3 July 2015
EMA/CHMP/496296/2015 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Farydak

International non-proprietary name: Panobinostat

Procedure No. EMEA/H/C/003725/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ASCT	Autologous stem cell transplantation
AE	Adverse Event
BTZ	bortezomib
CEP	Certification of suitability of European Pharmacopoeia monographs
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameter
CRF	Case Report/Record Form
CR	Complete response
DAC	deacetylase
Dex	dexamethasone
DoE	Design of experiments
DOR	duration of response
EBMT	European Group for Blood and Marrow Transplantation
EC	European Commission
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy-General
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
FAS	full analysis set
GC	Gas chromatography
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
Hsp90	heat shock protein 90
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry

IL-6	interleukin-6
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPC	In-process control
IR	Infrared
IRC	Independent Review Committee
ISS	International Staging System
iv	intravenous(ly)
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
mEBMT	modified European Group for Blood and Marrow Transplantation
MM	Multiple myeloma
MR	minimal response
MRR	minimal response rate
MTD	maximum tolerable dose
NCI	National Cancer Institute
nCR	Near complete response
NMR	Nuclear magnetic resonance
ORR	overall response rate
OS	overall survival
PAN	panobinostat
PAR	Proven Acceptable Range
PBO	placebo
PCTFE	Polychlorotrifluoroethylene
PD	progressive disease
PE	Polyethylene
PEP	Protein electrophoresis
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PR	partial response

PRO	patient-reported outcome
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QoL	quality of life
QP	Qualified person
RH	Relative humidity
RR	response rate
sCR	stringent complete response
SCT	stem cell transplantation
SD	stable disease
sFLC	serum free light chain
SmPC	Summary of product characteristics
TGA	Thermogravimetric analysis
TIW	three times per week
TP1	Treatment phase 1
TP2	Treatment phase 2
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TTP	time to progression
TTR	time to response
VGPR	very good partial response
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 5 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Farydak, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013.

Farydak, was designated as an orphan medicinal product EU/3/12/1063 on 8 November 2012. Farydak was designated as an orphan medicinal product in the following indication: Treatment of multiple myeloma.

The applicant applied for the following indication:

Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Farydak as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Panobinostat was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance panobinostat (as lactate anhydrous) contained in the above medicinal product to be considered as a new active substance in itself as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 29 August 2006, 18 October 2006 and 31 January 2008. The Protocol Assistance pertained to quality and clinical aspects of the dossier.

Licensing status

Farydak has been given a Marketing Authorisation in the United States on 23 February 2014.

A new application was filed in the following countries: Switzerland, Australia, Colombia, Indonesia, Japan and South Africa.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Filip Josephson

- The application was received by the EMA on 5 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2014
- During the meeting on 11 September 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 January 2015.
- The integrated inspection report of the GCP inspections carried out at three clinical investigator sites, of which two in China and one in Egypt, during September 2014, was issued on 7 November 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 March 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 April 2015.
- During a meeting of SAG on 4 May 2015, experts were convened to address questions raised by the CHMP.
- During the meeting on 7 May 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.

- During the CHMP meeting on 18-21 May 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22-25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Farydak.
- A revised opinion was adopted by the CHMP on 3 July 2015 in order to better clarify the benefit-risk balance.

2. Scientific discussion

2.1. Introduction

Problem statement

Multiple myeloma (MM) is a malignant proliferation of plasma cells and accounts for 10% 15% of all haematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow. Multiple myeloma (MM) is an incurable disease and accounts for 1% of all cancers and around 10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year; the mortality is 4.1/100 000/year (ESMO guidelines 2013). MM is also slightly more frequent in men than in women (approximately 1.4:1). MM is a disease of older adults. The median age at diagnosis is 66 years; only 10 and 2 per cent of patients are younger than 50 and 40 years, respectively (Kyle et al., 2003; Bladé et al., 1998).

Multiple myeloma (MM) is a malignant plasma cell proliferation that occurs within a spectrum of diseases that includes monoclonal gammopathy of undetermined significance, primary amyloidosis, non-secretory myeloma, and solitary plasmacytoma (IMWG, BJH, 2003).

According to clinical guidelines, treatment should be initiated in all patients with active myeloma fulfilling the CRAB criteria, (hypercalcaemia >11.0 mg/dl), creatinine >2.0 mg/ml, anaemia (Hb <10 g/dl), active bone lesions), and in those symptomatic due to the underlying disease.

Therapies for myeloma currently consist of the following 6 main classes of agents: proteasome inhibitors (bortezomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), corticosteroids, alkylators, anthracyclines, nitrosoureas (to a lesser extent), plus high-dose chemotherapy and autologous or allogeneic haematopoietic stem cell transplantation (ASCT) for those who are eligible.

About the product

Farydak is a histone deacetylase (HDAC) inhibitor that 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. Increased levels of acetylated histones were observed in xenografts from mice that were treated with panobinostat. Panobinostat shows more cytotoxicity towards tumour cells compared to normal cells (SmPC, section 5.1; see Non-clinical aspects).

The sponsor applied for the following indication: Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The recommended indication for approval is: Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.Treatment with Farydak should be initiated by a physician experienced in the use of anti-cancer therapies (see SmPC, section 4.2).

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).

Panobinostat is administered in combination with bortezomib and dexamethasone, as shown in Tables 1 and 2. The bortezomib and dexamethasone prescribing information should be consulted prior to the start of the combination treatment to assess whether a dose reduction is required.

The recommended dose of bortezomib is 1.3 mg/m^2 given as an injection. The recommended dose of dexamethasone is 20 mg taken orally on a full stomach.

Table 1: Recommended dosing schedule of panobinostat in combination with bortezomib and dexamethasone (cycles 1-8)

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

Table 2: Recommended dosing schedule of panobinostat in combination with bortezomib and dexamethasone (cycles 9-16)

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

Farydak should be administered orally once daily on scheduled days only, at the same time each day. The capsules should be swallowed whole with water with or without food (see section 5.2), and they should not be opened, crushed or chewed. If a dose is missed, it can be taken up to 12 hours after the specified dose time. If vomiting occurs the patient should not take an additional dose, but should take the next usual prescribed dose (see SmPC, section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 10, 15 or 20 mg of panobinostat as active substance.

Other ingredients are:

Capsule contents:

Magnesium stearate, mannitol, microcrystalline cellulose and pregelatinised starch (maize).

Capsule shell:

Gelatin, titanium dioxide (E171), brilliant blue FCF (E133, 10 mg capsule), iron oxide yellow (E172, 10 and 15 mg capsules) and iron oxide red (E172, 15 and 20 mg capsules).

Printing ink:

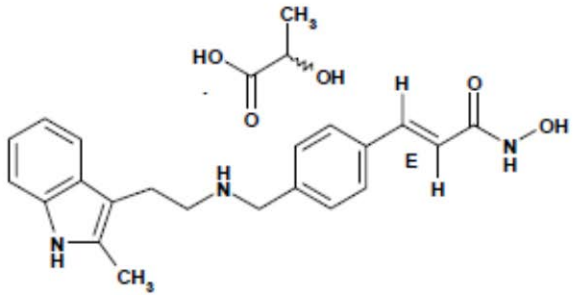
Iron oxide black (E172), propylene glycol (E1520), shellac glaze and ethanol.

The product is available in PVC/PCTFE/alu blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of panobinostat is (2*E*)-*N*-hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1) and it has the following structure and properties:



Molecular formula: $C_{21}H_{23}N_3O_2$ - Relative molecular mass: 439.51 $gmol^{-1}$

The structure of panobinostat was inferred from the route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRPD.

The active substance is a white to slightly yellow or brownish, slightly hygroscopic, light sensitive crystalline powder, slightly soluble in water and ethanol but insoluble in acetonitrile and *n*-octanol. Since it is slightly basic, panobinostat is more soluble at the lower pH found in the stomach. The active substance is de-lumped and sieved to ensure content uniformity in the finished product and rapid dissolution *in vivo*.

Panobinostat free base is achiral although the lactate counter-ion contains a single chiral centre. Racemic lactic acid is used resulting in a racemic active substance. The olefin is produced in the *E* configuration.

Polymorphism has not been observed for panobinostat, although a solvated and a hydrated form are known, the latter having been used in early clinical studies. The proposed anhydrous form is thermodynamically stable relative to the other two and is formed by the commercial manufacturing process.

Panobinostat is considered to be a new active substance. It is neither an active metabolite, nor a pro-drug of any other active substance authorised within a medicinal product in the EU.

Manufacture, characterisation and process controls

Panobinostat is synthesized convergently in five main steps using commercially available well defined starting materials with acceptable specifications. Two manufacturers are responsible for production of intermediates and the third for synthesizing the active substance. The olefin geometry is controlled by the process and the minor *Z* isomer is limited both in an intermediate and the active substance specifications. The starting materials were re-defined during the procedure in order to address a major objection raised by CHMP. As a result, the originally-proposed starting materials are now classed as intermediates, new starting materials have been defined, and new manufacturers responsible for the additional manufacturing steps have been added. The route of synthesis of these intermediates remains the same although additional steps will now be carried out under GMP. The applicant has committed to provide data demonstrating equivalence of the intermediates made under GMP to those manufactured previously, as well as a revised QP declaration and certificates of analysis of the new starting materials by September 2015.

Adequate in-process controls are applied during the synthesis and the critical elements of the process required to ensure the quality of panobinostat have been discussed in detail. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised. A genotoxic impurity is present in one of the re-defined starting materials which is currently controlled as a regular impurity. Given its structure and the opportunity for depletion in the intervening synthetic steps (it hydrolyses rapidly in the presence of water), it is

highly unlikely to be present in the active substance which is itself genotoxic. Nonetheless, the applicant has committed to develop an analytical method specific to this impurity and provide the details to CHMP by September 2015, including data to demonstrate its depletion.

The active substance is packaged in PE bag stored inside a sealed laminated foil bag. The packaging materials comply with the EC Directive 2002/72/EC and EC Regulation 10/2011.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for appearance, identity (IR, XRPD), assay (HPLC), impurities (HPLC), genotoxic impurity (IC), residual solvents (GC), water content (coulometric oven method), loss on drying (TGA), heavy metals (ICP-MS), sulphated ash (micro method), microbial enumeration (Ph. Eur., skip testing), lactate assay (potentiometric titration), particle size (laser diffraction) and colour and clarity of solution (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. One genotoxic impurity is controlled below the TTC level in the active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on twenty four pilot and commercial scale batches of the active substance used for toxicology, clinical and stability studies are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (25 ^{o}C / 60% RH), for up to 24 months under intermediate conditions (30 ^{o}C / 75% RH), and for up to 6 months under accelerated conditions (40 ^{o}C / 75% RH) according to the ICH guidelines were provided. In addition, data was provided for the same three batches stored under refrigerated conditions (5 ^{o}C) for up to 12 months. The following parameters were tested: appearance, identity (XRPD), assay (HPLC), impurities (HPLC), genotoxic impurity (IC), loss on drying (TGA), and colour and clarity of solution (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating.

No significant trends were observed in any batches under any of the conditions tested. These batches were manufactured before the starting materials were re-defined. However, they were made using exactly the same process, albeit with two steps carried out outside of GMP. The applicant has committed to present comparability data between intermediates manufactured both under and outside of GMP by September 2015. Additional stability studies are considered unnecessary.

Photostability testing following the ICH guideline Q1B was performed on one batch which was also used for forced degradation work. Stressed conditions included aqueous solutions in the presence (or absence) of acid, base and oxidant and at elevated temperatures and solid state studies at high temperature and humidity, exposed to oxygen. The active substance is slightly sensitive to light and degrades significantly in aqueous solution under all conditions, being susceptible to oxidation and hydrolysis.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable when protected from light and moisture. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of development was to identify an immediate release solid oral dosage form of panobinostat. Early clinical studies used hard capsules manufactured using a hydrate form of the active substance, made *via* simple dry blending. Issues with the flow properties and content uniformity of the bulk powder indicated that an alternative formulation was required, in order to supply larger scale trials and eventually, the commercial market. A switch was made to the anhydrous form of panobinostat and the bulk blend was manufactured by a more scalable wet granulation process. Despite the slight hygroscopicity of the active substance, it was shown to be stable to hydration and to changes in polymorphic form in the presence of water. The two formulations have the same quantitative composition, other than a slight increase in lubricant content, compensated for by a reduction in filler weight in the latter. The same bulk powder blend is used for the manufacture of each tablet strength, only the amount encapsulated and the capsule size being different. The redeveloped formulation solved the content uniformity issues. Compatibility of panobinostat with the excipients was demonstrated by a series of stability studies on binary mixtures.

In order to develop a suitable manufacturing process, a qualitative risk analysis was undertaken to identify factors likely to impact the performance of the product based on previous knowledge of panobinostat properties and of wet granulation and encapsulation processes in general. Parameters identified for further investigation were granulation water amount, granulation time, final blending revolutions, and encapsulation speed. These factors were investigated using a design of experiments (DoE) approach on full scale batches of the 15 and 20 mg strengths. It was found that a combination of high water content and long granulation time resulted in denser granules which dissolve more slowly. Based on these results, five full scale batches of the 10 mg strength were manufactured varying the various parameters within the tighter limits shown by the DoE to afford finished product of suitable quality and with an acceptable dissolution profile.

No formal design space is claimed by the applicant despite the multi-variate experiments carried out. The claimed proven acceptable ranges (PARs) and set-points are considered acceptable.

The formulation used during the later clinical studies is the same as that intended for marketing.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The discriminatory power of the dissolution method has been demonstrated by comparison of profiles of batches manufactured with the critical process parameters (CPPs) set just outside the PARs. The dissolution profiles of the two clinical formulations were compared and despite differences at neutral pH (although the end-point is the

same), the high solubility of the active substance in acidic media means complete dissolution in the stomach is expected, especially under the prescribed fasting conditions.

The primary packaging is PVC/PCTFE/alu blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: blending of part of the intra-granular excipients with panobinostat and wet granulation; drying and milling; blending with the remaining portions of intra-granular excipients and further wet granulation; drying and milling; blending with extra-granular excipients; encapsulation; packaging. The process is considered to be a standard manufacturing process.

The wet granulation steps are key to ensuring adequate content uniformity of the blend. PARs for added water and granulation time were set in order to achieve the desired granule size and density. Since water content can adversely affect capsule filling, an in-process control (IPC) for LOD following granulation and drying is included and PARs for number of blending revolutions and encapsulation speed are defined. In practice, the defined ranges are rather tight, cover likely variability in the process, and are justified by multi-variate experiments. IPCs are also included for appearance, weight, length and disintegration time of the bulk capsules. Stability data supports a bulk holding time for the hard capsules stored inside LDPE bags in sealed metal containers of up to 12 months.

Major steps of the manufacturing process have been validated on three commercial scale batches of each strength, manufactured at the intended set-points. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (UV, HPLC), dissolution (Ph. Eur.), impurities (HPLC), water content (KF), assay (HPLC), uniformity of dosage units (Ph. Eur.) and microbial enumeration (Ph. Eur., skip-testing).

One impurity, also a metabolite of the active substance, has been qualified at the appropriate level and is controlled in the finished product specification. Another specified impurity is controlled below the qualification threshold. The same genotoxic impurity as is limited in the active substance specification is also controlled in the finished product specification according to the TTC approach.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for six commercial scale batches of the 10 and 20 mg strengths and three batches of the 15 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data was provided on three commercial scale batches of the 10 and 20 mg strengths of finished product only. This bracketing approach is acceptable since these strengths represent the extremes and the capsules are quantitatively proportionate in terms of composition and manufactured from a common blend. The batches of finished product were identical to those proposed for marketing and samples were stored in two packaging formats for up to 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH), according to the ICH guidelines, were provided. One packaging format (PVC/PCTFE/alu blister packs) represents the intended commercial pack whilst the other (PVC/PVDC blister packs) was the originally proposed pack. Samples were tested for appearance, dissolution, water content, impurities and assay. No out of specification results were observed under either condition. A slight increase in one specified impurity and an increase in water content were observed after 24 months under long term conditions whereas under intermediate conditions, a slight increase in two specified impurities, an increase in water content, and a decrease in assay were observed. The PVC/PCTFE/alu packaging material affords better moisture protection and was thus selected for the commercial product. Stability data was generated under accelerated conditions (40 ºC / 75% RH) using batches packed only in PVC/PVDC blisters. Although this is not the packaging proposed for marketing, the approach is considered acceptable since it represents a “worst case scenario” with the commercial packaging offering better protection.

One batch each of the 10 and 20 mg strengths was also tested under the following conditions: 5 ºC / ambient RH; -20 ºC / ambient RH; 50 ºC / ambient RH; freeze/thaw cycles between -20 ºC and 25 ºC / ambient RH. Results showed no significant trends other than a reduction in water content at 50 ºC. This study allowed assessment of acceptable transport conditions.

One batch each of the 10 and 20 mg strengths was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant trends were observed indicating that the product stored in the intended packaging is not photosensitive.

Based on available stability data, the shelf-life (3 years) and storage conditions (do not store above 30 ºC) as stated in the SmPC are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture is provided.

Magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no formal design space is claimed for the manufacturing process. The defined PARs are considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should provide the representative certificates of analysis for one batch of each of the starting materials issued by the recipient of the batches by July 2015.
2. The applicant should submit the comparability data for batches of intermediates made under GMP following re-definition of the starting materials with batches of those intermediates previously classed as starting materials no later than September 2015.
3. The applicant should provide the revised QP declarations no later than September 2015.
4. The applicant should develop an analytical method specifically to control the genotoxic impurity present in one starting material and submit the method and results confirming its depletion in the relevant intermediate by September 2015.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal toxicity studies were performed in compliance with GLP with exception of some of the safety pharmacology studies, which were conducted prior to the implementation of ICH S7A/B guidelines.

