ and Dex with respect to age and gender (Table 4-8, Table 4-9, and Table 4-10).

Table 4-7 Clinical trial exposure to study treatment by age and gender

	Patients		Patient-Months	
Age group	Male n (%)	Female n (%)	Male	Female
Pooled Data: PAN + BTZ + Dex N=451				
<35 years	2 (0.4)	0 (0.0)	5.62	0
35 years ≤ 55 years	48 (10.6)	37 (8.2)	277.36	218.22
55 years ≤ 65 years	102 (22.6)	78 (17.3)	672.30	478.98
65 years ≤ 75 years	73 (16.2)	70 (15.5)	418.92	426.41
75 years ≤ 85 years	16 (3.5)	24 (5.3)	86.31	104.84
≥ 85 years	0	1 (0.2)	0.00	0.92
Randomized blinded trial: PAN + BTZ + Dex N=381				
<35 years	2 (0.5)	0	5.62	0.00
35 years ≤ 55 years	37 (9.7)	30 (7.9)	227.68	188.58
55 years ≤ 65 years	85 (22.3)	67 (17.6)	550.97	428.85
65 years ≤ 75 years	64 (16.8)	62 (16.3)	361.89	375.26
75 years ≤ 85 years	13 (3.4)	21 (5.5)	67.75	90.45
≥ 85 years	0	0	0.00	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377				
<35 years	0	1 (0.3)	0.00	4.50
35 years ≤ 55 years	47 (12.5)	25 (6.6)	280.74	180.57
55 years ≤ 65 years	74 (19.6)	70 (18.6)	492.55	495.84
65 years ≤ 75 years	70 (18.6)	62 (16.4)	422.11	402.07
75 years ≤ 85 years	14 (3.7)	14 (3.7)	56.54	80.20
≥ 85 years	0	0	0.00	0.00

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only

Source: EU RMP v4.0 Annex 12-Table 4-2.1

Table 4-8 Clinical trial exposure to panobinostat by age and gender

	Patients		Patient-Months	
Age group	Male n (%)	Female n (%)	Male	Female
Pooled Data: PAN + BTZ + Dex N=451				
<35 years	2 (0.4)	0	5.62	0.00
35 years ≤ 55 years	48 (10.6)	37 (8.2)	276.86	216.74
55 years ≤ 65 years	102 (22.6)	78 (17.3)	668.81	477.73
65 years ≤ 75 years	73 (16.2)	70 (15.5)	417.77	424.25
75 years ≤ 85 years	16 (3.5)	24 (5.3)	84.83	104.67
≥ 85 years	0	1 (0.2)	0.00	0.85
Randomized blinded trial: PAN + BTZ + Dex N=381				
<35 years	2 (0.5)	0	5.62	0.00
35 years ≤ 55 years	37 (9.7)	30 (7.9)	227.25	188.39
55 years ≤ 65 years	85 (22.3)	67 (17.6)	547.81	427.86
65 years ≤ 75 years	64 (16.8)	62 (16.3)	360.97	373.78
75 years ≤ 85 years	13 (3.4)	21 (5.5)	66.27	90.28
≥ 85 years	0	0	0.00	0.00

	Patients		Patient-Months	
	Male	Female		
Age group	**n (%)**	**n (%)**	**Male**	**Female**
Randomized blinded trial: PBO + BTZ + Dex N=377				
<35 years	0	1 (0.3)	0.00	4.50
35 years ≤ 55 years	47 (12.5)	25 (6.6)	279.89	179.98
55 years ≤ 65 years	74 (19.6)	70 (18.6)	487.20	493.24
65 years ≤ 75 years	70 (18.6)	62 (16.4)	421.26	398.69
75 years ≤ 85 years	14 (3.7)	14 (3.7)	56.41	79.44
≥ 85 years	0	0	0.00	0.00

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only

Source: EU RMP v4.0 Annex 12-Table 4-2.2

Table 4-9 Clinical trial exposure to bortezomib by age and gender

	Patients		Patient-Months	
	Male	Female		
Age group	**n (%)**	**n (%)**	**Male**	**Female**
Pooled Data: PAN + BTZ + Dex N=451				
<35 years	2 (0.4)	0	5.55	0.00
35 years ≤ 55 years	48 (10.6)	37 (8.2)	253.90	214.24
55 years ≤ 65 years	102 (22.6)	78 (17.3)	616.31	457.36
65 years ≤ 75 years	73 (16.2)	70 (15.5)	386.33	417.64
75 years ≤ 85 years	16 (3.5)	24 (5.3)	71.89	100.80
≥ 85 years	0	1 (0.2)	0.00	0.92
Randomized blinded trial: PAN + BTZ + Dex N=381				
<35 years	2 (0.5)	0	5.55	0.00
35 years ≤ 55 years	37 (9.7)	30 (7.9)	204.94	184.90
55 years ≤ 65 years	85 (22.3)	67 (17.6)	510.03	412.16
65 years ≤ 75 years	64 (16.8)	62 (16.3)	332.35	366.82
75 years ≤ 85 years	13 (3.4)	21 (5.5)	53.82	86.54
≥ 85 years	0	0	0.00	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377				
<35 years	0	1 (0.3)	0.00	4.47
35 years ≤ 55 years	47 (12.5)	25 (6.6)	268.55	172.12
55 years ≤ 65 years	74 (19.6)	70 (18.6)	472.08	479.44
65 years ≤ 75 years	70 (18.6)	62 (16.4)	406.37	375.89
75 years ≤ 85 years	14 (3.7)	14 (3.7)	47.74	69.62
≥ 85 years	0	0	0.00	0.00

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only

Source: EU RMP v4.0 Annex 12-Table 4-2.3

Table 4-10 Clinical trial exposure to dexamethasone by age and gender

	Patients		Patient-Months	
	Male	Female		
Age group	**n (%)**	**n (%)**	**Male**	**Female**
Pooled Data: PAN + BTZ + Dex N=451				
<35 years	2 (0.4)	0	5.62	0.00
35 years ≤ 55 years	48 (10.6)	37 (8.2)	266.61	212.93
55 years ≤ 65 years	102 (22.6)	78 (17.3)	612.70	464.10
65 years ≤ 75 years	73 (16.2)	70 (15.5)	410.81	421.72
75 years ≤ 85 years	16 (3.5)	24 (5.3)	76.52	95.80
≥ 85 years	0	1 (0.2)	0.00	0.92
Randomized blinded trial: PAN + BTZ + Dex N=381				
<35 years	2 (0.5)	0	5.62	0.00
35 years ≤ 55 years	37 (9.7)	30 (7.9)	218.71	184.44
55 years ≤ 65 years	85 (22.3)	67 (17.6)	508.58	415.97
65 years ≤ 75 years	64 (16.8)	62 (16.3)	357.55	371.75
75 years ≤ 85 years	13 (3.4)	21 (5.5)	58.09	81.51
≥ 85 years	0	0	0.00	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377				
<35 years	0	1 (0.3)	0.00	4.50
35 years ≤ 55 years	47 (12.5)	25 (6.6)	274.33	168.61
55 years ≤ 65 years	74 (19.6)	70 (18.6)	480.43	470.08
65 years ≤ 75 years	70 (18.6)	62 (16.4)	417.28	390.51
75 years ≤ 85 years	14 (3.7)	14 (3.7)	54.60	79.57
≥ 85 years	0	0	0.00	0.00

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only

Source: EU RMP v4.0 Annex 12-Table 4-2.4

Exposure by race

Exposure by race was similar in both the treatment arms with predominance of Caucasian, followed by Asian patients (>90% of population). Other race (including Blacks) contributed to <10% of population in both the treatment arms (Table 4-11). Exposure to study drug, BTZ, and Dex by race in both the treatment groups was similar to that of study treatment as a whole (Table 4-12, Table 4-13 and Table 4-14).

Table 4-11 Clinical trial exposure to study treatment by race

Race group	**Patients n (%)**	**Patient-months**
Pooled Data: PAN + BTZ + Dex N=451		
Caucasian	301 (66.7)	1791.67
Asian	127 (28.2)	724.11
Other	23 (5.1)	174.09
Randomized blinded trial: PAN + BTZ + Dex N=381		
Caucasian	244 (64.0)	1490.23
Asian	127 (33.3)	724.11
Other	10 (2.6)	82.69

Race group	Patients n (%)	Patient-months
Randomized blinded trial: PBO + BTZ + Dex N=377		
Caucasian	247 (65.5)	1564.02
Asian	103 (27.3)	662.28
Other	27 (7.2)	188.81

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- Patients with missing race are excluded from this analysis

Source: EU RMP v4.0 Annex 12-Table 4-3.1

Table 4-12 Clinical trial exposure to panobinostat by race

Race group	Patients n (%)	Patient-months
Pooled Data: PAN + BTZ + Dex N=451		
Caucasian	301 (66.7)	1783.23
Asian	127 (28.2)	722.89
Other	23 (5.1)	172.02
Randomized blinded trial: PAN + BTZ + Dex N=381		
Caucasian	244 (64.0)	1483.60
Asian	127 (33.3)	722.89
Other	10 (2.6)	81.74
Randomized blinded trial: PBO + BTZ + Dex N=377		
Caucasian	247 (65.5)	1551.74
Asian	103 (27.3)	660.07
Other	27 (7.2)	188.78

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- Patients with missing race are excluded from this analysis

Source: EU RMP v4.0 Annex 12-Table 4-3.2

Table 4-13 Clinical trial exposure to bortezomib by race

Race group	Patients n (%)	Patient-months
Pooled Data: PAN + BTZ + Dex N=451		
Caucasian	301 (66.7)	1689.79
Asian	127 (28.2)	679.00
Other	23 (5.1)	156.16
Randomized blinded trial: PAN + BTZ + Dex N=381		
Caucasian	244 (64.0)	1412.60
Asian	127 (33.3)	679.00
Other	10 (2.6)	65.51
Randomized blinded trial: PBO + BTZ + Dex N=377		
Caucasian	247 (65.5)	1470.78
Asian	103 (27.3)	649.59
Other	27 (7.2)	175.90

Race group	Patients n (%)	Patient-months

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- Patients with missing race are excluded from this analysis

Source: RMP v4.0 Annex 12-Table 4-3.3

Table 4-14 Clinical trial exposure to dexamethasone by race

Race group	Patients n (%)	Patient-months
Pooled Data: PAN + BTZ + Dex N=451		
Caucasian	301 (66.7)	1696.79
Asian	127 (28.2)	699.07
Other	23 (5.1)	171.86
Randomized blinded trial: PAN + BTZ + Dex N=381		
Caucasian	244 (64.0)	1420.98
Asian	127 (33.3)	699.07
Other	10 (2.6)	82.17
Randomized blinded trial: PBO + BTZ + Dex N=377		
Caucasian	247 (65.5)	1499.17
Asian	103 (27.3)	654.00
Other	27 (7.2)	186.74

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- Patients with missing race are excluded from this analysis

Source: EU RMP v4.0 Annex 12-Table 4-3.4

5. Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1. Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Cardiac related parameters: Patients with congenital long QT syndrome or QTcF >450 msec before initiating treatment with panobinostat.	Based on non-clinical reports and literature from clinical trials with other DAC inhibitors (Molife et al 2007), QTc prolongation and changes in the ST segment or T waves have been proposed as class effects of DAC inhibitors. Available Phase I clinical data (Study LBH589A2101 and Study LBH589A2102) further suggest QTc prolongation to be formulation, dose and schedule dependent. A single case of torsade de pointes was observed in a patient in Study LBH589A2101 with multiple risk factors, who developed torsade de pointes on Day 3 following continuous daily dosing with iv panobinostat at 20 mg/m^2. Subsequently, no instances of torsades de pointes have been observed in any study with the oral formulation. Electrocardiogram (ECG) tracings have been intensively monitored in a number of clinical trials including over 500 patients treated with oral PAN with three times a week (TIW), every week (QW) or every other week (QOW) schedules. Overall, the clinical effect of QTc prolongation associated with oral PAN appeared to be moderate (Weber et al 2009). Only a very low proportion of patients treated with oral PAN QW or QOW experienced an absolute QTcF prolongation of >500 ms (0.5% on QW schedule vs. 0% on QOW PAN up to 40 mg). Patients with congenital long QT syndrome, QTcF >450 msec or taking medications with relative risk of prolonging the QT interval or inducing Torsade de pointes may be at higher risk of QTC prolongation.	No	It is a routine practice during clinical development that patients with certain risk factors are excluded from clinical trials when the risk benefit has not yet established. Given the potential risk for QTc prolongation associated with panobinostat and other potential cardiac toxicity, this group of patients was excluded from the studies. However, the safety findings from these trials for MM patients treated with this combination regimen with panobinostat, bortezomib and dexamethasone did not suggest significant safety concerns regarding QTc prolongation and other cardiac toxicity. In the context of favourable risk benefit profile now demonstrated for this indication and regimen, patients with such cardiac risk factors should be allowed for this new treatment regimen, with appropriate screening and monitoring per the instructions presented in the SmPC.
Patients taking medications with relative risk of prolonging the QT	QT prolongation, a known class effect of HDAC inhibitors, appears to be formulation, dose and schedule dependent. In the pooled analysis of the	No	No new safety concern regarding the use in patients with cardiac diseases has been identified from the post