The applicant did not seek scientific advice on non-clinical issues at the CHMP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The inhibitory effect of panobinostat (NVP-LBH589) on the HDAC enzymes was evaluated and compared to other HDAC inhibitors in several assays (Study RD-2008-51291). By using immunopurified HDAC enzymes (isoforms 1-11) and an artificial substrate it was shown that panobinostat potently inhibits both class I and class II HDACs (Table 4). Furthermore it was shown that panobinostat exposure could enhance P21 expression levels both at protein level and using p21 promoter-Luc reporter gen into H1299 human lung carcinoma cells (Table 3).

Table 3. In vitro activity profile of NVP-LBH589 in comparison with other histone deacetylase inhibitors

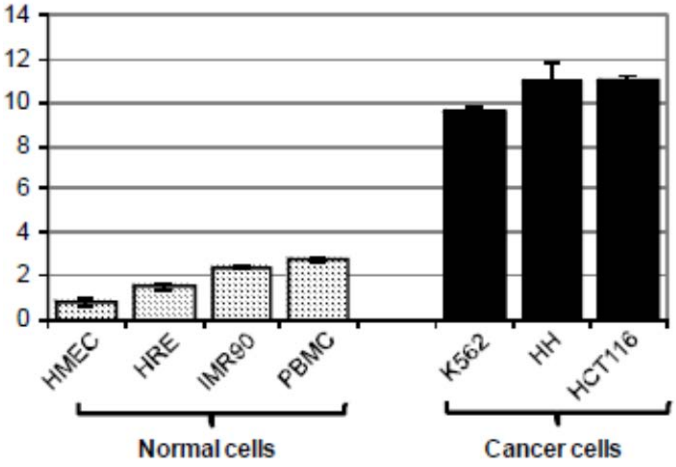
		NVP-LBH589	NVP-LAE066 (SAHA)	NVP-LCG900 (PXD-101)	NVP-BRZ022 MGCD0103
Inhibition of Enzyme Activity IC_{50} [nM]	HDAC1	2.5	75.5	17.6	142
	HDAC2	13.2	362	33.3	147
	HDAC3	2.1	57.4	21.1	205
	HDAC4	203	15,056	1236	> 30,000
	HDAC5	7.8	163	76.3	1889
	HDAC6	10.5	27.1	14.5	> 30,000
	HDAC7	531	12,522	598	> 30,000
	HDAC8	277	1,069	157	28,167
	HDAC9	5.7	78.1	44.2	1,177
	HDAC10	2.3	88.4	31.3	54.9
	HDAC11	2.7	109	44.2	104
p21 Promoter Activation AC_{50} [nM]		46	9,800	>10,000	12,900

Panobinostat was shown to inhibit cell proliferation of a variety of cancer cell lines representing different tumour types with IC50 in low nanomolar range) and induced cell death in these cancer cell lines (LD50 nanomolar, LD90 submicromolar range). Compared to cancer cells, normal cell lines appeared less sensitive to panobinostat and required much higher concentrations of NVP-LBH589 to inhibit their proliferation or the induction of apoptosis (Table 4, Figure 1).

Table 4. Effect of NVP-LBH589 on cell proliferation and viability in cancer and normal cell lines

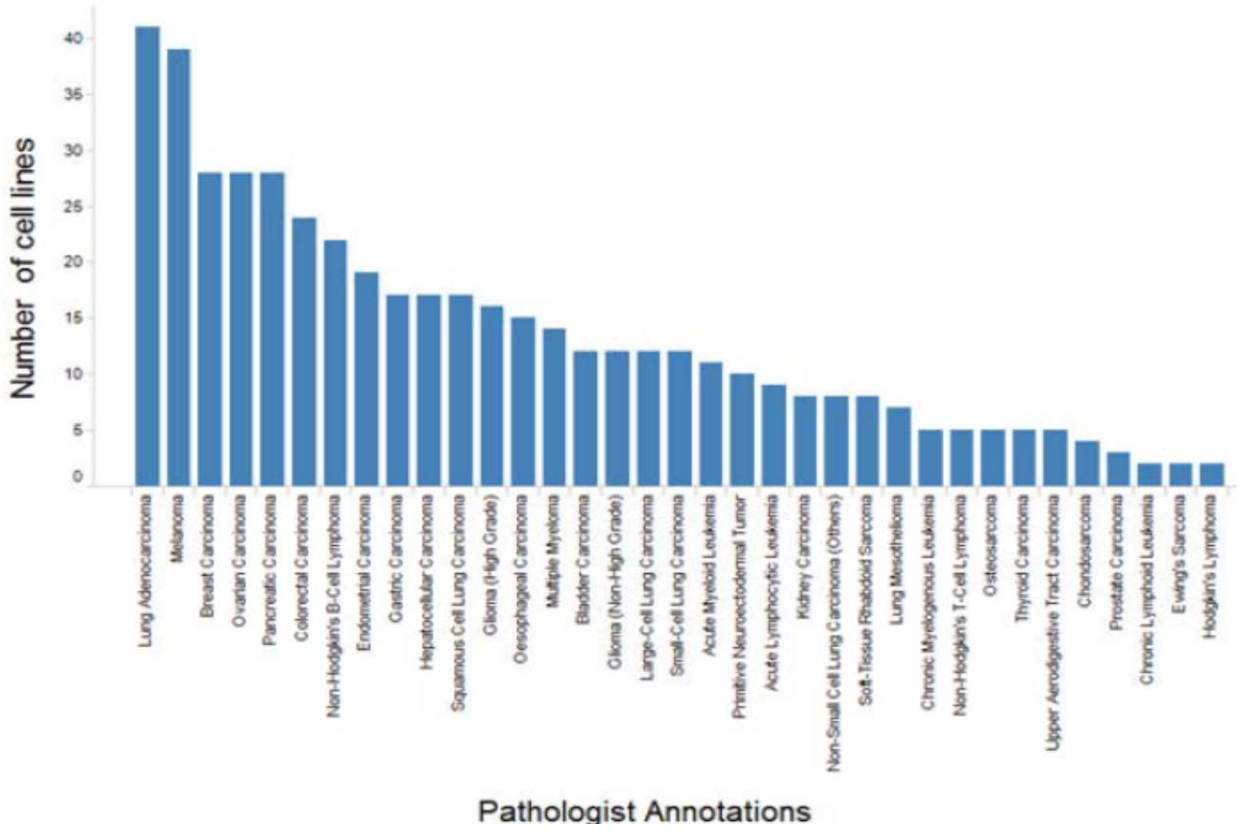
		NVP-LBH589		
Cell Lines	**Cell Type**	**IC_{50} [nM]**	**LD_{50} [nM]**	**LD_{90} [nM]**
HH	CTCL	0.7	4.3	14
K562	CML	3.8	9.3	20.6
KG-1a	AML	3	7.1	14.8
L-428	HL	10.5	26.1	57.5
BT-474	Breast Cancer	2.6	22.4	306
LNCaP	Prostate Cancer	1.4	16.6	134
HCT116	Colon Cancer	7.1	51.7	344
Bx-PC3	Pancreatic Cancer	15.9	105	541
HMEC	Normal Human Mammary Epithelial	97.3	1526	> 5,000
HRE	Normal Human Renal Epithelial	186	653	> 5,000

Figure 1. NVP-LBH589 displays cancer-cell selective induction of apoptosis by Caspase activation assay



The effect of panobinostat on a panel of cell lines (n=472, representing 36 tumour types) was tested in study RD-2013-50424. Panobinostat was found to exhibit potent *in vitro* activity against most cell lines. Figure 2 lists the distributions of different cancer types among the remaining cell lines.

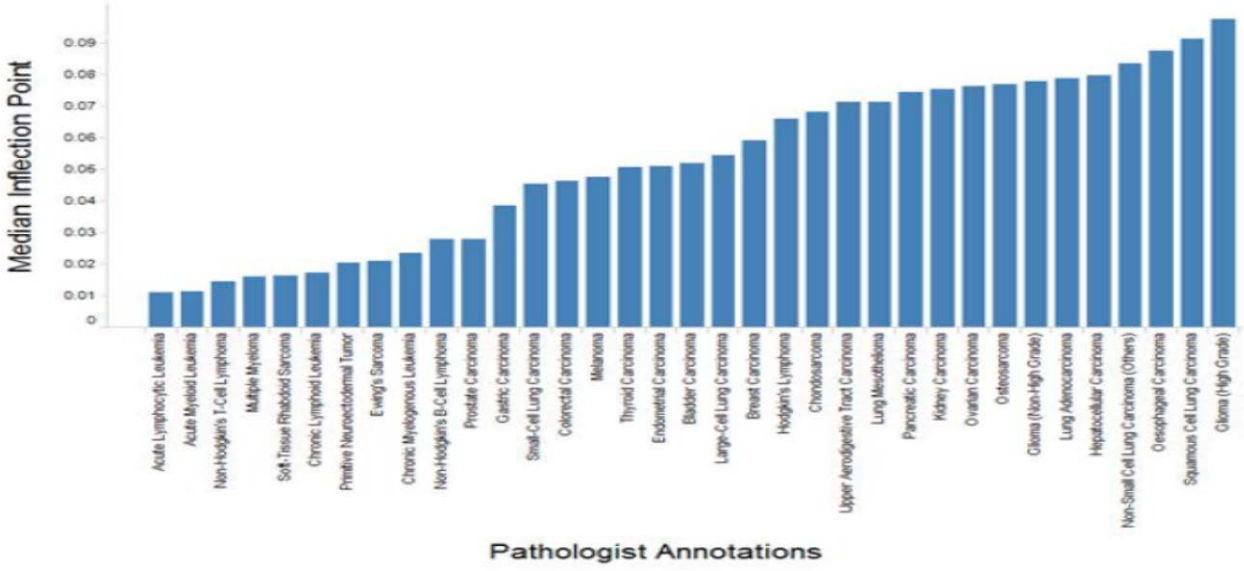
Figure 2. Cancer type distribution of the 472 cell lines with valid LBH589 IP values and pathologist annotations



Multiple myeloma cell lines (n=14) were among the four most sensitive tumour types to panobinostat in this assessment. Only Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, and non-Hodgkin's T-cell Lymphoma

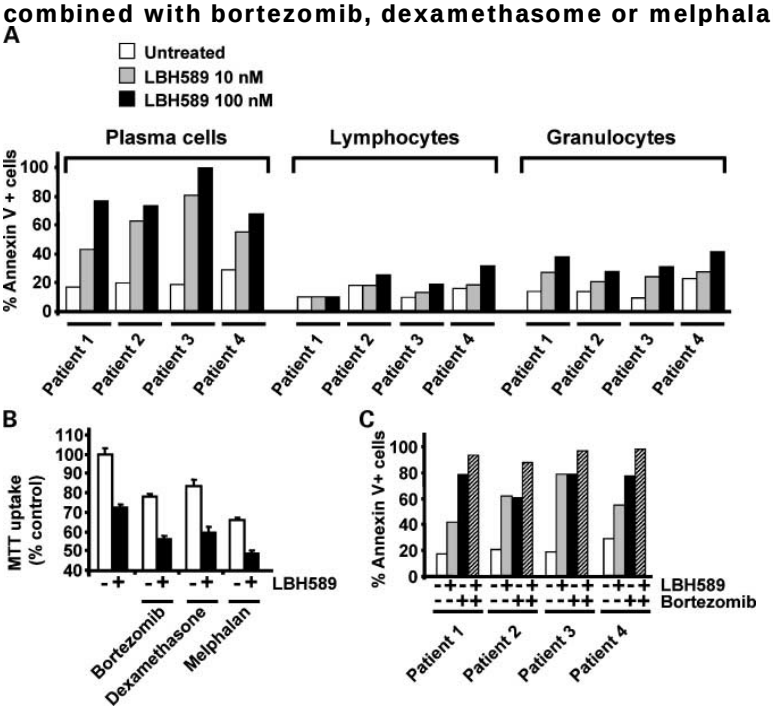
were slightly more sensitive (Figure 3). In this experiment, the drug concentration at the “inflection point” is analogous to the IC50.

Figure 3. Median inflection points of different lineages to LBH589



Panobinostat was found to be a potent antimyeloma agent (IC_{50} < 40 nmol/L) on 2 MM cell lines (MM1, U266) and fresh cells from multiple myeloma patients (n=4), including cells resistant to conventional chemotherapeutic agents (Maiso et al., 2006). Only minor toxicity was seen to normal lymphocytes present in the same patient sample (Figure 4). In addition, panobinostat potentiated the action of drugs, such as bortezomib, dexamethasone, or melphalan, but not of doxorubicin, revlimid, arsenic trioxide or azacytidine.

Figure 4. Effect of panobinostat on patient cells with MM and the antimyeloma activity when combined with bortezomib, dexamethasome or melphalan

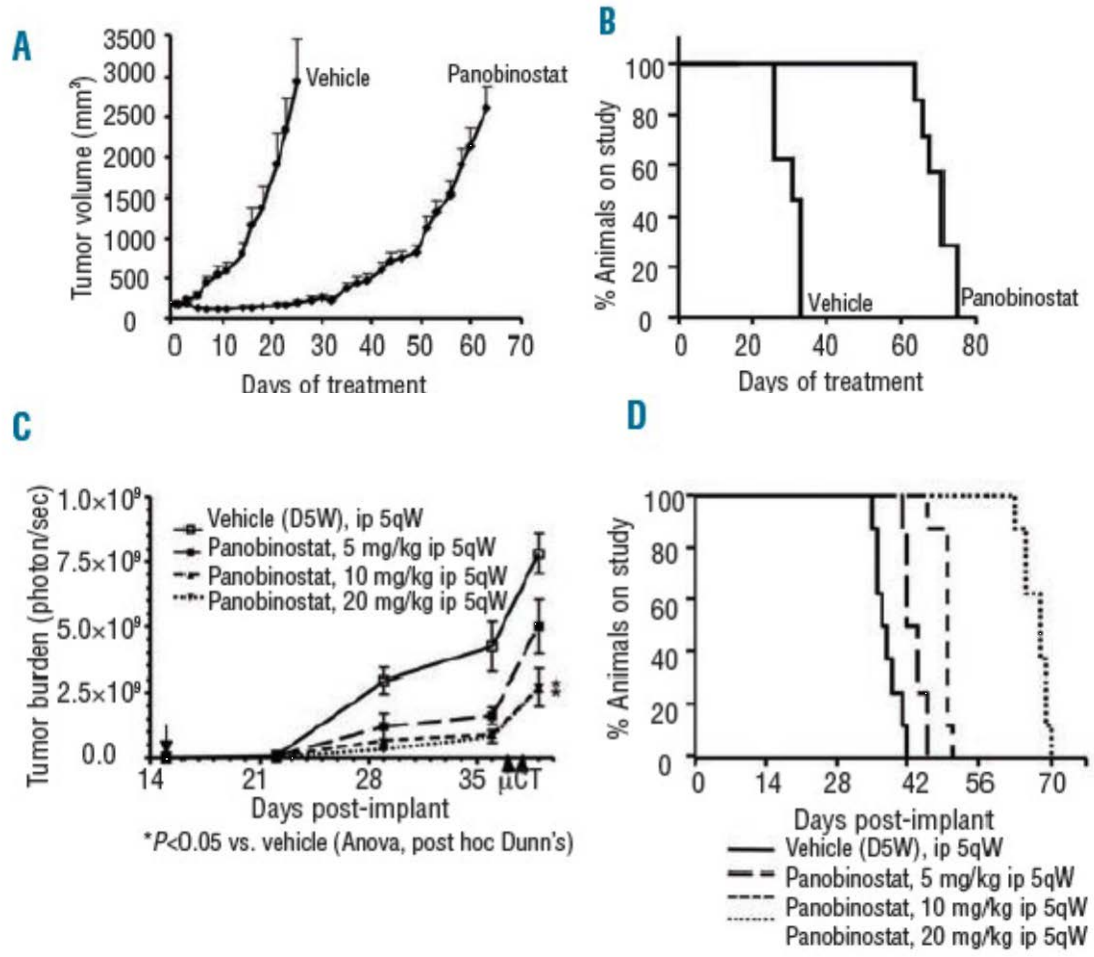


A: Apoptotic effect of panobinostat (LBH589) on cells from patients with multiple myeloma. B, Cytotoxic effect of panobinostat (3 nmol/L) was combined with bortezomib (2 nmol/L), dexamethasone (1 µmol/L), or melphalan (2.5 µmol/L) on MM1S cells, C: Cytotoxic effect of combination of panobinostat LBH589 with bortezomib on patient multiple myeloma cells.

The *in vivo* antimyeloma activity as single agent was investigated in two murine xenograft models; one of subcutaneous plasmacytoma (CB17-SCID mice s.c. implanted with $3x10^6$ MM1S cells in matrigel) and one of disseminated MM1S cells (i.v. injection of $2x10^6$ luciferase expressing MM1S cells) (Ocio et al. 2010).

In the s.c plastocytoma model, treatment with panobinostat (10mg/kg i.p. 5 days weekly for 21 days, and 5 mg/kg on the same schedule on subsequent days) significantly decreased the growth of the plasmacytoma, and the inhibition of tumour growth correlated with an improvement in time to endpoint (TTE: tumour diameter ≥2 cm or moribundity) from median of 30 days to 70 days in animals treated with the vehicle and Panobinostat, respectively (Figure 5). Similar results were obtained in a disseminated luciferase model.

Figure 5. Panobinostat treatment in s.c. plasmacytoma model and disseminated MM model

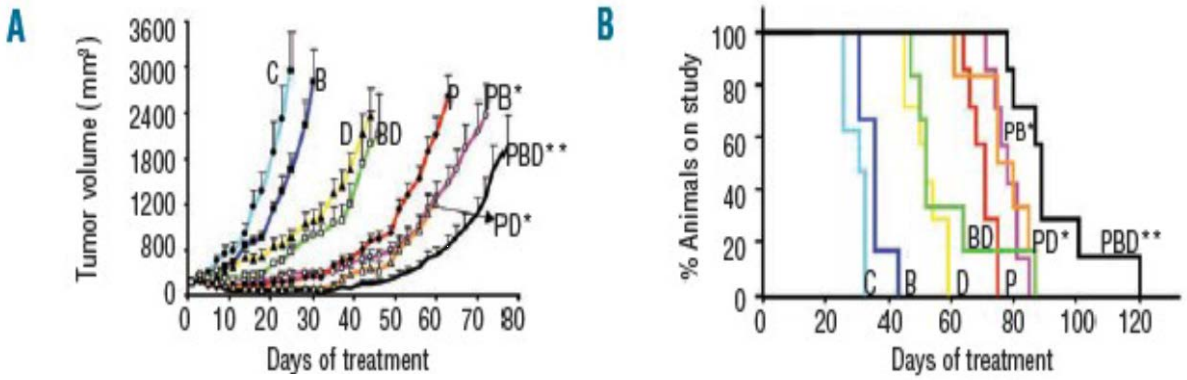


Effect of single-agent panobinostat on tumour growth (A,C) and survival (B,D) in plasmacytoma model (A,B) and disseminated MM model (C,D) as compared with vehicle control.

Panobinostat was evaluated in combination with standard of care therapeutic agents for multiple myeloma to capture potential synergies for safe combination treatments in the clinic. Double and triple combination of Panobinostat with bortezomib and/or dexamethasone was assessed in the subcutaneous human plasmacytoma model. Suboptimal doses of bortezomib (0.1mg/kg i.p., 5 days weekly), dexamethasone (1mg/kg i.p., 5 days

weekly, were used in order to assess possible synergistic effects. The dose of Panobinostat was originally used at 10mg/kg i.p., 5 days weekly but decreased to 5mg/kg after 21 days of treatment, due to the high anti-tumour activity. It was found that Panobinostat significantly potentiated the effects of bortezomib and dexamethasone and the triple combination demonstrated significantly greater effects than either double combination ($P<0.05$) (Figure 6).

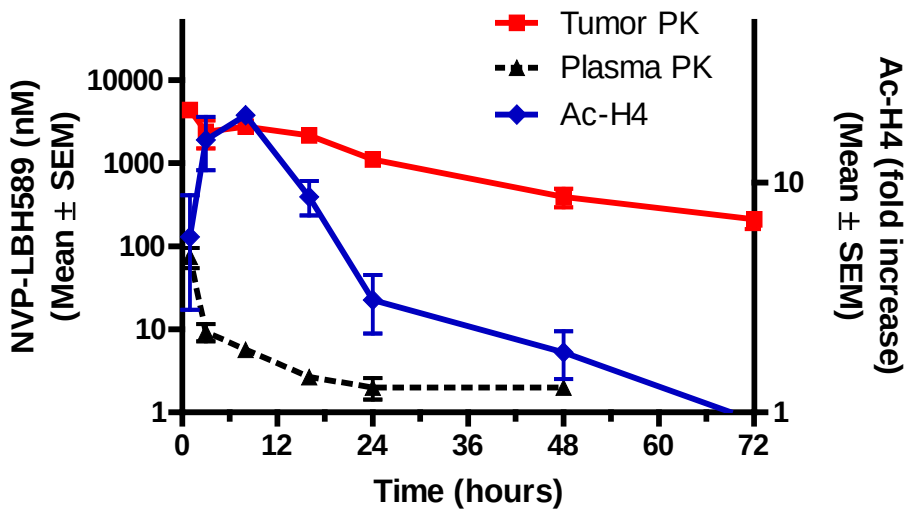
Figure 6. Effect of single-agent, double and triple combination of panobinistat (P) bortezomib (B) and/or dexamethasone (D) on tumour growth (A) and survival (B) in plasmacytoma model



Immunohistochemistry analysis was performed to assess changes in markers of apoptosis and proliferation. Tumours from mice treated with the triple combination PBD showed a decrease in expression of the proliferation marker Ki67, as well as increased expression of apoptotic markers cleaved caspase 3 and PARP.

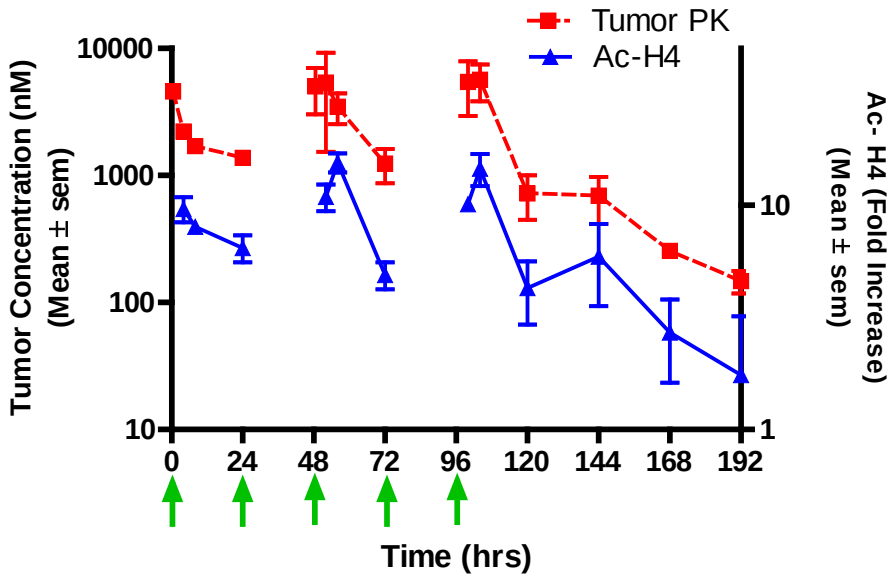
The correlation between dose of Panobinostat and histone acetylation in tumour lysates from treated tumour-bearing animals was investigated in Study RD-2010-50113. To assess whether compound exposure correlated with a pharmacodynamic response, histone acetylation was monitored in tumour tissue harvested from subcutaneous HCT116 tumours over a 72 hour time course following a single dose of Panobinostat. After a single dose of Panobinostat at 19.8 mg/kg, tumours were excised at various time points (1, 3, 8, 16, 24, 48, and 72 hr; n = 3) for PD and PK analysis. Panobinostat treatment resulted in increased acetylation of histone H4 in HCT116 tumour lysates. Maximal acetylation occurred at approximately 8 hours following treatment and trended towards baseline at 72 hours. Similar kinetics was observed for acetylation of histone H3 (Figure 7).

Figure 7: Correlation of acetylated histone H4 and drug concentrations (nM) in HCT116 tumours following a single dose of Panobinostat



In a separate experiment, HCT116 tumour-bearing animals were treated with Panobinostat for 5 consecutive days. Panobinostat was dosed at 11.9 mg/kg, iv, qd for 5 days. After dosing on days 1 and 3, tumour and plasma samples were collected at 0.5, 4, 8, and 24 hours for PD and PK analysis. Following a final dose on day 5, samples were collected up to 96 hours following treatment. Panobinostat dosed at 11.9 mg/kg, iv, qd for 5 days resulted in an approximate 10-20-fold maximum increase in acetylated histone H4 in HCT116 tumour tissue. When tumours were analyzed after dosing on days 1, 3, or 5, there was a similar trend in pharmacodynamic response, with peak response occurring 4-8 hours following treatment. Following a final dose on day 5, acetylation of histone H4 trended to levels of vehicle control animals by 96 hours following treatment (Figure 8).

Figure 8: Multiple dose PK/PD correlation of Panobinostat and acetylated histone H4 in HCT116 tumour lysates



The *in vivo* anti-tumour activity of Panobinostat against the HCT116 human colon xenograft model with an intact p53-p21 pathway was evaluated in study RD-2001-50288. The initial dosing schema which was tested included increasing doses of panobinostat administered i.v., 5 times per week for three weeks in HCT116 colon tumours in athymic mice. Dose dependent anti-tumour activity was observed, with 40mg/kg resulting in tumour regression, and was tolerated with less than 15% body weight loss during the treatment period. There was one death in the 40 mg/kg dose group in a repeat study which was deemed unrelated to treatment (data not shown).

Secondary pharmacodynamic studies

As bone disease is highly relevant to the pathogenesis of multiple myeloma (MM), the effect of panobinostat on bone damage was explored. The anti-tumour and bone-anabolic activity of panobinostat as a single agent or in combination with bortezomib was assessed in the (luciferized) MM1.S xenongraft model (Study RD-2008-51313). Treatments were initiated on day 11 following tumour cell implantation (2×10^6 luciferase labeled MM1.S cells, iv). Animals were treated for 4 weeks; panobinostat was administered at 10, 15 or 20 mg/kg i.p. 5 times weekly, bortezomib at 0.2 mg/kg/week or 1 mg/kg twice/week ip. A dose-related reduction in tumour burden was seen in all treatment groups. The combination of panobinostat (10 mg/kg dose) with bortezomib (0.2 mg/kg dose) did not result in enhanced anti-tumour activity as compared to either single agent.

MicroCT was used to evaluate the effects on trabecular bone. An effect on trabecular parameters (increased bone density, trabecular density, number and thickness, normalisation of trabecular spacing) was observed following treatment with panobinostat, the higher dose of bortezomib (1 mg/kg), or the combination of panobinostat at 10 mg/kg and bortezomib at 1 mg/kg twice weekly as compared to vehicle treated control. Again, no difference was observed in combination relative to single agent therapy (data not shown).

Safety pharmacology programme

Safety pharmacology studies were conducted with panobinostat to assess the effects of panobinostat on vital organ systems. Studies included CNS evaluation in mice, an assessment of the respiratory system in rats, cardiovascular telemetry studies in dogs, in vitro electrophysiological and HERG trafficking studies.

Potential effect on CNS was evaluated in Study 0280108 using male mice as test model. Animals were observed up to 24 hr post dosing following iv dosing. The 30 mg/kg was the lowest dose in this study. At this non-lethal dose there were no effects on behaviour in mice. At higher doses (60 and 100 mg/kg) decreased motor activity, wobbly gait, convulsions and death (1/10 at 60 mg/kg and 5/10 at 100 mg/kg) was observed up to1 hr post dose. In the highest dose decreased grip strength and body temperature were seen at 1 hr post dosing.

There were no effects of panobinostat on respiratory function in male rats (Study 0280118) through the highest doses tested (10 mg/kg, i.v.) (Last time point was 6hr following dosing).

Panobinostat was assessed in two hERG channel patch-clamp assays (Studies 0280136 and 0870294) and the estimated IC50 values were approximately 5.8 µM and 3.5 µM at 33 to 35°C (Hill coefficient = 1.2). One of 75 human metabolites of panobinostat, 519-07 (also known as BJB432 or M37.8), had an estimated IC50 value of 1.6 µM (Hill coefficient = 1). Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by 83.1 ± 2.8% (Study 0870294). When tested in the Langendorff perfused rabbit heart model, concentrations at and above 1 µM panobinostat resulted in delayed repolarization, induced triangulation, decreased coronary perfusion, increased pacemaker activity and favoured the development of ventricular tachycardia which degenerated into fibrillation (Studies RD-2001-50377 and 0350418). Panobinostat did not show any risk of QT prolongation and related arrhythmias after 150 minutes of exposure at 0.5 µM (Studies 0618524 and 0618523). When assessed in the same model, BJB432 delayed repolarization process at ≥ 1 µM, caused instability (3 µM), early after depolarization (10 µM), and induced triangulation and Torsade de pointes (30 µM) (Study 0618585). In an intravenous safety pharmacology screening study in dogs conducted at 1 and 3 mg/kg prolongation of the heart rate corrected QT interval (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 QTc interval were seen at doses ≥ 0.2 mg/kg (Study 0210083). To support the current three times weekly clinical oral dosing regimen (Days 1, 3 and 5) a repeated oral dose telemetry study in Dogs/Beagle was conducted at a dose of 1.5 mg/kg. Based on the results, no related changes or cumulative effects in the hemodynamic or electrocardiographic parameters were observed with the exception of QTc prolongation, where prolongation in QTc upwards of 25 msecs was noted in within some animals over the monitoring period (Study 0680202). Panobinostat was combined with (non-effective doses of) docetaxel (1 µM, study 0616811), trastuzumab (1µM, study; 0616812), 5-azacytidine (1 µM; study 0616812), and a partially active dose of nirlotinib (0.3 µM, study 0516281). It was found that docetaxel and not trastuzumab or 5-azacytidine increased potency of panobinostat to inhibit hEG current. Co-administration of panobinostat and nirlotinib increased hERG inhibitory potency.

Pharmacodynamic drug interactions

No Pharmacodynamic drug interactions studies have been conducted with panobinostat (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

All *in vivo* studies using radiolabeled panobinostat were conducted with ^{14}C-labeled drug substance. The ^{14}C-labeled material with uniform labelling located on the indole ring ([$^{14}C_6$]panobinostat) was used in the *in vitro* blood distribution and plasma and serum protein binding study, *in vitro* plasma stability study, *in vitro* across-species liver slice study, and an *in vivo* rat i.v. study.

The radioactivity concentrations in plasma, blood, and feces homogenate were determined by dissolution of the samples with a commercially available tissue solubilizer, addition of liquid scintillation cocktail, and subsequent liquid scintillation counting (LSC). Radioactivity concentrations in the urine were determined directly by the addition of scintillation cocktail and LSC. The radioactivity concentrations in organs and tissues were determined by quantitative whole body autoradiography (QWBA). Plasma and in some studies, tissue concentrations, of panobinostat were determined by LC-MS/MS analysis in the radiolabeled animal absorption, distribution, metabolism and excretion (ADME) studies, the radiolabeled human ADME study, and other pharmacokinetic (PK) studies in, rat, dog, and tumour bearing mice.

The mean pharmacokinetic parameters of [14C] panobinostat related radioactivity in plasma are presented in Table 5.

Table 5: Mean pharmacokinetic parameters of [14C]panobinostat related radioactivity in plasma

Species	Route	Dose	Tmax	Cmax	Cmax / dose	AUClast	AUClast / dose	Apparent T1/2	Absorption
		mg/kg	h	ngEq/mL	(ngEq/mL)/ (mg/kg)	ngEq•h/mL	(ngEq•h/mL)/ (mg/kg)	h	
Rat	i.v.	10	0.083	2180 ± 226	218	6110 ± 470	611	30	-
	i.v.	10	0.083	3220	322	6120	612	-	
	oral	10	ND	93	9.3	1042	104	-	17%
Dog	i.v.	0.5	0.083	161	322	2610	5220	140	
	oral	1.5	1	270	180	5310	3540	-	68%
Rabbit	i.v.	8	0.083	15400	1925	80100	10013	19	
	oral	40	0.5*	8650	216	249000	6220	-	62%
Human	oral	0.3**	2*	156 ± 40.1	520	7120 ± 1270	23733	68.6 ± 12.5	

ND= not determined; *median value; **single 20 mg [^{14}C]panobinostat dose; mean body weight 67.2 kg.

The mean pharmacokinetic parameters of panobinostat in plasma following an oral dose and an intravenous dose in various species are presented in Tables 6 and 7 respectively.

Table 6: Mean pharmacokinetic parameters of panobinostat in plasma following an oral dose in various species

Species	Dose	Tmax	Cmax	Cmax / dose	AUClast	AUClast / dose	Bioavailability	Apparent T1/2
	mg/kg	h	ng/mL	(ng/mL)/ (mg/kg)	ng•h/mL	(ng•h/mL)/ (mg/kg)		h
Rat	10	ND	BLQ	ND	ND	ND	~6%*	
Dog	1.5	0.25**	95.2 ± 30	63	226 ± 86	151	52 ± 19%	
Rabbit	40	0.25**	103 ± 137	2.6	260 ± 248	6.5	2.4%	
Human	0.3***	0.8**	24.3 ± 12	81	107 ± 43.6	357		30.6 ± 2.4

ND= not determined; BLQ = below limit of quantification; *estimate is based on low levels of urinary excretion in the p.o. study, an estimate of the bioavailability by comparison of the two i.v. studies with oral doses of 30 and 60 mg in rat, found the bioavailability ~6-22%; **median value; ***single 20 mg [^{14}C]panobinostat dose; mean body weight 67.2 kg

Table 7: Mean pharmacokinetic parameters of panobinostat in plasma follow an intravenous dose in various species

Species	Dose	Cmax	Cmax / dose	AUClast	AUClast / dose	T1/2	CL	Vss
	mg/kg	ng/mL	(ng/mL)/ (mg/kg)	ng•h/mL	(ng•h/mL)/ (mg/kg)	h	L/h/kg	L/kg
Rat (1)	10	787 ± 166	78	705 ± 131	80	ND	ND	ND
Rat (2)	10	1016*	102	459** ± 70	46	3.81 ± 1.39	22.1 ± 3.49	40.2 ± 16
Dog	0.5	76.7	153	125	250	16	3.3	41.6
Rabbit	8	3610	451	2200	275	18	3.55	12.6

ND= not determined; rat 1Study R0101753, rat 2 Study R0201550-02; dog Study R0300092; rabbit Study R0700878; * n=1; **AUCinf

Panobinostat was moderately bound to plasma proteins and binding was independent of concentration over the 0.1 to 100 μg/mL test range in the mouse, rat, dog, and human. Binding was independent of temperature over a 4 to 37°C range. The bound fraction in dogs averaged 0.787 ± 0.037 (37°C) and 0.805 ± 0.085 (4°C). The bound fraction was 0.828 ± 0.022 (4°C) in the mouse, 0.889 ± 0.015 (4°C), in the rat and 0.896 ± 0.028 (37°C) in human.