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
interval or inducing Torsade de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting treatment with panobinostat Patients with other cardiac diseases - left ventricular ejection fraction <LLN of institutional norm, as determined by ECHO or MUGA - obligate use of a permanent cardiac pacemaker. - history or presence of ventricular tachyarrhythmias - resting bradycardia defined as <50 beats per minute - complete left bundle branch block, bifascicular block - any clinically significant ST segment and/or T-wave abnormalities - presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria. - MI or unstable angina pectoris ≤ 6 months prior to starting study drug - symptomatic congestive heart failure (New York Heart Association class III-IV)- other clinically significant heart disease and vascular disease (e.g.	3 MM combination studies, QTcF ≥ 480 ≤ 500 msec was relatively uncommon (5/451, 1.1%), while QTcF >500 msec was not observed. There were 38.8% of patients who reported newly occurring on-treatment T wave changes with the PAN combination, but there was no apparent correlation between T wave changes and significant cardiac events. ST-T segment changes were reported in 20.8% of patients, primarily involving ST-T depression. The magnitude of this finding is consistent with the cumulative clinical experience with PAN. Since ST-T depression is potentially indicative of myocardial ischemia, ischemic heart disease is therefore closely monitored as a clinically notable AE for this compound. Based on data from D2308 trial, in agreement with Oncology Drugs Advisory Committee (ODAC) FDA recommended to enhance communication on cardiac toxicities (ischemia, arrhythmias and ECG changes), among the other known toxicities. Safety results from trial D2308, a large, international, randomized (1:1), double-blinded, placebo-controlled trial in which 768 subjects with relapsed MM were treated with bortezomib and dexamethasone with or without panobinostat. Patients with 1 to 3 prior treatments were eligible. Safety was evaluated in 758 patients with relapsed MM who were treated with panobinostat-bortezomib-dexamethasone (381), or Placebo-bortezomib-dexamethasone (377) demonstrated Treatment emergent ECG changes, occurred in 64% of patients in the panobinostat-containing arm and 42% in the control arm. New T-wave changes were reported in 40% of patients in the panobinostat arm compared with 18% in the placebo arm. ST-segment depressions were reported in 22% of patients in the panobinostat arm, compared with 4% in the placebo arm. Arrhythmias occurred more frequently in patients receiving panobinostat compared to the control arm (12% vs. 5%).		marketing study cumulative data. No additional pharmacovigilance (PhV) activities are planned and no significant safety information is expected from the ongoing study or routine PV to further characterize this missing information and the available data so far do not suggest a change in the safety profile. The risk of QT prolongation is properly communicated in the SmPC and risk management is integrated into clinical practice.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
uncontrolled hypertension)	All grade ischemic events were increased by 3% by the addition of panobinostat to bortezomib and Dexamethasone, and three patients in the panobinostat arm. Three patients died due to cardiac ischemia and none in the placebo arm.		
Patients with hepatic impairment • Aspartate Transaminase (AST)/ Serum Glutamic Oxaloacetic Transaminase SGOT and Alanine Transaminase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT) ≥ 2.5 x ULN • Serum total bilirubin (TBL) ≥ 1.5 ULN (or ≥ 3.0 x ULN if patient has Gilbert syndrome)	Routine practice in clinical trials to exclude patients with more severe liver dysfunction	No	Safety results from the studies for MM patients treated with this combination regimen with panobinostat, bortezomib and dexamethasone did not suggest significant safety concerns regarding hepatotoxicity. In addition, results from a pharmacokinetic study single agent panobinostat in 24 solid tumor patients with varying degrees of hepatic impairment (Study X2101) showed that the systemic exposure of panobinostat increased with the severity of hepatic impairment. Mild and moderate hepatic impairment per NCI-CTEP classification increased panobinostat plasma exposure by 43% and 105%, respectively, with no apparent impact on patients' AE profiles. No pharmacokinetic (PK) data for severe hepatic impaired patients are available. In the context of favourable risk benefit profile now demonstrated for this indication and regimen, patients with risk factors for hepatic dysfunction should be allowed for this new treatment regimen, with appropriate monitoring per the instructions presented in the label
Patients with impaired renal function: • Serum creatinine levels ≥ 1.5 x ULN, or calculated CrCl <60 ml/min	Routine practice in clinical trials to exclude patients with more severe renal dysfunction.	No	Safety results from the studies for MM patients treated with this combination regimen with panobinostat, bortezomib and dexamethasone did not