A modest species difference in panobinostat blood-to plasma concentration ratios was observed. The highest ratio, 2.2 ± 0.45, was observed in dogs, the average ratios in the other species were: 1.7 ± 0.12 (mouse), 1.5 ± 0.11 (rat), and 1.4 ± 0.12 (human).

The distribution of radioactivity into the tissues of pregnant rats following an oral dose of 100 mg/kg of [^{14}C] panobinostat was evaluated on gestational day 12 and 17. On gestational days 12 and 17 the highest radioactivity concentrations in the fetus were seen at 3 hours post dose. On gestational day 12 the fetal levels at 3 hours were ~ 3-fold maternal blood levels. By 24 hours post dose the fetal levels were ~ 1/3 of the maternal blood values. On gestational day 17, the fetal tissue levels were consistently below those in the maternal blood.

The plasma levels of panobinostat and its metabolites in rat, rabbit, dog and human are displayed in Table 8.

Table 8: Plasma AUC% of panobinostat and circulating metabolites after an oral radiolabeled dose in various species

AUC % of panobinostat and circulating metabolite				
Metabolite	Rat (10 mg/kg)	Rabbit (40 mg/kg)	Dog (1.5 mg/kg)	Human (0.29)
panobinostat	4.10	0.02	8.57-11.8	7.31
M24.2 / BJC330	-	0.54	4.20	2.39
M24.3	1.92	-	5.24	≤ 7.02
M34.4 / BJB876	≤ 50.2	0.67	-	≤ 0.53
M26.8	10.1-13.1	-	1.75	-
M36.9	4.08-30.4	5.39	50.1-52.1	≤ 5.81
M37.8 / BJB432	6.95	0.10	≤ 3.98	≤ 5.81
M40.8	2.16	<0.01	≤ 3.98	7.55
M43.5 / AFN835	1.92	1.75	≤ 8.15	≤ 3.88
M44.6	-	-	≤ 8.15	≤ 3.88
P15.2	-	76.7	-	-
P38.8	-	1.02	-	2.66
T18b	-	-	-	2.36
T19d	-	-	-	≤ 3.94
T20b	-	-	-	≤ 1.13
T21d	-	-	-	≤ 5.05
T21e	-	-	-	≤ 5.05
T22e	-	-	-	≤ 2.06
T23c	-	-	2.12	≤ 3.08
T23f	6.24	-	-	≤ 0.57
T24.0	-	-	2.20	≤ 17.33
T24b	-	-	-	≤ 1.13
T24d	-	-	-	≤ 5.15
T24i	-	-	-	≤ 0.90
T25d	-	-	-	≤ 2.94
T25e	-	-	0.46	≤ 2.94
T25f	-	-	-	≤ 0.84
T26f	-	-	-	1.79
T27d	≤ 33.8	-	-	≤ 0.53
T27e	-	-	-	≤ 1.89
T33a	-	-	-	9.20

Following an oral dose of panobinostat in humans, radioactivity excretion is both renal and fecal, with a small preference for fecal elimination. Excretion in rabbits and dogs also involved both renal and fecal routes following oral or intravenous dosing, with a preference for fecal elimination. In the rat following an oral dose elimination was almost solely in the feces. Following an intravenous dose in the rat, fecal elimination was predominant with renal excretion being minor. In bile duct cannulated rats dosed intravenously excretion was principally in bile (~62%) followed by urinary excretion (~30%), about 10% was eliminated in the feces within 72 h.

2.3.4. Toxicology

Single dose toxicity

A summary of the results from the single-dose toxicity studies is presented in table 9.

Table 9: Summary of the results from the single-dose toxicity studies on panobinostat

Study ID	**Species/ Sex/Number/Group**	**Dose/Route**	**Approx. lethal dose / observed max non-lethal dose**	**Major findings**:
0270147	Mouse, CD-1 3-5 M+5 F	0, 10, 50, 75, 100 mg/kg intravenous	Lethal: 75 mg/kg Males 100 mg/kg Females Non-Lethal: 50 mg/kg Males 75 mg/kg Females	Death occurred often within 15 minutes of dosing. **Adverse clinical sings:** ≥50 mg/kg: ptosis, reduced feces, decreased locomotor activity; at doses of 75 mg/kg: swollen muzzle; at doses of 100 mg/kg: laboured respiration, saltatory spasms, sedation, muscle flaccidity, hunched posture, sunken eyes. Test article related body weight loss on day 4 at all dose levels. **Vehicle effects:** hind limb impairment, muscle tremors, loss of consciousness, slight decreased locomotor activity. Test article related lesions: dark or red discoloration of the lungs.

0270146	Rat, Wistar 5 M + 5 F	0, 1, 10, 50, 100 mg/kg intravenous	Lethal: 100 mg/kg Males 50 mg/kg Females Non-lethal: 50 mg/kg Males 10 mg/kg Females	Most animals died shortly after dosing showing tremors before the death. **Adverse clinical sings:** ≥10 mg/kg: ptosis, wet staining of fur; at doses ≥50 mg/kg: decreased locomotor activity, hypothermia, impaired righting reflex, recumbency, fecal changes. 1 mg/kg: loss of consciousness, increased respiration, abnormal gait/limited hind limb mobility. Body weight loss on Day 4 at 10 & 50 mg/kg. **Macroscopic pathology**: haemorrhage in thoracic and abdominal cavity; red discoloration/mottling of the lung, oedema of mesentery, mottling of kidneys, small spleens.

Repeat dose toxicity

The results of the repeated dose toxicity studies are presented in Table 10.

Table 10: Repeated dose toxicity studies: rat and dog administered panobinostat oral and iv

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
RAT oral					
0370080 Non GLP	Wistar Rat Tox:5/sex/dose TK.: 5/sex/dose	0, 0.797, 2.39 & 7.97 mg/kg/day Oral gavage (Mon. Wed. Fri.)	2 wks @ d1, 3, 5, 8, 10, 12, 15	NOAEL 0.797 mg/kg/day	**≥ 2.39** ↑ Thyroid weight (abs / rel. to Body and Brain weight) **= 7.97** ↓ secr. Gran. Parotid sal. Gland (2/5f) ↑ Lymphoid depletion Mand. & Mes. LN (2/5f),↑ incidence (m>f) haemorrhage (medulla) thymus, vac. & hypertrophy thyroid epithelial cells (1m)
0370121 GLP	Wistar Rat 10/sex/dose + 6/sex for control and high dose for recovery	0, 3, 10, 30 Oral gavage (Mon. Wed. Fri.)	4 wks + 4 wks rec.	NOAEL could not be determined	**≥3** ↓ thyroid w **≥10** ↓ platelets (m), ↓ spleen (f), cyt. vacuolation in the follicular epithelium (3m) **=30** ↓ BW gain (f) d22-d29, ↓ WBC, lymphocytes and platelets, ↑ reticulocytes (f), ↓ RBC and RBC corpus Hgb (f), ↓ P (m), ↓ total protein ↓ thymus, ↓ pituary gland (m), small thymus (2f, 2m), ↓ min. to slight extramedullary hematopoiesis (f) + lymphoid content of the spleen (2f), ↓ lymphocyte population and thin thymal cortex (7f), min to mod cytoplasmic vacuolation of thyroid follicular epithelium + ↓ colloid (5f, 3m) **REC** ↓ monocytes (m), ↓ RBC corpsular Hgb
0680019 GLP Main study	Wistar Rat 10/sex/dose + 6/sex for control and high dose for recovery	0, 10, 30, 100 oral gavage (Mon. Wed. Fri.)	13 wks + 4 wks rec.	NOAEL could not be determined	**≥10** ↑ agitation to dosing, ↓ erythroid cells, M:E ratio ± shift to left in maturation (1f), ↑ inc & sev. pigment spleen & marrow atrophy femur / sternum **@ 5 wks** ↓ MCV (m), MCHC (f), WBC (m), N(m), L(m), LUC (m) ↓ ALT (m) **@ 14 wks** ↑ phos, T. Bi (f) ↓ K (f), @11 wks : ↓ rT3 (dose rel. not sign.) ↓ rT4 (m, only sign @ 100 mg/kg), ↑ Troponin I (dose related @ day 5 & wk 14) **≥30** ↓FC (m), @ 5 days) ↓ CKMB (f) ↑ inc & sev. atrophy thymus **@ 5 wks** MCH,

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
					MCV, WBC, L, N, M, Eos (f), B, LUC ↓ AST (m) ↓ CPK, ↑ T. Bi (f), ↓ ALT & TP (f) **14 wks**: ↓ MCH, ↓ WBC. ↓ Lymph (m), ↓ Neut (f), ↓ Mono (f), ↓ ALT & TP & Alb (f)↓ erythroid cells, M:E ratio ± shift to left in maturation (2f) @ 13 wks ↓ S.G.(f) ↓ Thymus W., ↓ Adrenal & sal. Gland & liver (f), all covariant **=100 ↓** BW gain, ↓ FC, ↓ erythroid cells, M:E ratio ± shift to left in maturation (4m, 5f), mat. Arrest granulocytic cells, late stage gran. Have slight abn. Nuclear shapes, (5m,5f, granulocytic hypoplasia (4m, 1f), ↑ mature adipocytes (1f, 1m), mild haemodilution (2f), lymphoid atrophy and depletion spleen mand. LN & PP, granulocytic aplasia & hyperplasia, haematopoiesis spleen, hyperostosis, ↑ # females in oestrus part of cycle **@ 5 wks** of treatment : ↓ of Hb, RBC, Hct, MCH, MCV, WBC, L, N, M, Eos, B, LUC and Plat, ↓ CKMB (m also @ 5days)**@ 14 wks** : ↓ MCHC, ↓ Hb. ↓ Lymp, ↓ Neut,, ↓ EOS (m), ↓ plat (f), ↓ K (m), ↑ Phos., ↑ T. Bi (m), ↑AST, ↑ Urea, @11 wks : ↓ rT3 (dose rel. not sign.) ↓ rT4 (m, sign. & f), @ 13 wks ↑ U-vol, ↓ S.G. , ↓ sal. Gland & prostate (m), all covariant **Rec** ↓ FC (m),↑ pigment spleen ↓ MCHC, ↑ MCV (f), ↓ Glob (m) ↑ A:G (m) , ↓ sal. Gland (f) & prostate (m), ↑ thymus & epididymis (m) all covariant
0680134 GLP	Wistar Rat 20/sex/dose + 10/sex for control and high dose for recovery TK: 8/sex/dose	0, 10, 30, 75 oral gavage (Mon. Wed. Fri.)	26 wks + 4 wks rec.	NOAEL could not be determined	**≥10** ↓ BW gain (m), ↓ MCH (m), ↓ MCV, N, LUC, Plat (only week 26,m) ↓ WBC (only wk 26), ↓ L (only wk 26 , f) ↓ rel Sal. Gland (f), ↑ foll. cell. hypertrophy thyroid, ↑ fatty atrophy sternum, ↑ heamosiderin spleen, trend of ↑ # of females in oestrus phase of cycle BoneMarrow smears: ↓ # erythroid cells & ↑ M:E, ↑ proportion of eosinophilic cells ± abnormal morphology, ↑ # of granulocytic cells show maturation arrest. (all effects are associated with each other) **≥30** ↓ FC (m), ↓ Hb (m), MCV, MCHC, WBC, L, N, Eos, B (m), LUC (m, f only wk 13))), Plat (wk13 & 26) ↓ MCH (f) ↓ ALT (m), ↓ TP (f), ↓rT3 (f) ↑ rel. brain & testes (m) ↓ thymus & Sal. Gland, ↓ rel. spleen ↑ min-mod atrophy thymus and min-mild acinar atrophy male mammary gland (m) **=75 ↓** BW gain (f), ↓ FC (f: incidental and slight), ↓Hb, ↓ B ↓ Hct, ↓ Mono (only wk 13), ↓ CPK (only wk13) & CKMB (day 5 & wk 13: m, wk 26: f), males: ↑ Urea, ↓ AST, ↓ TP, ↑ Phosp (all wk 13), Glob (m+f), ↑ A;G, (wk 13 and wk 26, ↓ Gluc, ↓ ALT, ↓ K, females: ↓Alb, ↓ Zn (only wk 26)↓ Tp (wk 26), ↑ U-vol ↓ S. G. ↑ rel. lung & ovary (f), ↓ rel. prostate (m), ↑ fatty atrophy sternum, ↑ (germinal centre) atrophy Mand. LN, ↑ atrophy PALS spleen, Erythrophagocytosis Mes. LN,

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
					REC ↑ BW gain, ↑ RBC (m), ↓ MCH (m), MCV (m), MCHC (m) , Ret (m), ↓ WBC, L, ↑ Urea (m) , ↓ Urea, Creatinine and Zn (f), ↑ rel. epididymis, kidney, liver, lung, testes, thyroid (m), ↓ Adrenal, Sal. Gland, Spleen (f), heamosiderin spleen, foll. Cell. Hypertrophy thyroid. ↓ # erythroid cells (5/12 but also in 1/12 control) , ↑# of granulocytic cells show maturation arrest. (1f**) follicular cell adenoma in the thyroid (1 m), focal C-cell hyperplasia (1f)**
RAT intra venous					
0270059 Non-GLP	Rising dose: 2/sex Consecutive – 2 wks: 2/sex/dose	10→30→10 0.5, 2.5 & 10 IV	Rising dose: 1wk d1:10, d3: 30, d5: 20 Cons dose: 2wk - Daily		Consecutive dose **≥0.5** red. Feces, piloerection, swollen muzzle and injection site bruising, BW loss starting d4, ↓ FC d14, ↑ sev. panleukopenia & thrombocytopenia, ↓ RBC (f), Hbg, HCT, Reticulocytes (severity increases with dose), ↓ ALP (m), ↓ phosphorus, ↓ triglyc. (f), ↓ thymic and spleen weight, lymphoid necrosis and atrophy thymus, **≥2.5** d6-8 all euthanized due to adverse clinical signs, BW loss, red. FC, dec. loc. Activity, chromorhinorrhea, ↓ FC d4 (m,) d8 (all) ↓ ALT, ALP, ↓ total protein ((f), ↓ albumin, ↑ globulin, ↓ triglyc. , No organ weights collected, erythropoiesis (f), BMW depletion and heamorhage (including sparseness megakaryocytes, & thrombocytopenia) heamorhage lung, ovaries, blood in LN (m) **=10** 1m,3f died, 2m,1f euthanized, pale appearance, cold tot ouch, thin, dehydration, head tilt, hunched posture unkempt coat, ataxia, impaired righting reflex, etc, etc, ↓ FC d4, no blood samples & organ weights coll., lymphoid depl. And erythropoiesis spleen, heamorhage adrenal cortex, glandular stomach, lung, blood in LN (all), erosion/ulceration glandular stomach Rising dose **10-30-20**: 1 death @d8, clin. Signs see above, BW loss and ↓ FC @d4, after dose of 30 mg/kg, dark discoul. Adrenal glands, pale discoul. Liver (1m, 1f)
0270103 GLP	Wistar Rat 10/sex/dose + 6/sex for control and high dose for recovery	0.05, 0.3 & 0.9 mg/kg/day IV	3 days on/ 4 days off	NOAEL could not be determined	**≥0.05** ↓ platelets, ↓ P (m), ↓ thymus W (m), ↓ adrenal weight (m), ↑ inc. & sev of ↓ cell. spleen **≥0.3** ↓ BW d4 (m), ↓ WBC, N, L, ↑ % ret. (f) ↓ adrenal weight, ↓ pituatary W, ↑ inc. & sev of ↓ cell. Thymus (more pronounced in male) **=0.9** ↓ BW d4, ↓ BW gain (m), ↓ FC F: d8, 22,28 & m ↑ % ret. Myelopoiesis (m: complete, f: 3#) but left shifted with metamyelocytes and myelocytes predominating, occasional polyploid forms, good cellularity in males. Females: variable cell. More broken & distorted cells & overall incr. myelopoiesis, ↓ albumin & tot.