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			suggest significant safety concerns regarding renal toxicity, considering MM patients are frequently associated with renal dysfunction. In addition, the effect of renal impairment on the pharmacokinetics of panobinostat was assessed in a Phase I study in 37 patients with advanced solid tumors with varying degrees of renal functions. Mild, moderate and severe renal impairment based on Baseline urine CrCl did not alter panobinostat plasma exposure. Panobinostat has not been studied in patients with end stage renal disease or patients on dialysis. In the context of favourable risk benefit profile now demonstrated for this indication and regimen, patients with risk factors for renal dysfunction should be allowed for this new treatment regimen, with appropriate monitoring per the instructions presented in the SmPC.
Hematologic parameters: • ANC ≤ 1.5 x 10^9 /L • Platelet count ≤ 100 x 10^9/L	Routine practice in clinical trials to exclude patients with more severe hematologic abnormalities	No	With demonstrated overall favourable risk benefit profile for this treatment regimen for the MM patients, such patients could be effectively managed via routine clinical practice with appropriate monitoring and dose adjustments per the instructions presented in the label.
Other abnormal conditions: • ECOG performance ≥ 2	Routine practice in clinical trials to exclude patients with certain conditions	No	With demonstrated overall favourable risk benefit profile for this treatment regimen for the MM patients, such patients could be effectively managed via routine clinical practice with appropriate monitoring and treatment per the instructions presented in the label.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
• Serum potassium, magnesium, phosphorus abnormal range (relevant to QT prolongation concern with panobinostat) • Grade ≥ 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain (relevant to the known risk for bortezomib) • Mucosal or internal bleeding (relevant to risk of thrombocytopenia for both panobinostat and bortezomib) • Unresolved diarrhoea ≥ CTCAE grade 2 (relevant to gastrointestinal (GI) toxicity for both panobinostat and bortezomib) Uncontrolled medical conditions			With respect to diarrhoea, at the first sign of abdominal cramping, loose stools, or onset of diarrhoea, it is recommended that the patient be treated with anti-diarrheal medication or any additional treatment in accordance with local treatment guidelines. Replacement iv fluids and electrolytes may be used as appropriate. The use of drugs with laxative properties should be used with caution because of the potential for exacerbation of diarrhoea. Patients should be advised to contact their physician to discuss any laxative use.
Special populations: • Paediatric ≤ 18yrs Women who are pregnant	Reproductive studies performed in pregnant rats and rabbits revealed embryo-foetal-lethality and increased skeletal variations and abnormalities (extra vertebrae, extra ribs, and increases in minor skeletal variations) at doses that also produced maternal toxicity and lower foetal body weight. Based on this animal data, the likelihood of panobinostat increasing the risk of both foetal death and developmental skeletal abnormalities is predicted to be high.	No	Given MM is primarily a disease for adult patients, no data have been generated in patients <18 years. Studies in animals have shown reproductive and embryo-foetal toxicity. Given its cytostatic/cytotoxic mode of action and foetal outcomes following exposure in pregnant animals, the time of gestation at which embryo-foetal risk may be greatest is anticipated to be early in pregnancy (during organogenesis), therefore, the risks to the foetus of inadvertent exposure may be considered to be greatest

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			during the early gestation period. Panobinostat should be used during pregnancy only if the expected benefits outweigh the potential risks to the foetus. If it is used during pregnancy or if the patient becomes pregnant while using it, the patient must be informed of the potential risk to the foetus.

5.2. Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effects and adverse reactions with long latency.

5.3. Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with cardiovascular impairment	Patients with uncontrolled or significant cardiac disease (e.g. unstable angina, congestive heart failure, recent MI or clinically significant bradycardia) have not been studied and were excluded from current clinical trials.
• Patients with a disease severity different from inclusion criteria in clinical trials	Heavily pretreated patients who have received more than 3 lines of prior therapy; patients with primary refractory myeloma (that is, patients who have never achieved a minor response with any therapy); patients refractory to bortezomib (that is, patients non-responsive while on bortezomib therapy or who progressed within 60 days of last therapy) have been excluded.
Population with relevant different ethnic origin	Panobinostat population PK model analysis showed that race was a statistically significant

Type of special population	Exposure
	covariate on panobinostat clearance and central volume of distribution with a representation from Asian (n=27), Black (n=34), and others (n=24) representing <6% of the studied population (n=581) with the large majority being Caucasians (PPK report).
Subpopulations carrying relevant genetic polymorphisms	Genotype status of CYP3A was analyzed at Baseline in all 14 patients in study B2110. Eleven patients had homozygous CYP3A5*3 genotype and 3 patients had heterozygous CYP3A5*1/*3 genotype. Panobinostat PK parameters were compared between carriers of these different alleles and there was no apparent difference in panobinostat Cmax or AUC values between patients carrying CYP3A5*1/*3 and CYP3A5*3/*3 alleles. However, this result should be interpreted in the context of the small number of patients studied.
Other	
• Children and adolescents <18 years of age	Not included in the clinical development program
• Elderly (patients ≥ 65 years	In the pooled data set, there were 41 MM patients ≥ 75 years of age, 143 patients aged 65 to <75 years and 267 patients <65 years of age in the PAN+BTZ+Dex treatment group.

Exposure in special population

Due to inclusion/exclusion criteria specified in the clinical trial program, there is no data available for following special population: pregnant, lactating, cardiac impaired and immunocompromised patients. Since MM is primarily a disease of adult population, no patient below 18 years of age was enrolled in the clinical trials; therefore, exposure data in pediatric population is not available. A waiver for pediatric development has been granted in the EU.

Renal impairment

A slightly longer exposure to study drug (panobinostat) of 1101 patient-months in patients with mild renal impairment versus 946 patient-months in patients with no renal impairment was reported (Table 5-4). The exposure duration to BTZ and Dex is similar compared to exposure with PAN in patients with mild and no renal impairment, respectively (Table 5-5, Table 5-6). Similar data was reported in the PBO+BTZ+Dex arm of Study D2308, with 859 and 891 patient-months in patients with mild and no renal impairment respectively. A shorter exposure was observed for patients with moderate and severe renal impairment in the PAN+BTZ-Dex arm of the pooled data set; 561 and 64 patient-months, respectively. A similar trend was seen in the PBO+BTZ+Dex arm of Study D2308. The duration of exposure observed in patients with moderate and severe renal impairment was 604 and 46 patient-months, respectively. However, in both arms, the number of patients with severe renal impairment was much lower (Table 5-4). Further detailed exposure is provided in the tables below: Exposure to study treatment – Table 5-3, Exposure to study drug

(Panobinostat) - Table 5-4, Exposure to Bortezomib – Table 5-5, Exposure to Dexamethasone - Table 5-6.