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
					protein, ↓ P (all), ↓ thymus W, small thymus (5m, 3f), 4/10 m prominent granulopoietic cells, min. cort. Adrenal, atrophy (m), thymic and parotid salivary gland atrophy, extramedullary hematopoiesis spleen (2f) ↓ cell. Red pulp (2m) **REC** ↑ RBC Distr. Width, ↓ WBC/L partially res. (m)
0670757-01 GLP	Wistar Rat 10-12/sex/dose + 6→4/sex for control and high dose for recovery	0, 0.3, 1.0, 3.0 IV	once weekly	NOAEL 0.3 mg/kg	**≥0.3** mild ↓ FC, ↓ MCHC (m), ↑ MPV(m), ↑ T3 (m) **≥1.0** red or blue skin & skin scab at injection sites, ↓ BW wk12-on (m), ↓ WBC/L(m)/LUC (m) , Hb (m)/ Plt/ Retic/↑ MPV(all) ↓ MCV (f), ↑ T4 (f), ↓ TSH (f), ↓ kidney & thymus (m), lymphoid atrophy thymus (aff medulla) & spleen (aff. Periarteriolar sheeth) **=3.0**↓ BW wk6-on @ end 10.7%(m), ↓ BW @ end 8.1 %(m), ↓ Eos, ↓ RBC (m), ↑ RDW ↓ L (f), ↓ LUC (f), ↓ Hb (all) ↓ Ht (f), ↓ MCH (f), ↓ AST & CK (m), ↓ liver, ↓ prostate & spleen (m), ↓ heart &thymus (f), ↑ inc. of pigment deposit in macorphages↑ inc & sev. extramedullary hematopoiesis **REC** ↑ gluc(m), ↓ Na (m), ↑ Chol (f), ↑ Ca (f), ↓ spleen (m), ↑ thymus
0270151 Batch comparison study GLP	**Male** Wistar Rat 8/dose + 6 for control and high dose for recovery	0, 0,9 & 2 Latter two Stressed & unstressed To compare	1 weeks 3 days on/ 4 days off 2 wks rec	Stressed batch not more toxic then unstressed batch	**Unstressed** **≥2.0** min. focal myocarditis & min. lymphocyte inf. stomach **Stressed** **≥ 0.9** ↓ Hg **≥ 2.0** ↓ HCT ↓ AST, ↓ A/G ratio, ↓ Na, small thymus **REC:** empty epididymus & atrophy testis (1/6), necrosis/ haemorrhage/ inflammation harderian gland
DOG oral					
0270176 Non GLP	Beagle Dog 1/sex rising phase & 2/sex consecutive phase	3→10 (single dose) 4 (consecutive phase) Oral gavage	Single dose on day 1 and 5 followed by 4-5 days consecutive phase		**Rising dose** **=10** diarrhea, hyperthermia, rigid muscle (f), dehydration (f), tonic convulsion(f), tremors (f), ↓ locomotor activity, recumbency (f), no feces(f), irregular respiration → sacrificed @ d5, atretic follicles in the ovary and uterine atrophy **Cons. Dose** **=3** sign mainly noted on day 5: ↓ locomotor activity, ataxia, cold to touch , diarrhea, soft feces, reddened ear, emesis, 1 found dead @ d5, other sacrificed @d5
0370089 Non GLP	Beagle Dog 1/sex control, low and mid dose & 2/sex high dose	0, 0.15, 0.5, 1.5 Oral gavage (Mon, Wed, Fri)	2 weeks	NOAEL 0.5 mg/kg	**≥0.5** clinical signs (fecal changes), body weight loss, decreases in food consumption, increases in red blood cell parameters , decreases in absolute lymphocyte counts **=1.5**: increases in myeloid:erythroid ratio and activated partial thromboplastin time
0370122-01 GLP	Beagle Dog, 3/sex/dose + 2/sex in control and high dose	0, 0.15, 0.5, 1.5 Oral gavage (Mon, Wed, Fri)	4 weeks (dosed on Mon, Wed, Fri)		**≥ 0.15** ↓ thyroid W, ↓ colloid & vacuolar changes thyroid epithelium, min atrophy gastric gland + fibrous tissue lamina propria, thymic atrophy (f) **≥ 0.5** ↑ creatinine, depletion lymphoid

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
					tissue spleen (f) **= 1.5** BW loss (f), ↓ lymphocytes. ↑ aPTT, ↓ kidney, spleen, testis, prostate (m), Thymic atrophy (f+m), depletion lymphoid tissue mand. LN, mes. LN, ileal tissue, ↓ cell. BM, attenuation prostic epithelium (red. Secr. Ves.) (m), ↑ lum. Debris epididymis **REC** BW gain (f) ↓ testis (m), lymphoid depletion spleen (f) & mand LN (1m), decreased cell. BM (f), Oligospermia, ↑ epididymal debris & testicular degeneration (1m)
0680020-01 GLP	Beagle Dog, 4/sex/dose + 2/sex in control and high dose	0, 0.15, 0.5, 1.5 →1.0 (in week 7) Oral gavage (Mon, Wed, Fri)	13 weeks with 4 weeks rec.	NOAEL could not be determined	**≥ 0.15 ↓** Hb & Hct (f), ↓ ALT, oligospermia (1m) **≥ 0.5 ↓** Ret (m), ↓ RBC (f), ↓ L, ↓ E, B, LUC (m), ↑ Plat (m) **= 1.5 → 1.0** liquid/soft feces (1,5 mg/kg/day), thin appearance (3m/1f), BW loss & ↓ FC (up to week 7). ↓ RBC, Hct, MCH, MCHC (m), ↓ WBC (m) ↑ Plat (f), ↑ aPTT, ↓ ALP, ↑ K (m), ↓ Chol (m), ↓ dT3(f), ↑ U-Vol, only @ wk 7, depletion lymphoid tissue submandibular and mes. LN, 1 male with thymic atrophy, multifocal acute pneumonia and immutare genital tract, oligospermia and epididymal debris (m) **REC** BW gain (f) but total BW not rec. as control, improved FC
0680133 GLP	Beagle Dog, 4/sex/dose + 2/sex in control and high dose	0, 0.15, 0.5, 1.0 Oral gavage (Mon, Wed, Fri)	39 weeks with 4 weeks rec.	NOAEL could not be determined	**≥ 0.15** ↓ ALP (f), small thymuses. ↑ thymic atrophy (involution present in 2/4 controls and some treated animals) **≥ 0.5 ↓** Hb (m), ↓ MCV, MCH, ↓ Chol (f), ↓ ALT (m), ↓ ALP (m), **=1.0** Slight increase liquid/soft feces (f), BW loss (f), ↓ BW gain (m) & ↓ FC ↓ RBC, Hb (f+m), MCH, MCHC (m), ↓ L/Eos/Bas, ↓ mono(f) ↑ aPTT, ↑ Fib (f), , ↓ AST, ↑ Urea(f), ↑ (mod) heamosiderin deposit macrophages spleen, Lymphoid depletion Mes. LN, interstitial inflam. Lung, granuloma lung, pigmented epithelium kidney, pigmented hepatocytes & kupfer cells. shift to immaturity myeloid cells (2/8) and decrease in mature neutrophils **REC** BW gain (f) but total BW not rec. as control, improved FC
DOG intra venous					
0170106 Non GLP	Beagle Dog 2/sex rising phase	1 (4 days) 3 (1 day, d8), IV	5 days	NOAEL could not be determined	**≥1 (4 days)** 1f sacrificed at day 8, lacrimation, red. FC, reddened skin, emesis with blood, BW loss (m: 9%, f 11-14%) **Washout:** absent / reduced feces, diarrhea, red-no FC, decreased activity, emesis **=3 (1 day)** fecal changes, poor-no FC, emesis (with)out feed, warm to touch, decr. Locomotor activity, abnormal gait, thin appearance, lacrimation, QT intervals of 0.3 sec (can be due to poor health) severe leukopenia, moderate thrombocytopenia, minimal prolongation

Study ID	Species/Sex/ Number/Group	Dose / Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
					of APTT, blood sacrifieced animal (d8) was continuously clotted in this dog, ↑ AST, ↑ ALT (f), ↓ Ca (m), ↓ Na & Cl (f), ↑ glob, crea, chol & triglyc. (f), min. to marked depletion lymphoid tissue, incl. lymph nodes, thymus, spleen and intestinal tissue and sometimes necrosis, depl. Myeloid and erytrhoid components of BMW, necrosis intestinal epithelium, deposition of hemosiderin and lipofuscin pigments in liver and renal epithelium (due to insertion arterial device?)
0270069 GLP	Beagle Dog, 3/sex/dose + 2/sex in control and high dose	0, 0.06, 0.2 & 0.6 IV (3 days on / 4 days off)	4 weeks + 4 weeks rec.	NOAEL could not be determined	**≥ 0.06** ↓ Thyroid (f), red. Vol. of foll. Colloid and/or hypertrophy of foll. Epithelium of thyroid gland (m) **≥ 0.2** leukophenia 1/3 m, ↑ # of myelocytes, metamyelocytes and band cells and re. fewer segmented cells, ↓ liver, spleen & testis (m) red. Vol. of foll. Colloid and/or hypertrophy of foll. Epithelium of thyroid gland (all) hemosiderin in bronchial LN macrophages (m) depletion LN and intestinal lymph tissue (m), min. red. In hematopoietic component of BMW, **= 0.6** ↓ BW (gain) M: red. To 83%, f : sing. Losses @ d8, 22, 28, leukopenia, ↓ Thyroid (all), spleen (all), ↓ prostate, hemosiderin in bronchial LN macrophages (all) focally groups of alveolar macrophages (f), depletion (red. In lymphocytes & increase in macrophages in intestinal lymphoid tissue) LN and intestinal lymph tissue (all), ↑ inc. of basophilic tubules and focal renal cortical fibrosis -> due to increase in intercurrent infectious disease **REC** ↓ Spleen, testes & prostate (m), ↓ ovaray (f) red. Vol. of foll. Colloid and/or hypertrophy of foll. Epithelium of thyroid gland, depletion LN and intestinal lymph tissue (all)
0670758 GLP	Beagle Dog, 3/sex/dose + 2/sex in control and high dose	0, 0.2, 0.6 & 1.2IV (once weekly)	13 weeks + 4 weeks rec.	NOAEL= 0.2 mg/kg/day	**≥ 0.2** ↓ uterus weight (n. sign.) **≥ 0.6** ↓ BW gain (f, dose related), oligospermia epidydimus (m), ↑ atrophy LN : decrease in presence and activity of germinal centers, ↓ M;E cells of BMW (m) **= 1.2** ↑ inc. fecal changes (f), ↑ inc. / sev. post puncture swelling (red, swollen, warm to touch aff. Limbs), 1 m clear eye discharge, ↓ FC (f), ↓ Testis weight (sign), ↓ prostate (n. sign.), min-slight testicular degeneration (m), minor diminution amount of follicular colloid in thyroid and slight hypertrophy foll. cells, ↓ M;E cells of BMW, min ↓ # late stage myeloid cells

Genotoxicity

A summary of the results of mutagenicity studies on panobinostat is presented in Table 11.

Table 11. Summary of design and results of mutagenicity studies on panobinostat

Type of test	Test system	Concentration range / Metabolising system	Results Positive / negative / equivocal
Ames screen assay	S. typhimurium TA98 & TA100	15-5000 µg/plate +/- S9	Mutagenic in strain TA98 without S9 at ≥ 1250 µg/plate
Ames main test	S. typhimurium: TA1535, TA97a, TA98, TA100, TA102	4-5000 µg/plate +/- S9	Mutagenic in strains TA1535 and TA97 at ≥ 625 µg/plate
Comet screen assay, in vitro	L5178Y mouse lymphoma cells	55.5-222.2 µg/ml (-S9) 20.9-166 µg/ml (+S9)	Induction of DNA damage
Chromosomal aberrations, in vitro	Human peripheral blood lymphocytes	0.4 -2.4 µg/ml (-S9, 20h) 0.01-9.52 µg/ml (-S9, 3h + 17h recovery) 0.1-21.0 µg/ml (+S9, 3h + 17h recovery)	Strong increase in the frequency of polyploid cells with and without S9

Carcinogenicity

No carcinogenicity studies have been conducted with panobinostat (see discussion on non-clinical aspects).

Reproduction Toxicity

Table 12 : Overview of reproductive and development toxicity studies on panobinostat

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Male and female fertility – 0670759	Wistar Rat 25/sex/dose	0, 10, 30 & 100	M: 4-wks prior to & during mating F: 2 wks prior to & druing mating and GD0, 3 & 6	**≥10**↓ BW intermit. Stat. sign. (m) **≥30** ↓ BW during gestation (f) ↓ FC d0-3 gest. (f), d0-5 (m), ↑ early resorptions & post implantation losses ↓ live embryos **≥100** ↑ salivation, signs of dehydration, decreased activity, thin, hunched posture and fur erected(m), ↓ BW & BW gain during premating (m/f) & gestation (f), ↓ FC (m) during gestation (f), ↑ incidence of small prostate, ↑ rel. testis	Fertility, early embryonic developme nt and maternal toxicity NOAEL = 10 mg/kg/day

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
				weight,	
Embryo-fœtal development – DRF – 0570309 – GLP	Wistar Rat, MAIN: 10F/dose, TK: 3F (control), 8F (drug)	Oral gavage **DAILY**, 0, 3, 10, 30 (vehicle: pure water)	GD6-GD17	No dose related finding However @ dose of 10 mg/kg ↑ # early resorptions & ↓ viable foetuses and fetusses in 3 litters had malrotated limbs	F0 30 mg/kg F1 30 mg/kg AUC 0-24h = 124 ng.h/mL
Embryo-fœtal development – main – 0670511 - GLP	Wistar Rat, MAIN: 22F/dose, TK: 4F (control), 5F (drug)	Oral gavage **DAILY**, 0, 30, 100, 300 (vehicle 0.5% (w/v) hydroxypropylcellulose (grade HF) NF (Klucel)	GD6-GD17	**≥30** **F0** ↓ BW GD9 – GD21, ↓ BW gain GD6-GD18, ↓ FC GD3-GD18, ↑ early resorptions & post implantation losses, ↓ litter weight, **F1** ↑ incidence of fetus with extra presacral vertebrae and extra 14th rib & unossified/incomplete/semi-bipartite/bipartite sternebrae 1-4 (related to lower fetal weights) **≥100** **F0:** 2 dead and 9 euthanized Macr & Micr: enl. & dark adrenal + hyperplasia & hypertrhophy, thickened stomach with nodules, raised/depr areas, thickened duodenum + dark foci, ulcerative lesions, necrosis, bacterial colonies-often with vascular lumenae, intestines & pyloric stomach, pale & dark areas heart + extensive myocardial degeneration + necrosis and bacterial colonisation, depr. & raised areas liver + hepatocellular necrosis & presence of bacteria , tinctorial changes thymus + atrophy and reactive LN with erythrocytosis and haemorrhage **=300** **F0** 2 deaths GD9, others euthanized GD7-GD10) due to ↓ BW & FC, mac. signs above for adrenals, stomach,	NOAEL for F0 & F1 could not be determined in this study

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
				duodenum and thymus already seen at GD7	
Embryo-fœtal development – DRF – 0680018 – no GLP	Rabbit (NZW), 3f/dose	Oral gavage 1st round: 0, 1, 3, 10, 30 vehicle = water 2nd round 0, 60, 100, 200, 300 Vehicle = Klucel	GD7-20	**≥100** deaths (1@GD19, 1@ GD20) ↓ activity, ↓ stool, soft stool, and red stains in the cage pan, ↓ BW GD10-21, ↓ FC GD7,8 &10-21, ↓ mean foetal weight (although only from 1 litter) **≥200** all euthanized between GD13-23, ataxia, ↓ BW GD14-24, ↓ FC GD16-27 **≥300** all euthanized @ GD12	NOAEL for F0 & F1= 60 mg/kg/day
Embryo-fœtal development - 0670512	Rabbit (NZW) 21F/dose main and 4/dose TK	Oral gavage, 0, 10, 40, 80	GD7-20	**≥40** ↓ fecal output, ↓ FC GD22-24, ↓ fetal weight (females & all), ↑ inci. Incompl. Ossification hyoid bone, ↑ # foetuses with sternebral variants **≥80** 2 deaths and 1 euthanized (latter had test article related gastrointestinal findings) ↓ FC GD19-22, 1 doe total resorption and 1 doe aborted (due to low FC), ↑ # foetuses with minor skeletal anomalies and 13th rib	NOAEL for F0 & F1 = 10 mg/kg/day

Toxicokinetic data

The $AUC_{0\text{-}24h}$ values obtained in Study 0570309 designed to investigate the effects of panopbinostat when administered by oral gavage, on the reproduction and fertility of rats of the F0 generation and on the early in utero development of the F1 generation are summarised in Table 13.

Table 13: Mean Toxicokinetic parameters after oral dosing with panobinostat in female rats (Study 0570309)

	Group 2	Group 3	Group 4
Dose (mg/kg/day)	3	10	30
N	4	5	5
Mean TK Parameters		Day 17	
$AUC_{(0\text{-}24h)}$ ± SD	6.03*± 4.67	36.4 ± 21.1	124 ± 36.8
$AUC_{(0\text{-}24h)}$/Dose ± SD/Dose	2.01 ± 1.56	3.64 ± 2.11	4.13 ± 1.23
C_{max}± SD	0.655 ± 0.0849	4.84 ± 4.36	15.8 ± 3.66
C_{max}/Dose ± SD/Dose	0.218 ± 0.0283	0.484 ± 0.436	0.527 ± 0.122
t_{max}	1.9	0.6	0.5

*Three animals were used for the mean AUC value.
Units for the TK parameters are: $AUC_{(0\text{-}24h)}$ [ng-h/mL]; $AUC_{(0\text{-}24h)}$/dose) [(ng-/mL)/(mg/kg/day)]; C_{max} [ng/mL]; C_{max}/dose [(ng/mL)/(mg/kg/day)]; t_{max} [h].

The mean toxicokinetic parameters of panobinostat in rat plasma (Study 0670511) are presented in Table 14.

Table 14: Mean Toxicokinetic parameters of panobinostat in rat plasma (Study 0670511)

Dose (mg/kg/day)	$AUC_{(0\text{-}24h)}$ (ng*h/mL)	AUC/dose (ng*h/mL)/ (mg/kg/day)	C_{max} (ng/mL)	C_{max}/dose (ng/mL)/ (mg/kg/day)	t_{max} (h)	SE of mean $AUC_{(0\text{-}24h)}$ (ng*h/mL)	SE of mean AUC/dose (ng*h/mL)/ (mg/kg/day)
30 (n = 3 to 4)	289	9.63	56.0	1.87	2.0	21.7	0.723
100 (n = 1 to 2)	816	8.16	277	2.77	0.5	Not applicable	Not applicable

The toxikokinetic parameters of panobinostat in an oral gavage EFD study (0670512) in rabbits are presented in Table 15.

Table 15: Toxicokinetic parameters of panobinostat in an oral gavage EFD study in rabbits (0670512)

	Group 2	Group 3	Group 4
Dose (mg/kg/day)	10	40	80
$AUC_{0\text{-}24h}$ (ng•h/mL)	49.6	305	585
$AUC_{0\text{-}24h}$/Dose (ng•h/mL)/(mg/kg/day)	4.96	7.62	7.32
C_{max} (ng/mL)	15.1	112	410
C_{max}/Dose (ng/mL)/(mg/kg/day)	1.51	2.81	5.13
T_{max} (h)	0.8	0.5	0.5

Local Tolerance

The potential irritation and local tolerance of panobinostat after single intravenous, intra-arterial and perivenous injections were investigated in New Zealand White rabbits. The concentration of panobinostat solution injected

was 0.78 mg/mL freebase in vehicle. The control site received the control item, 7.206 mg DL lactic acid, 34.46 mg mannitol, 200 mg propylene glycol, sodium hydroxide q.s. to pH4 and water for injection q.s. with 5% dextrose in water. The outcome of the study was that a single injection of panobinostat was well tolerated by venous, arterial or perivenous administration. There were no toxicologically significant changes after intravenous injection. Erythema, that was reversible within 96 h of injection, was noted following intra-arterial injection. Perivenous injection was associated with slight to well-defined erythema that was accompanied by mild inflammation 48 h after injection. There were no in-life or microscopic findings present 14 days after injection, indicating reversibility.

Other toxicity studies

Two studies (one *in vitro* and one *in vivo*) were conducted in order to investigate thyroid effects in rats observed in repeat-dose toxicity studies. The purpose of the *in vivo* study was to investigate the mechanism of thyroid effects observed in the repeat-dose studies in rats and dogs. The duration of the *in vivo* study was one month and the dose given was 75 mg/kg three times a week by oral gavage. Propylthiouracil (PTU) was used as a positive control. Oral administration of the positive control thyroid toxicant propylthiouracil (PTU) to male rats for 5, 12, or 26 days produced time dependent changes in thyroid hormones (increases in TSH, decreases in T3 and T4) and organ weight increases with correlative microscopic changes in the thyroid (follicular cell hypertrophy) and pituitary (pars distalis hypertrophy). Oral administration of panobinastat produced minimal and often transient changes in thyroid hormone levels (increases in TSH, decreases in T3 and T4), which were not accompanied by organ weight or microscopic changes in the thyroid, pituitary or liver. Histone deacetylase (HDAC) activity was reduced in the thyroid, pituitary and liver of panobinastat treated animals on day 5, and in the liver on days 12 and 26.

In two mouse local lymph node assays (LLNA) (studies 0670352 and 0670584) covering a range of externally applied concentrations (0.1 to 10%), panobinostat showed contact allergen, irritant and sensitizing potential.

An assessment (study 0517503) of the Ultraviolet/Visible (UV/Vis) absorption spectrum for panobinostat lactate salt indicated light absorption within the range of natural sunlight. The phototoxic potential of panobinostat was evaluated in the 3T3 NRU phototoxicity assay (study 0580320) performed with Balb/c 3T3 clone 31. The EC_{50} values for panobinostat were 1.3 µg/mL (-UV) and 1.0 µg/mL (+UV). The resulting Photo Irritation Factor was 1.3 and the calculated Mean Photo Effect was 0.027.

2.3.5. Ecotoxicity / environmental risk assessment

Table 16: Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	Log K_{ow} = 2.1	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} = 2.1	Not B
	BCF	not performed	
Persistence	DT50 or ready biodegradability	Not readily biodegradable	P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L			> 0.01 threshold (Y)
PEC surfacewater , refined	0.0032	µg/L			
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} (sludge) = 28600-41000 K_{oc} (soil) = 17300-72900			Terrester risk assessment triggered.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.4-0.5 days $DT_{50, sediment}$ = not reported $DT_{50, whole\ system}$ = not reported 59-84 % shifting to sediment =			Sediment risk assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	8.0	µg/L	*Selenastrum capricornutum*
Daphnia sp. Reproduction Test	OECD 211	NOEC	10.0	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	16.0	µg/L	Fathead minnow
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	174.0	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	**not performed**	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	0.7-1.5	days	
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	1.70	mg/kg	
Terrestrial Plants, Growth Test	OECD 208	NOEC	1000	mg/kg	Lettuce, Chinese cabbage, oat
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	1000	mg/kg	
Sediment dwelling organism	OECD 219	NOEC	0.1	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Panobinostat is a HDAC inhibitor, inhibiting all HDAC proteins of HDAC families I, II and IV in nanomolar range *in vitro*. In cellular assays it was shown that panobinostat enhances histone acetylation and affects processes known to be regulated by histone acetylation status (gene expression of p21, TPRM, Hep27, thymidine kinase). Inhibition of tumour cell proliferation of a variety of cancer cell lines in vitro was observed, with leukeamic cell lines, including multiple myeloma cell lines, among the most sensitive cells. Also inhibition of proliferation of patient MM tumour samples was seen. The effect on histone acetylation was confirmed *in vivo* in tumour tissue harvested from subcutaneous HCT116 (colon) xenograft tumours. Anti-tumour activity of single agent panobinostat was shown in several models including two multiple myeloma xenograft models (one with localised tumour formation, the other disseminated tumour burden). This was accompanied by increased survival. The

anti-tumourigenic potential of panobinostat is increased when combined with either agent, and most prominent in the triple therapy (panobinostat, bortezomib and dexamethasone).

Studies on potential effects on CNS and respiratory function are rather limited; however no cause for concern has been identified. Potential cardiovascular effects have been investigated in more depth; it can be concluded that panobinostat has the potential to prolong QTc interval (see SmPC section 4.4 and RMP).

No specific PD drug interaction studies have been provided apart from the combination studies with bortezomib and dexamethasone in the primary pharmacodynamics which was acceptable. As QTc prolongation occurs with panobinostat concomitant administration of medicinal products that are known to cause QTc prolongation should be used with caution (see SmPC section 4.5 and RMP). This potential risk has been classified as an important identified risk in the Risk Management Plan.

Mostly pharmacologically mediated effects were observed in the toxicity studies, including effects on the haematological system and correlating immunosuppression, effects on cell proliferation in GI tract and effects on different glands which are impaired in secretion function upon treatment with panobinostat, effecting among others testis / epididymis / salivary gland / thyroid gland.

The primary target organs of toxicity following administration of panobinostat in rats and dogs were identified as the erythropoietic, myelopoietic and lymphatic systems. The thyroid changes including hormones in dogs (decrease triodothyronine (T3)) and rats (decrease in triodothyronine (T3), tetraiodothyronine (T4) (males) and thyroid stimulating hormone (TSH)) were observed at exposures corresponding to 0.07-2.2 of the human AUC observed clinically (see SmPC section 5.3).

An increase in early resorptions was observed in female rats (doses ≥30 mg/kg). Prostatic atrophy accompanied by reduced secretory granules, testicular degeneration, oligospermia and increased epididymal debris were observed in dogs at exposures corresponding to 0.41-0.69 of the human clinical AUC and not fully reversible after a 4 week recovery period.

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, and DNA damage in an in vivo COMET study in mouse lymphoma L5178Y cells, that are attributed to the pharmacological mode of action (see SmPC section 5.3).

Due to its cytostatic/cytotoxic mode of action, panobinostat can influence the quality of sperm formed during treatment. Sexually active men taking panobinostat and their female partners should use a highly effective method of contraception during the man's treatment and for six months after his last dose of panobinostat (see SmPC section 5.3). Reduced fertility in males has been classified as a potential risk in the Risk Management Plan.

Based on animal data, the likelihood of panobinostat increasing the risk of foetal death and developmental skeletal abnormalities is predicted to be high. Developmental toxicity has been classified as a potential risk in the Risk Management Plan. Embryo foetal lethality and increases in skeletal anomalies (extra sternabrae, extra ribs, increases in minor skeletal variations, delayed ossification and variations of the sternabrae) were seen above exposures corresponding to 0.25 of the human clinical AUC (see SmPC section 5.3). When panobinostat is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of hormonal contraceptives needs to be considered (see Risk Management Plan). Women of child bearing potential taking panobinostat in combination with bortezomib and dexamethasone must use a highly effective method of contraception during treatment and

for three months after the last dose of panobinostat. Women using hormonal contraceptives should additionally use a barrier method of contraception (see SmPC sections 4.6 and 5.3).

The effects of panobinostat on labour and post-natal growth and maturation were not evaluated in animal studies (see SmPC section 5.3).

Given panobinostat's cytostatic/cytotoxic mode of action, the potential risk to the foetus is high. Farydak should only be used during pregnancy 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 (see SmPC section 4.6 and Risk Management Plan).

It is unknown whether panobinostat is excreted in human milk. Given its cytostatic/cytotoxic mode of action, breastfeeding is contraindicated during Farydak treatment (see section 4.6).

The Applicant has submitted an Environmental Risk Assessment in accordance with the Guideline (EMEA/CHMP/SWP/4447/00). All calculated PEC/PNEC quotients were well below 1 and it is concluded that the use of panobinostat constitutes no risk for the environment, including microbial communities in sewage treatment plants, surface waters, groundwater, sediments and terrestrial compartments.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.3, 4.4, 4.6, 5.1 and 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 17: Overview of efficacy studies

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

[1] Study D2308: At the time of the data cut-off on 10-Sept-2013, 58 patients were being followed for disease progression and 416 patients were being followed for survival.
[2] Study DUS71: At the time of the data cut-off on 04-Dec-2012, 2 patients were on-going and 21 patients were being followed for survival.
[3] Study B2207: At the time of the data cut-off on 10-Aug-2011, 8 patients were on-going treatment.

2.4.2. Pharmacokinetics

A total of 14 clinical studies were submitted characterizing the pharmacokinetics of panobinostat monotherapy. Across study analyses have been performed: population PK analysis, exposure- thrombocytopenia relationships and PK-QTc relationships. Additionally, *in vitro* studies with human biomaterials were performed in order to assess the potential of panobinostat to act either as a substrate, inhibitor, or inducer of drug metabolizing enzymes and drug transporters.

Absorption

Panobinostat is rapidly and almost completely absorbed with T_{max} reached within 2 hours of oral administration in patients with advanced cancer. The absolute oral bioavailability of panobinostat was approximately 21%.

After oral administration, panobinostat pharmacokinetics appears to be linear in the dose range 10-30 mg, but AUC increases less than proportionally with dose at higher doses (see SmPC section 5.2).

Table 18: Absolute bioavailability of panobinostat estimated from data from 2 studies with iv dosing and 8 studies with oral dosing

Oral doses (No. of pt.)	Adjusted geometric mean (AUCinf/dose)	GMR (p.o./i.v*)	90% CI
All oral doses (n=196)	6.43	0.28	0.25-0.32
20 mg FMI (n=25)	6.58	0.29	0.24-0.35
20 mg CSF (n=32)	7.71	0.34	0.29-0.40
30 mg CSF (n=25)	7.83	0.35	0.29-0.41
40 mg CSF (n=22)	6.40	0.28	0.23-0.35
45 mg CSF (n=18)	6.90	0.30	0.25-0.37
60 mg CSF (n=47)	5.06	0.22	0.19-0.26

*Adjusted geometric mean AUCinf/dose i.v. (n=69) from two i.v. studies: 22.699 CSF: clinical service form; FMI: final market image; GMR: geometric mean ratio

Overall panobinostat exposure and inter-patient variability remained unchanged with or without food, whereas C_{max} was reduced by <45% and T_{max} prolonged by 1 to 2.5 hours with food (i.e. both normal and high-fat breakfasts). Since food did not alter overall bioavailability (AUC), panobinostat can be administered regardless of food in cancer patients (see SmPC section 5.2).

Table 19: Study 2111-Summary of pharmacokinetic parameters by treatment

PK parameter (unit)	Fasting (N = 33)	High Fat (N = 34)	Normal meal (N = 31)
Cmax (ng/mL)	22.7 (86.02)	11.94 (63.36)	13.7 (64.87)
AUC(0-24) (h.ng/mL)	126.3 (61.20)	93.7 (58.35)	96.2 (57.93)
AUC(0-inf) (h.ng/mL)	176.4 (58.52)	143.89 (58.86)	152.7 (58.87)
T_{max} (h)	1.50 (0.50- 6.00)	4.00 (1.00- 8.07)	2.50 (0.50- 6.00)
$T_{1/2}$ (h)	14.5 (32.21)	13.7 (35.75)	15.7 (48.72)

Values are median (range) for Tmax and arithmetic mean (CV%) for all other parameters.

Distribution

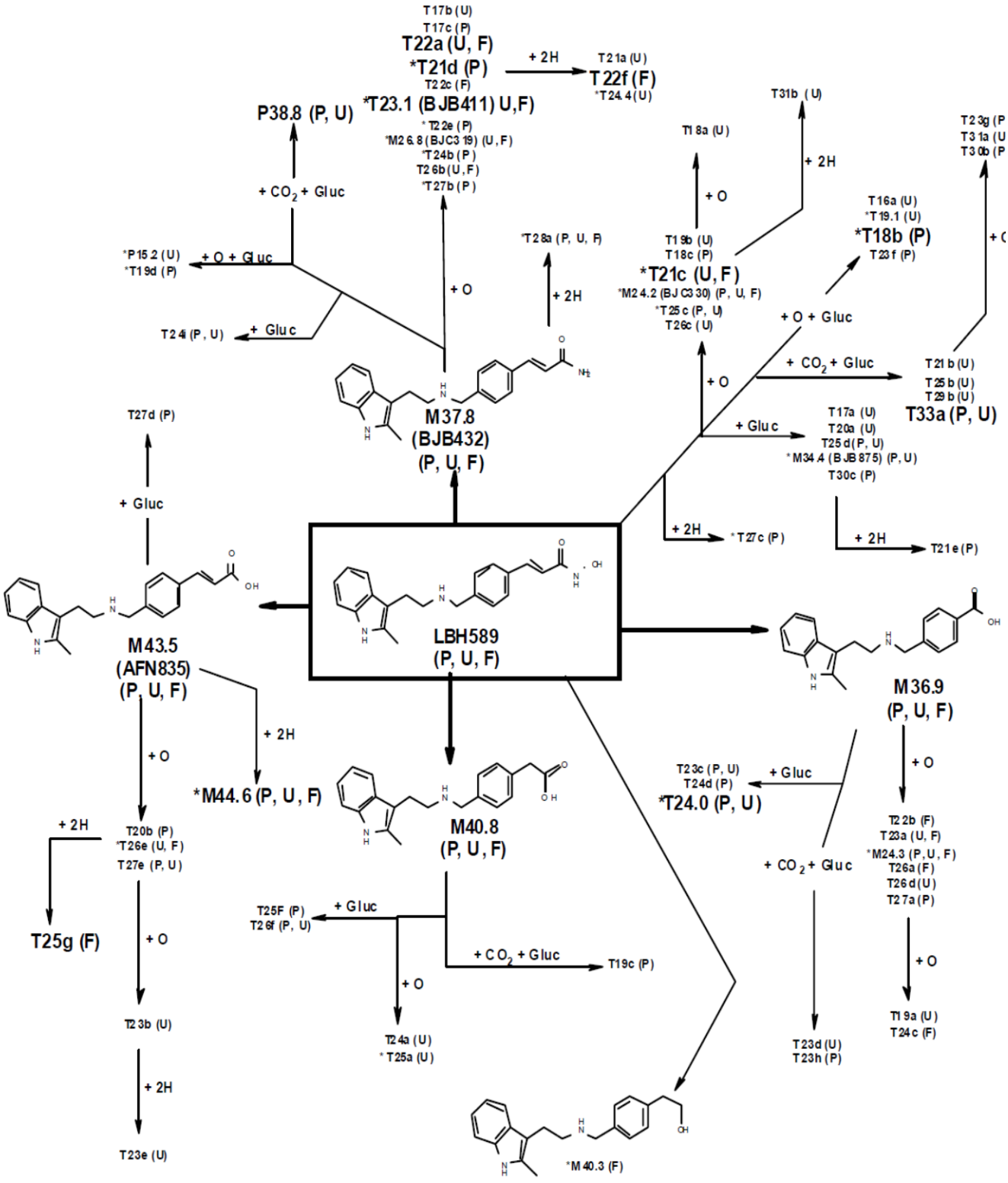
Panobinostat is moderately (approximately 90%) bound to human plasma proteins. Its fraction in the erythrocyte is 0.60 in vitro, independent of the concentration. The volume of distribution of panobinostat at steady state (Vss) is approximately 1,000 litres based on final parameter estimates in the population pharmacokinetic analysis (see SmPC, section 5.2).

Elimination

Panobinostat is extensively metabolised, and a large fraction of the dose is metabolised before reaching the systemic circulation. Pertinent metabolic pathways involved in the biotransformation of panobinostat are reduction, hydrolysis, oxidation and glucuronidation processes. Oxidative metabolism of panobinostat played a less prominent role, with approximately 40% of the dose eliminated by this pathway. Cytochrome P450 3A4 (CYP3A4) is the main oxidation enzyme, with potential minor involvement of CYP2D6 and 2C19 (see SmPC section 5.2).

The biotransformation of panobinostat is presented in Figure 9.

Figure 9: Panobinostat metabolic scheme



Panobinostat represented 6 to 9% of the drug related exposure in plasma. The parent substance is deemed to be responsible for the overall pharmacological activity of panobinostat (see SmPC section 5.2).

After a single oral dose of [14C] panobinostat, 29 to 51% of administered radioactivity is excreted in the urine and 44 to 77% in the faeces. Unchanged panobinostat accounted for <2.5% of the dose in urine and <3.5% of the dose in faeces. The remainders are metabolites. Apparent panobinostat renal clearance (CLR/F) was found to range from 2.4 to 5.5 l/h. Panobinostat has a terminal elimination half-life of approximately 37 hours based on final parameters estimate in the population PK analysis (see SmPC section 5.2).

Dose proportionality and time dependencies

Dose proportionality

For the investigation of the oral multiple dose proportionality, pooled information (Studies B1101, B2101 and B2102) was used, presented in Table 20.