Hepatic impairment

A shorter exposure to study drug of 358 patient-months in patients with mild hepatic impairment compared to 2309 patient-months in patients with no hepatic impairment has been observed. The exposure duration to BTZ and Dex is similar compared to exposure with PAN in patients with mild and no hepatic impairment, respectively. A similar trend of exposure to study drug of 279 versus 2113 patient-months has been reported in the PBO+BTZ+Dex arm of Study D2308 in patients with mild and no hepatic impairment respectively (Table 5-3, Table 5-4, Table 5-5, Table 5-6).

Table 5-3 Clinical trial exposure to study treatment by special population

Special population	Patients n (%)	Patient-months
Renal impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No renal impairment	147 (32.6)	951.16
Mild renal impairment	182 (40.4)	1104.89
Moderate renal impairment	108 (23.9)	564.37
Severe renal impairment	13 (2.9)	63.77
Kidney failure	1 (0.2)	5.68
Randomized blinded trial: PAN + BTZ + Dex N=381		
No renal impairment	118 (31.0)	749.93
Mild renal impairment	157 (41.2)	982.97
Moderate renal impairment	94 (24.7)	497.94
Severe renal impairment	11 (2.9)	60.52
Kidney failure	1 (0.3)	5.68
Randomized blinded trial: PBO + BTZ + Dex N=377		
No renal impairment	139 (36.9)	895.44
Mild renal impairment	131 (34.7)	866.79
Moderate renal impairment	96 (25.5)	607.01
Severe renal impairment	11 (2.9)	45.86
Kidney failure	0	0.00
Hepatic impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No hepatic impairment	383 (84.9)	2319.64
Mild hepatic impairment	64 (14.2)	359.26
Moderate hepatic impairment	2 (0.4)	3.02
Severe hepatic impairment	0	0.00
Randomized blinded trial: PAN + BTZ + Dex N=381		
No hepatic impairment	322 (84.5)	1969.94
Mild hepatic impairment	55 (14.4)	316.12
Moderate hepatic impairment	2 (0.5)	3.02
Severe hepatic impairment	0	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377		
No hepatic impairment	327 (86.7)	2125.77
Mild hepatic impairment	49 (13.0)	280.80

Special population	Patients n (%)	Patient-months
Moderate hepatic impairment	0	0.00
Severe hepatic impairment	0	0.00

- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308
- Randomized blinded trial data are from study D2308 only
- Patients with missing Baseline impairment (renal/ hepatic) status are excluded from this analysis

Source: EU RMP v4.0 Annex 12 -Table 4-4.1, Table 4-5.1

Table 5-4 Clinical trial exposure to panobinostat by special population

Special population	Patients n (%)	Patient-months
Renal impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No renal impairment	147 (32.6)	946.43
Mild renal impairment	182 (40.4)	1101.01
Moderate renal impairment	108 (23.9)	561.35
Severe renal impairment	13 (2.9)	63.67
Kidney failure	1 (0.2)	5.68
Randomized blinded trial: PAN + BTZ + Dex N=381		
No renal impairment	118 (31.0)	746.45
Mild renal impairment	157 (41.2)	980.21
Moderate renal impairment	94 (24.7)	495.38
Severe renal impairment	11 (2.9)	60.52
Kidney failure	1 (0.3)	5.68
Randomized blinded trial: PBO + BTZ + Dex N=377		
No renal impairment	139 (36.9)	891.40
Mild renal impairment	131 (34.7)	859.20
Moderate renal impairment	96 (25.5)	604.16
Severe renal impairment	11 (2.9)	45.83
Kidney failure	0	0.00
Hepatic impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No hepatic impairment	383 (84.9)	2308.83
Mild hepatic impairment	64 (14.2)	358.47
Moderate hepatic impairment	2 (0.4)	2.92
Severe hepatic impairment	0	0.00
Randomized blinded trial: PAN + BTZ + Dex N=381		
No hepatic impairment	322 (84.5)	1961.69
Mild hepatic impairment	55 (14.4)	315.70
Moderate hepatic impairment	2 (0.5)	2.92
Severe hepatic impairment	0	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377		
No hepatic impairment	327 (86.7)	2113.35
Mild hepatic impairment	49 (13.0)	278.87
Moderate hepatic impairment	0	0.00
Severe hepatic impairment	0	0.00

Special population	Patients n (%)	Patient-months
- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category		
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308		
- Randomized blinded trial data are from study D2308 only		
- Patients with missing Baseline impairment (renal/ hepatic) status are excluded from this analysis		
Source: EU RMP v4.0 Annex 12 Table 4-4.2, Table 4-5.2		

Table 5-5 Clinical trial exposure to bortezomib by special population

Special population	Patients n (%)	Patient-months
Renal impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No renal impairment	147 (32.6)	919.10
Mild renal impairment	182 (40.4)	1000.61
Moderate renal impairment	108 (23.9)	536.84
Severe renal impairment	13 (2.9)	62.85
Kidney failure	1 (0.2)	5.55
Randomized blinded trial: PAN + BTZ + Dex N=381		
No renal impairment	118 (31.0)	728.15
Mild renal impairment	157 (41.2)	892.65
Moderate renal impairment	94 (24.7)	471.16
Severe renal impairment	11 (2.9)	59.60
Kidney failure	1 (0.3)	5.55
Randomized blinded trial: PBO + BTZ + Dex N=377		
No renal impairment	139 (36.9)	850.63
Mild renal impairment	131 (34.7)	816.82
Moderate renal impairment	96 (25.5)	583.52
Severe renal impairment	11 (2.9)	45.31
Kidney failure	0	0.00
Hepatic impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No hepatic impairment	383 (84.9)	2177.58
Mild hepatic impairment	64 (14.2)	339.35
Moderate hepatic impairment	2 (0.4)	2.89
Severe hepatic impairment	0	0.00
Randomized blinded trial: PAN + BTZ + Dex N=381		
No hepatic impairment	322 (84.5)	1852.62
Mild hepatic impairment	55 (14.4)	296.48
Moderate hepatic impairment	2 (0.5)	2.89
Severe hepatic impairment	0	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377		
No hepatic impairment	327 (86.7)	2027.17
Mild hepatic impairment	49 (13.0)	260.57
Moderate hepatic impairment	0	0.00
Severe hepatic impairment	0	0.00