Table 20: Summary of panobinostat PK parameters following multiple p.o. dose, selected schedules, by actual dose

PK Parameters	10 mg	15 mg	20 mg	30 mg	40 mg	60 mg	80 mg
N*	3	7	32	18	22	17	4
Tmax (h)	1 (0.5-4)	1 (0.4-2)	1 (0.5-8)	2 (0.7-4)	1.1 (0.5-4)	1.1 (0.5-6)	1.5 (0.7-2)
Cmax (ng/mL)	12.7 (191%)	12.9 (46%)	21.6 (83%)	25.3 (97%)	28.4 (120%)	43.4 (74%)	66.1 (38%)
AUC0-24h (ng*hr/mL)	77 (75%)	91 (36%)	139 (71%)	174 (92%)	185 (74%)	222 (48%)	274 (70%)
AUC0-48h (ng*hr/mL)	134 (63%)	126 (37%)	199 (63%)	224 (83%)	228 (68%)	275 (50%)	319 (77%)
AUCinf (ng*hr/mL)	163 (65%)	158 (46%)	200 (53%)	288 (67%)	322 (67%)	313 (51%)	303 (96%)
T1/2 (h)	17.6 (40%)	18.3 (29%)	16.9 (33%)	16.9 (34%)	20.0 (39%)	17.4 (26%)	15.7 (71%)
CL/F (L/h)	61.5 (65%)	94.9 (46%)	99.8 (53%)	99.9 (70%)	124.1 (67%)	192 (51%)	264.6 (96%)
Vz/F (L)	1951 (58%)	2303 (25%)	2337 (53%)	2004 (75%)	2906 (57%)	4626 (63%)	6000 (21%)

*N: number of patients having an eligible record a multiple dose p.o.. PK parameters reported such as AUCtau, T1/2, CL/F, Vz/F may have less number of patient than reported in the column header

Values are median (range) for Tmax and geo-mean (CV%) for all others.

CV% = coefficient of variation (%) = SD / mean*100

CV% associated with geometric mean = sqrt (exp (variance for log transformed data) - 1)*100

Over the dose range of 10 to 30 mg, C_{max} and AUC_{0-48h} increased less than dose proportionally with a slope of 0.74 (90%CI 0.20-1.28) for C_{max} and 0.62 (90%CI 0.20-1.04) for AUC_{0-48h}.

Time dependency

Data from 3 studies (Studies B1101, B2101 and B2102) was incorporated of oral multiple dose panobinostat administration. Pharmacokinetics of panobinostat at day 15 was compared to day 1. Rate of accumulation was calculated as the ratios of AUC_{0-48h} on day 15 to day 1 AUC_{0-48h} (Table 21).

Table 21: Panobinostat rate of accumulation for p.o. TIW a week and actual dose

	Geometric mean ratio (90% CI)			
	TIW weekly			TIW every other week
Parameters	15 mg (n=7)	20mg (n=23)	30mg (n=14)	30 mg (n=8)
Cmax	1.06 (0.68-1.64)	1.39 (1.14-1.71)	1.14 (0.85-1.54)	1.11 (0.84-1.45)
AUC0-48h	n/a	1.64 (1.37-1.97)	1.12 (0.89-1.41)	1.01 (0.86-1.18)

n: represented number of patients who contributed to AUC0-48h comparison. Patient who contributed to Cmax comparison is at least equal, if not larger than n per dose level

Special populations

In the phase III clinical study 162 out of 387 patients were aged 65 years or over. Plasma exposure of panobinostat in patients aged 65 years or younger was similar to those older than 65 years in the pooling of single agent panobinostat studies between the dose range of 10 mg and 80 mg (see SmPC, section 5.2). Panobinostat was not evaluated in multiple myeloma patients under 18 years of age (see SmPC, section 5.2). There is no relevant use of panobinostat in paediatric patients below the age of 18 years in the indication multiple myeloma (see SmPC, section 4.2).

The PK and safety of oral panobinostat in patients with advanced solid tumours and various degrees of renal function was evaluated in a phase I, open-label, multicenter study (LBH589X2105). A total of 37 patients were enrolled in the study, which included 11 patients with normal renal function, 10 patients with mild renal impairment, 10 patients with moderate renal impairment, and 6 patients with severe renal impairment. In the core phase of the study, patients received a single dose of oral 30 mg panobinostat. Serial blood samples for assessing the PK of panobinostat were obtained at pre-dose and over 96 hours post-dose for all patients in each group. The extension phase was designed to assess the safety of panobinostat following multiple oral doses of the drug in cancer patients with renal impairment. The safety findings suggest that various degrees of renal impairment did not impact adversely the safety profile of panobinostat in advanced cancer patients. The rates of grade ≥ 3 adverse events and serious adverse events in cancer patients with renal impairment were within the range of the rates in patients with normal renal function.

Mild, moderate and severe renal impairment based on baseline urinary creatinine clearance did not increase the panobinostat plasma exposure in mild, moderate and severe groups (see SmPC, section 5.2).

The PK and safety of oral panobinostat in patients with advanced solid tumours and various degrees of hepatic function was evaluated in a phase I, open-label, multicenter study (LBH589X2101). A total of 25 patients were enrolled in the study, 10 patients with normal hepatic function, 8 patients with mild hepatic dysfunction, 6 patients with moderate hepatic dysfunction, and 1 patient with severe hepatic dysfunction. The study consisted of a core Phase of seven days with a single dose of 30 mg panobinostat followed by an extension Phase of 28-day treatment cycles of 30 mg oral panobinostat three times a week every week. Last patient last visit in the study was on 30-Nov-2012.

Mild and moderate hepatic impairment as per NCI CTEP classification increased panobinostat plasma exposure by 43% and 105%, respectively. No pharmacokinetic data are available for patients with severe hepatic impairment (see SmPC, section 5.2).

Pharmacokinetic interaction studies

In vitro

Panobinostat oxidative metabolic enzyme identifications were investigated *in vitro* using pooled human liver microsomes and recombinant cytochrome P450 isozymes or CYP (study R0101764). To identify the P450 enzymes involved in the metabolism of [14C] panobinostat in humans, [14C] panobinostat (39 µM) was incubated with the recombinant human P450 enzymes: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9 (Arg144,Ile359), CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11 and in human liver microsomes using specific substrates and inhibitors were included. CYP3A4 was found to be the main enzyme involved in the oxidative metabolism of panobinostat (70-98%) with possible minor contributions by CYP2D6 and CYP2C19 (3.5- and 13-fold lower than the CYP3A4 contribution, respectively).

Panobinostat is a competitive CYP2D6 inhibitor *in vitro* with a Ki value of 0.17 µM (study R0201469) and a weak time-dependent inhibitor of CYP3A4 and shown to be panobinostat concentration dependent (Ki value of 12.0 µM and K_{inact} value of 0.0228 min^{-1}) *in vitro* in study R0700973.

Risk assessment of the time-dependent inhibition of CYP3A by panobinostat was investigated based on a steady-state mathematical algorithm and modelling using Simcyp (study R0800469-01). The time-based Simcyp model simulated panobinostat exposures that would cover the actual clinical exposures from doses of up to 80 mg. Simcyp predicted a median 1.18-fold change in AUC of midazolam using the more predictive time-based simulation model. Although generally over-predictive, the steady-state Simcyp model predicted less than a 2-fold change in midazolam AUC (1.76-fold).

In vitro permeability and transporter interaction of [14C] panobinostat was assessed across Caco-2 cell monolayers (study R0500488). The bidirectional transport experiments (apical-to-basolateral and basolateral-to-apical) were performed using a number of [14C] panobinostat concentrations (5-131 µM) and Caco-2 cells transfected with transport protein inhibitors of Pgp and MRP. Panobinostat showed a high efflux ratio across Caco-2 monolayers, which was reduced to unity in the presence of Pgp inhibitor but not in presence of MRP-2 inhibitor indicating that panobinostat is a good substrate for Pgp.

In study 0500600-01, the potential of panobinostat (0-100 µM) to inhibit P-glycoprotein was evaluated using rhodamine as Pgp substrate in MDA435 T0.3 cells. At the examined concentrations (up to a nominal concentration of 100 µM), panobinostat was not found to inhibit Pgp-mediated efflux of Rho123 in MDA435 T0.3 cells.

Panobinostat had no appreciable effect on the efflux activity of BCRP up to a concentration of 25 µM (study R1300018).

Based on the *in vitro* inhibition results of study R1200558, panobinostat was found to be an inhibitor of OATP1B1 with an IC50 of 51.0 µM and of OATP1B3 with an IC50 of 94.1 µM. Based on the *in vitro* inhibition results of study R1200559, panobinostat was found not to be an inhibitor of OAT1 up to the highest concentration investigated (400 µM). Panobinostat was found to be an inhibitor of OAT3 with an IC50 of 21.7 µM and a maximal inhibition of 39%. Based on the *in vitro* inhibition results of study R1200560, panobinostat was found to be an inhibitor of OCT1 with an IC50 of 4.4 µM and of OCT2 with an IC50 of 60.0 µM.

Study R0500725 was an evaluation of panobinostat as an inducer of cytochrome P450 enzymes and drug transporters in human hepatocytes after 72 hours of treatment. Panobinostat (0.01- 1 µM), was determined not to be 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 (P-gp) or ABCC2 (MRP2) mRNAs.

In vivo

Study B2109 was conducted in order to investigate the effect of oral panobinostat on dextromethorphan, a CYP2D6 substrate, and to assess the efficacy and safety of oral panobinostat in patients with advanced solid tumours who were intermediate, extensive or ultra extensive metabolisers for CYP2D6. In the core phase of the study, panobinostat 20 mg was administered once per day on days 3, 5, and 8. Oral dextromethorphan at 60 mg was administered on the mornings of Day 1 and Day 8. There was a high inter-subject variability in dextromethorphan pharmacokinetics even though only extensive CYP2D6 subjects were selected. Dextromethorphan C_{max} and AUC was increased by a mean of 1.83 (90% CI 1.44-2.34) and 1.64 (1.13-2.06) fold upon co-administration with panobinostat when compared with dextromethorphan administered alone in extensive CYP2D6 metabolizers.

Study B2110 was a phase 1B study to investigate the effect of ketoconazole on the pharmacokinetics of oral panobinostat. Twenty mg panobinostat was administered to 14 patients with solid tumours on day 1 and 8, and ketoconazole 400 mg OD was given on days 5-9. Co-administration with ketoconazole increased panobinostat exposure. Geometric mean ratio for C_{max} was 1.6 (90% CI 1.2-2.2) and AUC 1.8 (1.5-2.2), whereas T_{max} and half-life essentially remained unchanged.

In study B2207 the pharmacokinetics of panobinostat were assessed in combination with bortezomib and dexamethasone. In the dose expansion phase, dexamethasone was administered intermittently in combination with bortezomib and panobinostat (i.e. dexamethasone 20 mg was administered from cycle 2 on D1, D2, D4, D5, D8, D9, D11 and D12 during a 21-day cycle). An approximate 20% reduction on panobinostat exposure in combination with bortezomib was observed when dexamethasone was added to the treatment regimen than those from cycle 1 day 8, potentially as a result of CYP450 3A4 induction by dexamethasone. Bortezomib exposure was not affected by combination with dexamethasone.

Pharmacokinetics using human biomaterials

The pharmacokinetics studies using human biomaterials were described in section ''Pharmacokinetic interaction studies''.

2.4.3. Pharmacodynamics

Mechanism of action

No studies were submitted (see discussion on clinical pharmacology).

Primary and Secondary pharmacology

A semi-mechanistic indirect PK-PD model was used to describe the population platelet dynamics with effects resulting from panobinostat concentrations of an effect compartment following the treatment of single-agent panobinostat in 441 patients. Individual panobinostat concentrations were simulated based on the PK parameter estimates obtained from a prior population PK model. Model analysis showed a dose and schedule dependent relationship between panobinostat exposure and thrombocytopenia (TCP). The thrice weekly oral dosing schedule prevents excessive accumulation of drug and reduces occurrence of TCP, with an every other week dosing schedule predicted to facilitate platelet recovery in patients with lower platelet function at baseline. In addition, the risk of grade 3/4 thrombocytopenia is also determined by individual patient's baseline platelet count.

A linear mixed-effect model was used to describe time matched (within 60 minutes) plasma panobinostat concentration and QTc interval measurement corrected for heart rate in 499 patients treated with panobinostat

oral regimens across 12 studies with oral doses between 10 and 80 mg. Variables including baseline QTc intervals, panobinostat plasma concentrations, route of administration, and dosing schedule were included in the final model. Maximum QTcF prolongation was observed on Day 5 after initiation of single-agent panobinostat treatment. In the range of clinically relevant concentrations with 20 mg oral administration thrice weekly, no apparent relationship between QTcF and plasma concentration was observed. In addition, no apparent relationship between QTcF and metabolite BJB432 plasma concentration was observed. With intermittent dosing (TIW), the incidence of grade 3 QTc prolongation (QTcF >500 ms), continues to be uncommon at (about 1% overall) with the highest frequency of <5% seen in patients treated with the 60 mg oral dose in the TIW QW dosing schedule. Grade 4 QTc prolongation or torsade de pointes has not been reported in clinical trials with these oral intermittent schedules (data not shown).

The data above refers to panobinostat monotherapy, not to combination therapy with bortezomib and dexamethasone. For the combination of panobinostat, bortezomib and dexamethasone, reports of the clinical effect of QT prolongation and other ECG abnormalities are discussed in the safety section.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetic studies have been performed in patients only; this is acceptable due to possible genotoxicity; healthy volunteer studies were deemed unethical.

Two different oral formulations of panobinostat (FMI and CSF) have been used in the clinical studies. No bioequivalence study has been conducted to compare the two formulations (FMI and CSF). In the PPK analysis, a slower absorption rate was estimated for the FMI formulation compared to the CSF formulation resulting in an estimated 30% lower C_{max} but with no effect on the total exposure. However, in view of the total pharmacokinetic study package, the impact on the knowledge of the pharmacokinetic characteristics of panobinostat is expected to be minimal. The CSF formulation has been used only in the studies B1101, B2108, B2101 and B2102. Sufficient PK data are available for the FMI (the formulation to be marketed) which has been used in the pivotal study. No bioequivalence study is required to characterise the PK of the two formulations.

Panobinostat is a DAC inhibitor with in vitro activity against all class I, II and IV DACs and is reported to act through histone acetylation but also through non-histone proteins. Synergistic effects with BTZ and Dex have been shown in *in vitro* and *in vivo* models. The main MOA in MM is stated to be related to the clearance of misfolded para-proteins which are essential for MM cell survival.

The food effect has been properly investigated. The recommended intake of panobinostat in the pivotal phase 3 study B2308 is regardless of food intake. The difference in C_{max} under fasted and fed conditions might introduce pharmacokinetic variability. Overall panobinostat exposure and inter patient variability remained unchanged with or without food, whereas Cmax was reduced by <45% and Tmax prolonged by 1 to 2.5 hours with food (i.e. both normal and high fat breakfasts). Since food did not alter overall bioavailability (AUC), panobinostat can be administered regardless of food in cancer patients

Plasma protein binding was found to be consistent throughout the *in vitro* and *in vivo* (*ex vivo*) studies. No displacement interactions are to be expected. There was a trend for lower protein binding in patients with moderate and severe hepatic impairment.

The metabolism of panobinostat is extensive and diverse. The reduction of the hydroxamic acid moiety to the amide metabolite is likely catalysed by cytosolic or mitochondrial liver enzymes such as aldehyde oxidases, the metabolism of panobinostat to the carboxylic acid due to hydrolytic activity in blood plasma, formation of the direct glucuronide metabolite was found to be catalysed by several UGT enzymes and the one- and two-carbon shortening of the hydroxamic acid containing side chain is proposed to be mitochondrial. CYP enzyme mediated

metabolism is mainly by CYP3A4 and with minor contributions by CYP2D6 and CYP2C19 enzymes. Based on the effect of ketoconazole (1.8-fold increase in AUC), it was estimated that CYP3A4 contributed for 40% to the metabolic clearance. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of panobinostat. Panobinostat is a P gp substrate. Characterization and measured presence of the metabolites in plasma, urine and faeces are sufficient as the metabolites do not demonstrate activity to any of the HDAC isoforms.

Panobinostat showed less than proportional increase in exposure observed at higher doses, which may in part be related to solubility limitations. No unexpected accumulation of panobinostat was observed following multiple dosing.

Inter- and intra-subject variability was lower following IV administration compared to oral administration indicating that absorption and first-pass metabolism significant contribute to the variability. Inter-subject variability of clearance was also high 65% in popPK and was largely unexplained. No dose dependent absorption component seems to be used for the popPK, while across study comparison shows less than proportional pharmacokinetics following oral administration of panobinostat.

For patients >75 years of age, depending on the patient's general condition and concomitant diseases, an adjustment of the starting doses or schedule of the components of the combination regimen may be considered. Panobinostat may be started at a dose of 15 mg, and if tolerated in the first cycle escalated to 20 mg in the second cycle. Bortezomib may be started at 1.3 mg/m^2 once weekly on days 1 and 8, and dexamethasone at 20 mg on days 1 and 8 (see SmPC, section 4.2).

Special populations have been investigated by dedicated renal and hepatic impairment studies.

Plasma exposure of panobinostat is not altered in cancer patients with mild to severe renal impairment. Therefore, starting dose adjustments are not necessary. Panobinostat has not been studied in patients with end stage renal disease (ESRD) or patients on dialysis. Use in patients with renal impairment has been adequately reflected in the SmPC (see section 4.2 and 5.2) and in the Risk Management Plan.