Special population	Patients n (%)	Patient-months
- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category		
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308		
- Randomized blinded trial data are from study D2308 only		
- Patients with missing Baseline impairment (renal/ hepatic) status are excluded from this analysis		
Source: EU RMP v4.0 Annex 12 Table 4-4.3, Table 4-5.3		

Table 5-6 Clinical trial exposure to dexamethasone by special population

Special population	Patients n (%)	Patient-months
Renal impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No renal impairment	147 (32.6)	907.73
Mild renal impairment	182 (40.4)	1054.78
Moderate renal impairment	108 (23.9)	538.22
Severe renal impairment	13 (2.9)	61.40
Kidney failure	1 (0.2)	5.59
Randomized blinded trial: PAN + BTZ + Dex N=381		
No renal impairment	118 (31.0)	719.47
Mild renal impairment	157 (41.2)	943.51
Moderate renal impairment	94 (24.7)	475.07
Severe renal impairment	11 (2.9)	58.58
Kidney failure	1 (0.3)	5.59
Randomized blinded trial: PBO + BTZ + Dex N=377		
No renal impairment	139 (36.9)	850.56
Mild renal impairment	131 (34.7)	850.23
Moderate renal impairment	96 (25.5)	593.35
Severe renal impairment	11 (2.9)	45.77
Kidney failure	0	0.00
Hepatic impairment		
Pooled Data: PAN + BTZ + Dex N=451		
No hepatic impairment	383 (84.9)	2209.48
Mild hepatic impairment	64 (14.2)	347.27
Moderate hepatic impairment	2 (0.4)	3.02
Severe hepatic impairment	0	0.00
Randomized blinded trial: PAN + BTZ + Dex N=381		
No hepatic impairment	322 (84.5)	1885.70
Mild hepatic impairment	55 (14.4)	305.54
Moderate hepatic impairment	2 (0.5)	3.02
Severe hepatic impairment	0	0.00
Randomized blinded trial: PBO + BTZ + Dex N=377		
No hepatic impairment	327 (86.7)	2062.46
Mild hepatic impairment	49 (13.0)	269.11
Moderate hepatic impairment	0	0.00
Severe hepatic impairment	0	0.00

Special population	Patients n (%)	Patient-months
- Patient-month for a category is calculated as the sum of the duration of exposure of each patient in months in that exposure category		
- Pooled data PAN + BTZ + Dex are from study B2207 expansion cohort, study DUS71 and D2308		
- Randomized blinded trial data are from study D2308 only		
- Patients with missing Baseline impairment (renal/ hepatic) status are excluded from this analysis		
Source: EU RMP v4.0 Annex 12 Table 4-4.4, Table 4-5.4		

6. Part II Safety specification Module SV: Post-authorization experience

6.1. Part II Module SV.1. Post-authorization exposure

6.1.1. Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilogram (kg) of active substance sold cumulatively and the defined monthly dose by weight (DMD).

6.1.2. Part II Module SV.1.2. Exposure

Post marketing exposure is available until 10-May-2024.

The cumulative sales volume of Farydak was approximately 4.67 kg (active substance). The recommended monthly dose (RMD) for Farydak is 133 mg/month (anhydrous free base).

The cumulative patient exposure since the International Birth Date (IBD) of the product is estimated to be approximately 2926 PTY (up to 10-May-2024).

7. Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1. Potential for misuse for illegal purposes

A possible risk of misuse or dependence on panobinostat is not anticipated on the basis of its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials which would suggest a potential for abuse or dependence with panobinostat.

8. Part II Safety specification Module SVII: Identified and potential risks

8.1. Part II SVII.1 Identification of safety concerns in the initial RMP submission

This section is not applicable; the RMP was already approved.

8.2. Part II SVII.2 New safety concerns and reclassification with a submission of an updated RMP

In the current RMP, the following important identified/potential risks topics have been removed as per the revised list of safety concerns in accordance with the GVP Module 5 rev 2. Below is the list of safety concerns and the justification for the deletion.

Safety topics removed from the RMP:

Severe haemorrhage

Intracranial haemorrhage, gastrointestinal (GI) haemorrhage, haematochezia, haematoma, conjunctival haemorrhage, epistaxis, and haematuria are listed in the Farydak® SmPC as common ADRs, while shock haemorrhagic, haematemesis, pulmonary haemorrhage, haemoptysis and petechiae are listed as uncommon ADRs. Anaemia is included in SmPC as very common ADR.

Information and guidelines for the mitigation of the risk of haemorrhage in clinical practice are provided in the corresponding sections of the Farydak® SmPC and product information. Search of pharma& safety database including serious cases belonging to MedDRA SMQs ‘Haemorrhage laboratory terms’ (broad) and ‘Haemorrhage terms (excluding laboratory terms)’ (broad) with data lock point 10-May-2024 identified 466 cases, including 436 cases from the studies, 27 spontaneous cases and 3 cases from other sources. The most frequently reported PTs in serious cases were Haemoglobin decreased (n=136), Gastrointestinal haemorrhage (n=45), Epistaxis (n=42) and Haematuria (n=25) what is in line with approved product information.

Thrombosis and bleeding are associated with MM and as well as with MM treatments (Kulkarni et al 2023, Shaw et al 2021, Gibbins et al 2018).

In conclusion, results of analysis of available data are in line with known safety profile of panobinostat in relation with bleeding and background incidence/characteristics of bleeding in MM patients. Risk is considered well characterized. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the routine PV. The risk is properly and effectively communicated through the product information. Safety information is available in the public domain, including independent reviews (Kulkarni et al 2023, Shaw et al 2021, Gibbins et al 2018) and medical handbooks, and the risk management is considered integrated in clinical practice. Appropriate risk minimisation measures are in place. Therefore, we propose deletion of risk Severe haemorrhage from RMP.

Severe infections (including sepsis/pneumonia/reactivation of hepatitis B infection)

Pneumonia and upper respiratory tract infection are listed in the Farydak® SmPC as very common ADRs. Septic shock, urinary tract infection, viral infection, oral herpes, Clostridium difficile colitis, otitis media, cellulitis, sepsis, gastroenteritis, lower respiratory tract infection, candidiasis are listed as common ADRs, whereas pneumonia fungal, hepatitis B and aspergillosis are listed as uncommon ADRs.

Pertinent information and guidelines for the mitigation of the risk of infections in clinical practice are provided in the approved product information. Search of pharma& safety database of serious case with PTs belonging to MedDRA SMQs 'Sepsis' (broad), 'Infective pneumonia' (broad), 'Opportunistic infections' (broad), and 'Liver infections' (broad) with data lock point 10-May-2024 identified 1122 cases including 1061 CT cases and 56 spontaneous reports and 5 cases from other sources. The most frequently reported PTs were Pneumonia (n=459), Sepsis (n=161), Septic shock (n=65), Respiratory tract infection (n=34) what is in line with information available in approved SmPC. Only one case with PT Hepatitis B reactivation was identified.

Serious infections are associated with MM and as well as with MM treatments (Blimark et al 2015).

In conclusion, results of analysis of available data are in line with known safety profile of panobinostat in relation to infections and background incidence/characteristics of infections in MM. Risk is considered well characterized. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the routine PV. The risk is properly and effectively communicated through the product information. Safety information is available in the public domain, including independent reviews (Blimark et al 2015) and medical handbooks, and the risk management is considered integrated in clinical practice. Appropriate risk minimization measures are in place. Therefore, we propose deletion of risk Severe infections (including sepsis/pneumonia/reactivation of hepatitis B infection) from RMP.

Developmental toxicity

No ADRs pertaining to developmental toxicity are listed in the Farydak® SmPC. Information and guidelines for the mitigation of the risk in clinical practice are provided in the pertinent sections of the Farydak product information.

Cumulative search of pharma& database with data lock point 10-May-2024, identified 30 cases including 29 cases from the studies and only 1 spontaneous case of cases with relevant PTs.

The search did not identify cases of confirmed developmental toxicity.

Multiple myeloma (MM) is largely a disease of older adults. The median age at diagnosis is 65 to 74 years; only 10 and 2 percent of patients are younger than 50 and 40 years, respectively. MM in patients younger than 30 years accounts for only 0.3% of all myelomas. MM is also slightly more frequent in males than in females (approximately 1.4:1) (Kyle et al 2003, Bladé et al 1998).

In conclusion, considering following:

- there is no case report of exposure during pregnancy or developmental toxicity in approved indication
- there is only one early phase clinical study case of exposure during pregnancy in patient with Hodgkin's disease
- appropriate risk minimization measures are in place both in approved product information and standard clinical care of hematologic neoplasms

multiple myeloma is largely a disease of older adults and also slightly more frequent in males than in females, we are of the opinion that the risk of developmental toxicity is very low and does not represent important potential risk in clinical practice.

No further evaluation is planned as part of the PV plan and no significant safety information is expected from the routine PV.

Therefore, we propose deletion of important developmental toxicity from the RMP.

Carcinogenicity/Second primary malignancy

No ADRs pertaining to carcinogenicity/second primary malignancy are listed in the Farydak® SmPC. The relevant information is provided in the non-clinical safety sections of the Farydak® SmPC and patient leaflet. Carcinogenicity studies have not been performed with panobinostat. Panobinostat has demonstrated mutagenic potential in the Ames assay, endo reduplication effects in human peripheral blood lymphocytes in vitro. Additionally, in vivo DNA damage was observed in a COMET study in mouse lymphoma L5178Y cells and a dose-dependent molecular mechanisms study in murine bone marrow cells. The in vitro and in vivo findings are attributed to the pharmacological mode of action.

Cumulative analysis of pharma& safety database with data lock point 10-May-2024 identified 1025 cases with PTs belonging to SOC ‘Neoplasms benign, malignant and unspecified (incl. cysts and polyps)’, including 894 cases from studies, 119 spontaneous cases and 12 cases from other sources. The most frequently reported PTs were Plasma cell myeloma (n=394) and 'Malignant neoplasm progression (n=776). Cases that report progression of the indication and cases that report relapse or progression of pre-existing malignancy do not qualify as part of carcinogenicity/ second primary malignancy.

PT Second primary malignancy was identified in 37 cases. Among these 37 cases, panobinostat was used for MM in only 12 cases. In 12 cases where Panobinostat was used in MM and second primary malignancy was coded, the most frequent type of secondary malignancy was

haematological malignancy (n=4) what is in line with background incidence of secondary malignancy in MM (Poh et al 2021).

Causality assessment on case level is very difficult due to significant confounding by previous and concomitant treatments. Different anti-myeloma therapies pose different risks to SPM incidence, however an increased SPM risk, especially hematologic SPMs, were noted overall (Poh et al 2021). Prolonged treatment with alkylators, especially oral melphalan, was associated with an increased hematologic SPM risk. Likewise, ASCT also appeared to minimally increase SPM risk, while immunomodulatory drugs, specifically lenalidomide, was consistently associated with a hematologic SPM risk when used in multiple contexts such including induction, maintenance after ASCT, relapsed/refractory and transplant-ineligible setting. A trend for increased solid tumour SPM risk with lenalidomide was also noted in the maintenance setting.

In conclusion, during clinical development program and 9 years of intensive post-marketing monitoring no signal of increased SMP was detected from clinical data. No further evaluation is planned as part of the PV plan and no significant safety information is expected from the routine PV. Therefore, we propose to delete potential risk Carcinogenicity/Second primary malignancy from RMP.

Medication errors

Considering the complex dosing regimen, medication errors represented an important potential risk in the Farydak® RMP version 6. No ADRs pertaining to the topic are listed in Farydak® SmPC.
Detailed guidance on dosing schedule for prescribers and patients is provided in the approved product information.
The colour and the imprinting of the capsules, clearly identify the product and its strength to minimise the potential for any medication error.
The Farydak is available in packs containing 6, 12 or 24 capsules. The clinicians can prescribe small packs that contain only 6 capsules to patients under increased risk for medication errors.
Blister has special design acting as visual reminder to minimise dosing errors with printed days of the cycle on compartment with capsules when Farydak should be taken and empty blister compartments corresponding to the day of the cycle on which Farydak should not be taken including the rest period in week 3.
The additional risk minimisation activity (EU only) includes a patient card for patients with instructions on the dosing regimen for panobinostat, bortezomib and dexamethasone, as a reminder of the prescribed medication scheme. Therefore, blister design and patient card have overlapping role to remind the patient on appropriate schedule. The additional value of patient card is that reminds patient not only to panobinostat intake but also intake of bortezomib and dexamethasone. The additional value of specially designed blister in comparison to patient card is that compliance to the schedule is not dependant on patient ability to tick each intake of panobinostat, bortezomib and dexamethasone, instead by removing capsules from blister and scratching empty cavities patient tracks dosing schedule. Initially MAH committed to evaluate effectiveness of this RMM in a PASS (Non-Interventional Study for Protocol No. CLBH589D2408) but it was proven not to be feasible due to low number patients recruited. PRAC agreed to remove the study from the RMP

and that effectiveness of RMM can be assessed by routine pharmacovigilance (as per the final EC decision of EMA procedure number EMEA/H/C/003725/II/0013).
Cumulative analysis of pharma& safety database with data lock point 10-May-2024 identified 96 cases with 110 PTs belonging to SMQ Medication error (broad). Search strategy of using SMQ Medication error (broad) is good in sense that enables identification of all relevant cases for further in-depth assessment but without further in-depth assessment of relevant cases it is difficult to make proper conclusion on occurrence and root causes of medication errors.
As SMQ Medication error (broad) is not specific search for ME and does not contain only PTs (preferred term) describing ME but also off label use and quality issues, it is not surprise that majority of identified cases were cases of off label use with PT Product use in an unapproved indication (n=46), being the most frequently reported PT, followed by Product use issue (n=17).

As patient card was introduced due to complex dosing schedule in depth medical review of cases describing inappropriate schedule of product administration (n=20) were done. Inappropriate schedule of product administration can be done unintentionally, and such cases represent medication error but also intentionally and such cases do not represent cases of medication error. The analysis of cases of inappropriate schedule of product administration in pharma& safety database identified only 3 cases of medication error where it was clearly stated that inappropriate schedule of product administration was made by patient – in error in approved indication. However, two of these cases occurred in clinical trial setting before marketing authorization, meaning there was only one relevant case in post-marketing setting in more than 9 years since the IBD of 23-Feb-2015. The review of cases did not reveal a common pattern of error, nor in the pattern of adverse events. Two cases were reported in 2010 and one case was reported in 2020.

Literature search identified recent studies (Bird et al 2020, Maouche et al 2022) describing real life dosing of panobinostat in MM. Landscape of available therapies in MM changed significantly from approval of Farydak and in real life Farydak might be used in more heavily pretreated patients. These studies identified frequent practice of physicians to intentionally change approved dosing including frequency of dosing to improve tolerability due to use in heavily pre-treated patients in clinical practice. In such setting patient card is not useful to patients. These studies did not identify problems with off label dosing of panobinostat by physicians.

Scientific literature was also searched for publications assessing effectiveness of similar risk minimization measures. We identified a recent study funded by EMA measuring effectiveness of routine and additional RMM implemented due to medication errors of methotrexate related to the wrong dosing schedule. According to the results of the study higher number of patients was aware of box warning in patient leaflet and reminder on package than were aware of patient reminder card (Lysen et al 2024).

Sufficient time has passed since Farydak was the first introduced and stakeholders gained experience with such complex dosing. Clinicians treating MM are used to complex dosing schemes as the majority of the available treatments are used in combination with other medicinal products, not every day and with rest period between cycles. As panobinostat is used with bortezomib

applied by healthcare professionals, patients are regularly supervised by healthcare professionals throughout the cycle.

In conclusion, during 9 years of post-marketing monitoring of panobinostat, sufficient data was collected to better understand the potential risk Medication errors in clinical practice. Accumulating data shows impact to the individual is less than initially anticipated resulting in the potential risk not being considered important anymore. The routine risk minimisation measures are sufficient to ensure the correct use and are proportionate to level of the risk demonstrated in clinical practice.
No further evaluation is planned as part of the PV plan and no significant new safety information is expected from the routine PV.

8.3. Part II SVII.3: Details of important identified risks, important potential risks, and missing information

Not applicable.

9. Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Category	Safety Concern
Important identified risks	None
Important potential risks	None
Missing information	None

10. Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1. Part III.1. Routine pharmacovigilance activities

10.1.1. Routine pharmacovigilance activities beyond ADRs reporting and signal detection

None.

Other forms of routine pharmacovigilance activities

None.

10.2. Part III.2. Additional pharmacovigilance activities

None.

10.3. Part III.3. Summary Table of additional pharmacovigilance activities

Not applicable.

11. Part IV: Plans for post-authorization efficacy studies

There are no post-authorization efficacy studies that are currently ongoing or planned.

12. Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1. Part V.1. Routine risk minimization measures

Not applicable as there are no safety concerns for Farydak.

12.2. Part V.2. Additional Risk minimization measures

Not applicable as there are no safety concerns for Farydak.

12.3. Part V.3 Summary of risk minimization measures

Not applicable as there are no safety concerns for Farydak.

13. Part VI: Summary of the risk management plan: Farydak (panobinostat)

This is a summary of the risk management plan (RMP) for panobinostat. The RMP details important risks of panobinostat, how these risks can be minimized, and how more information will be obtained about panobinostat risks and uncertainties (missing information).

Panobinostat summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how panobinostat should be used.

This summary of the RMP for panobinostat should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of panobinostat RMP.

13.1. Part VI: I. The medicine and what it is used for

Panobinostat 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.

Further information about the evaluation of panobinostat benefits can be found in panobinostat EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page on the EMA webpage.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003725/WC500193301.pdf. (last accessed 21-May-2018).

13.2. Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of panobinostat, together with measures to minimize such risks and the proposed studies for learning more about panobinostat risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

13.2.1. Part VI – II.A: List of important risks and missing information

Important risks of panobinostat are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of panobinostat. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	None

13.2.2. Part VI - II B: Summary of important risks

Not applicable.

13.2.3. Part VI – II C: Post-authorization development plan

13.2.3.1. II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of panobinostat.

13.2.3.2. II.C.2. Other studies in post-authorization development plan

None.

14. Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities

None.

Annex 7 - Other supporting data (including referenced material)

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Zolinza USPI (2015).