A clinical study in cancer patients with impaired hepatic function showed that plasma exposure of panobinostat increased by 43% (1.4 fold) and 105% (2 fold) in patients with mild and moderate hepatic impairment, respectively. Patients with mild hepatic impairment should be started on panobinostat at a reduced dose of 15 mg during the first treatment cycle. A dose escalation from 15 mg to 20 mg may be considered based on patient tolerability. Patients with moderate hepatic impairment should be started on panobinostat at a reduced dose of 10 mg during the first treatment cycle. A dose escalation from 10 mg to 15 mg may be considered based on patient tolerability. Frequency of monitoring of these patients should be increased during treatment with panobinostat, particularly during the dose escalation phase. Panobinostat should not be administered in patients with severe hepatic impairment due to lack of experience and safety data in this population. Adjustment of bortezomib dose should also be considered (see SmPC, section 4.2).

In patients with hepatic impairment receiving concomitant medicinal products which are strong CYP3A4 inhibitors, treatment with panobinostat should be avoided due to lack of experience and safety data in this patient population (see SmPC, section 4.2).

In vitro studies to investigate the potential of pharmacokinetic drug interaction were in general well conducted in accordance with the Guideline on Investigation of Drug Interactions. However, since the *in vitro* study to assess the involvement of OATPs had technical drawbacks (too high concentrations, lack of validation of test system) the CHMP recommended the applicant to investigate *in vitro* the possible involvement of OATP1B1 and 1B3 uptake transport. Clinically relevant panobinostat concentrations should be used. A transfected cell system

is preferred, but if hepatocytes are used, the system should be fully validated verifying the function of transporters and inhibitors.

The panobinostat fraction metabolised through CYP3A4 is approximately 40%. In clinical studies in multiple myeloma, the exposure of panobinostat was decreased by approximately 20% by the concomitant use of dexamethasone, which is a dose dependent mild/moderate CYP3A4 inducer. Strong inducers are expected to have greater effects, and may reduce the efficacy of panobinostat, therefore the concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided (see SmPC section 4.5).

It is currently unknown whether panobinostat may reduce the effectiveness of hormonal contraceptives. In addition, when panobinostat is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of contraceptives needs to be considered. Women using hormonal contraceptives should additionally use a barrier method of contraception (see SmPC section 4.5). Interaction with strong CYP3A inducers has been classified as a potential risk in the Risk Management Plan.

Co-administration of a single 20 mg panobinostat dose with ketoconazole, a strong CYP3A inhibitor, increased the C_{max} and AUC of panobinostat by 1.6- and 1.8-fold, respectively, compared to when panobinostat was given alone. In patients who take concomitant medicinal products which are strong CYP3A and/or Pgp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, the dose of panobinostat should be reduced (see SmPC section 4.5).

Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice, as these are known to inhibit cytochrome P450 3A enzymes and may increase the bioavailability of panobinostat (see SmPC section 4.5).

In patients who take concomitant medicinal products which are strong CYP3A and/or Pgp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, the dose of panobinostat should be reduced (see section 4.2).

In vitro signals for enzyme inhibition was seen for CYP3A4 (TDI) and CYP2D6 (direct inhibition). Panobinostat increased the Cmax and the AUC of dextromethorphan (a substrate of CYP2D6) by 1.8 and 1.6 fold, respectively, and it cannot be excluded that the effect may be larger on a more sensitive CYP2D6 substrate. Avoid panobinostat use in patients who are taking CYP2D6 substrates with a narrow therapeutic index (including but not limited to pimozide). When Farydak is co administered with sensitive CYP2D6 substrates (e.g. atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, and pimozide) dose titrate individual CYP2D6 substrates based on tolerability and frequently monitor patients for adverse reactions (see SmPC section 4.5). Interaction with CYP2D6 substrates has been classified as a potential risk in the Risk Management Plan.

The potential *in vivo* relevance of the *in vitro* time dependent inhibition of CYP3A4 was addressed using PBPK modelling in Simcyp. Further model validation was performed in the second round of assessment, and it was concluded that the risk for panobinostat to affect CYP3A4 substrates via time-dependent inhibition was low. Available *in vitro* data was however not possible to use to exclude a risk for induction of CYP3A4 in the gastrointestinal tract, due to the low concentrations used in the *in vitro* experiments. The risk for moderate or strong induction was deemed unlikely based on the lack of obvious time-dependent pharmacokinetics of panobinostat itself (weak CYP3A4 substrate). Interaction with strong CYP3A4 inhibitors has been classified as a potential risk in the Risk Management Plan.

No data is available that can be used to exclude the risk that panobinostat could be a weak inducer of the enzyme CYP3A4 in the gastrointestinal tract. This could potentially lead to slightly decreased exposure to sensitive CYP3A4 substrates (see SmPC section 4.5). Interaction with sensitive CYP3A4 substrates has been classified as a potential risk in the Risk Management Plan.

Exposure-QTc prolongation and exposure- thrombocytopenia have been evaluated based on panobinostat monotherapy. Potential worsening of the effect by the combination therapy has not been evaluated by means of exposure-effect relationships. Grade 3 QTc prolongation (QTcF >500 ms) was observed at higher doses than the 20 mg. In the range of clinically relevant concentrations with 20 mg panobinostat oral administration thrice weekly (peak plasma concentration ~20 ng/ml), no apparent relationship between QTcF and plasma concentration of panobinostat or BJB432 was observed. However, there are several subjects with QTc changes more than 60 ms at low panobinostat plasma concentrations. This might also be related to electrolyte abnormalities (see safety part of AR). For the combination of panobinostat, bortezomib and dexamethasone, reports of the clinical effect of QT prolongation, defined as >500 ms, changes of >60 ms from baseline and other ECG abnormalities are discussed in the safety section.

Concomitant use of anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol) and other substances that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended. Anti-emetic medicinal products with a known risk of QT prolongation such as dolasetron, granisetron, ondansetron and tropisetron should be used with caution (see SmPC section 4.5). Interaction with drugs that may prolong the QT interval has been classified as a potential risk in the Risk Management Plan.

Panobinostat should be combined with dexamethasone and bortezomib, and limited data suggest that dexamethasone may decrease panobinostat exposure (at least 20%) compared to single panobinostat use. No sign of pharmacokinetic interactions with bortezomib has been observed, but no formal interaction study was performed. In general, the interaction potential of panobinostat should have been evaluated in the intended combination with dexamethasone and bortezomib, to evaluate the net interaction potential of all three drugs. In addition, concomitant use of the weak enzyme inducer dexamethasone could potentially mask or decrease an enzyme inhibitory effect of panobinostat. In this case, however, as the interaction potential of panobinostat appears to be low and the potential for PK interactions between the three agents seems low, the approach used investigating the interaction potential of panobinostat as a single agent is acceptable.

Regarding popPK-thrombocytopenia modelling, the used dose regimen of 2 weeks on/ 1 week off and combination therapy was not simulated and as dexamethasone decreases the exposure of panobinostat, this population PKPD modelling of platelet count is less representative for the combination therapy. However since the risk of thrombocytopenia is well recognized, no optimisation of the PKPD model is required.

The popPK-thrombocytopenia model did not simulate the dosing schedule of 2 weeks on/1 week off in combination with bortezomib and dexamethasone but it can be anticipated from the simulations that platelets will not be fully recovered within the 1 week off schedule. Risk of thrombocytopenia and recommendations for frequent monitoring of blood count have been addressed adequately in sections 4.2, 4.4 and 4.8 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetic and pharmacodynamics properties of panobinostat have been adequately investigated.

2.5. Clinical efficacy

2.5.1. Dose response study

Study CLBH589B2207 (B2207)

Study B2207 was a phase Ib, multi-center, open-label, dose-escalation study of oral panobinostat and iv bortezomib in adult patients with multiple myeloma. The primary objective of the study was to determine the maximum tolerated dose (MTD) of PAN in combination with BTZ. Dose limiting toxicity (DLT) was defined as an AE or abnormal laboratory value assessed as clinically relevant and occurring ≤ 21 days following the first dose of study treatment in Cycle 1.

A total of 62 patients were enrolled, including 47 patients in the dose escalation phase and 15 patients in the dose-expansion phase. The majority of patients enrolled in the dose escalation phase discontinued treatment (43/47 patients, 91.5%). The primary reasons for discontinuation of study treatment were AEs (38.3%) and disease progression (36.2%); in the MTD cohort (including a combined 17 patients from cohorts 3 and 6), 47.1% of discontinuations were due to AEs and 29.4% due to disease progression. At the time of the data cut-off, 4 patients from the dose escalation phase of the study were still ongoing; 2 patients each in the MTD (PAN 20 mg + BTZ 1.3 mg/m^2) and PAN 25 mg + BTZ 1.3 mg/m^2 cohorts.

The dose levels for PAN, BTZ and DEX in Study B2207 are presented in Table 22..

Table 22. Dose levels for PAN, BTZ and DEX in Study B2207

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

BTZ: bortezomib, Dex: dexamethasone, MTD: maximum tolerable dose, PAN: panobinostat

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

The following DLTs were reported in different dose levels during dose escalation phase:

• In the PAN 30 mg + BTZ 1.3 mg/m^2 (Cohort 4), DLTs were reported in 4 out of 6 evaluable patients. These included thrombocytopenia (2 patients), weakness (2 patients), anorexia, asthenia and fatigue (all in 1 patient). This led to de-escalation in PAN dose from 30 mg to 25 mg in next cohort (Cohort 5), keeping the BTZ dose at 1.3mg/m^2.

• In the PAN 25 mg + BTZ 1.3 mg/m^2 (Cohort 5), DLTs were observed in 2 out of 6 evaluable patients, including tumour lysis syndrome (1 patient) and thrombocytopenia (1 patient). This led to de-escalation in PAN dose from

25 mg to 20 mg in next cohort (Cohort 6) keeping the BTZ dose at 1.3mg/m^2 bringing it back to the dose tested in Cohort 3.

• In the PAN 20 mg + 1.3 mg/m^2 (Cohort 6), DLTs were observed in 3 out of 15 evaluable patients (6 patients in cohort 3 and 9 patients in cohort 6) and included thrombocytopenia, vomiting and orthostatic hypotension (1 patient each).

The observed overall response rate (≥ PR) was 44.7%. The response rate was highest in the following dose cohorts: PAN 20 mg + BTZ 1.3 mg/m^2 (52.9%, the MTD), PAN 25 mg + BTZ 1.3 mg/m2 (55.6%), and PAN 30 mg + BTZ 1.3 mg/m^2 (57.1%). The best overall response in the dose escalation phase included high quality responses of sCR and CR in 2 patients each and VGPR in 3 patients. In addition, 14 patients showed PR, 4 patients showed minor response and 8 patients presented with stable disease (SD) as their best overall response. The best overall response was unknown in 9 patients as they had no response category confirmed as per the response criteria.

In the MTD cohort (n=17) of patients, responses were observed in the majority of patients (52.9%). Best overall responses included high quality response of sCR in 1 patient, CR and VGPR in 2 patients each. In addition, 4 patients showed PR, 3 patients showed minor response and 2 patients showed SD. The best response was unknown in 3 patients, because there were no confirmed responses for these patients as per the response criteria.

Based on the data from on all patients in the dose escalation phase and the Bayesian Logistic Regression Model, the MTD was declared at 20 mg PAN TIW and 1.3 mg/m^2 BTZ iv (cohorts III and VI). Dose limiting toxicities were reported in 3/15 patients (20%) in the MTD cohort. Thrombocytopenia as a DLT (grade 4) was reported by 1 of 15 patients (6.7%) in the MTD cohort compared to more than 15% in the cohorts with higher doses of PAN.

Dose expansion phase

Following MTD determination of panobinostat in combination with bortezomib and safety data review, a protocol amendment was introduced prior to initiation of the dose-expansion phase. The purpose of the second, dose-expansion phase was to confirm safety and determine preliminary efficacy of the dose identified in the dose escalation phase.

In the dose expansion phase of Study B2207, a total of 15 patients with relapsed or relapsed and refractory MM were enrolled. In the expansion phase, patients received the MTD of panobinostat (20 mg) plus bortezomib (1.3 mg/m^2); however, panobinostat was administered using a non-continuous dosing schedule, similar to that for bortezomib (first 2 of 3 weeks), to manage thrombocytopenia and to allow for accelerated platelet recovery (Lin et al., 2009). Additionally, dexamethasone was administered to all patients because preclinical data (Ocio et al., 2010), showed that the triple combination of panobinostat, bortezomib, and dexamethasone yielded synergistically greater antimyeloma activity than any dual combination, and clinical data showed clinical benefit of dexamethasone when added to bortezomib in patients with relapsed/refractory MM. Twenty milligrams of dexamethasone was chosen based on evidence showing that for patients who had worsening disease/suboptimal response whilst receiving BTZ 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 to allow for analysis of panobinostat and bortezomib pharmacokinetics in the absence (Cycle 1) and presence (Cycle 2) of the drug.

The majority of patients in the expansion phase of Study B2207 responded to treatment with PAN + BTZ + DEX. Overall, 11/15 patients (73.3%) responded to treatment: 3/15 patients (20.0%) achieved VGPR, 8/15 patients

(53.3%) achieved PR and 2 patients (13.3%) showed confirmed minor response. Of the 4 BTZ-refractory patients in the expansion phase (FAS), 2 patients presented with PR.

The majority of patients in the expansion phase discontinued study treatment (11/15 patients, 73.3%). The remaining 4 patients were still on study treatment at the time of the data cut-off.

Throughout the dose expansion phase of the study, the primary reasons for discontinuation of study treatment were AEs (33.3%) and disease progression (20.0%); the rate of discontinuation due to AEs among patients in the dose expansion phase was lower compared to patients receiving the MTD in the dose escalation phase (33.3% vs 47.1%, respectively). In the dose expansion phase there were lower incidences of haematological AEs, as compared to the MTD cohort of dose escalation phase.

2.5.2. Main study

Study CLBH589D2308 (D2308/Panorama I)

Methods

Study CLBH589D2308 was a multicenter, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.

Study Participants

Inclusion criteria

Patients had to meet the following criteria:

1. Patient has a previous diagnosis of multiple myeloma, based on International Myeloma Working Group (IMWG) 2003 definitions and all three of the following criteria had been met:

• Monoclonal immunoglobulin (M component) on electrophoresis, and on immunofixation on serum or on total 24 hour urine (or demonstration of M protein in cytoplasm of plasma cell for non-secretory myeloma)

• Bone marrow (clonal) plasma cells ≥ 10% or biopsy proven plasmacytoma

• Related organ or tissue impairment (CRAB [elevated calcium, renal failure, anaemia, bone lesions] symptoms: anaemia, hypercalcaemia, lytic bone lesions, renal insufficiency, hyper viscosity, amyloidosis or recurrent infections)

2. Patient with 1 to 3 prior lines of therapy who requires re-treatment of myeloma (per IMWG guidelines 2003) for one of the 2 conditions below:

• Relapsed, defined by disease that recurred in a patient that responded to a prior therapy, by reaching a MR or better, and had not progressed under this therapy or up to 60 days of last dose of this therapy. Patients previously treated with BTZ may be eligible.

• Relapsed-and-refractory to a therapy provided that both of these conditions are met:

- patient has relapsed to at least one prior line, and
- patient was refractory to another line (except BTZ), by either not reaching a MR, or progressed while on this therapy or within 60 days of its last dose

3. Patient has measurable disease at study screening defined by at least one of the following measurements as per IMWG 2003 criteria: serum M-protein ≥ 1 g/dL (≥ 10 g/L); urine M-protein ≥ 200 mg/24 h

4. Patient treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, is eligible. Two weeks must have lapsed since last date of radiotherapy, which is recommended to be a limited field

5. Patient's age is ≥ 18 years at time of signing the informed consent

6. ECOG performance status (PS) ≤ 2

7. Patient has the following laboratory values within 3 weeks before starting study drug: ANC ≥ 1.5 x 109/L; Platelet count ≥ 100 x 109/L; Serum potassium, magnesium, phosphorus, within normal limits (WNL) for the institution; Total calcium (corrected for serum albumin) or ionized calcium greater or equal to lower limit of normal (>LLN) for institution, and not higher than CTCAE grade 1 in the case of an elevated value; Potassium, calcium, magnesium, and/or phosphorus supplements may be given to correct values that are <LLN; Aspartate aminotransferase/glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 x upper limit of normal (ULN); Serum total bilirubin ≤ 1.5 x ULN (or ≤ 3.0 x ULN if patient has Gilbert syndrome); Serum creatinine levels ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 ml/min.

Exclusion criteria

Any patient who met any of the following criteria was excluded:

1. Patients who have progressed under all prior lines of anti-MM therapy (primary refractory)

2. Patients who have been refractory to prior BTZ (i.e. did not achieve at least a MR, or have progressed on it or within 60 days of last dose)

3. Patient has grade ≥ 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination within 14 days before randomization

4. Patient received prior treatment with deacetylase inhibitors including panobinostat

5. Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment

6. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period)

7. Patient has secondary primary malignancy <3 years of first dose of study treatment (except for treated basal or squamous cell carcinoma, or in situ cancer of the cervix)

8. Patient who received: prior anti-myeloma chemotherapy or medication including immunomodulatory drugs and dexamethasone ≤ 3 weeks prior to start of study; experimental therapy or biologic immunotherapy including monoclonal antibodies ≤ 4 weeks prior to start of study; prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior start of study

9. Patient has impaired cardiac function, including any one of the following: LVEF <LLN of institutional normal, as determined by echocardiogram (ECHO) or multiple uptake gated acquisition scan (MUGA); obligate use of a permanent cardiac pacemaker; congenital long QT syndrome; history or presence of ventricular tachyarrhythmia; resting bradycardia defined as <50 beats per minute; QTcF >450 ms on screening ECG; 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; myocardial infarction 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 and vascular disease (e.g. uncontrolled hypertension)

10. Patient taking medications with relative risk of prolonging the QT interval or inducing Torsades de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug.

Multiple Myeloma disease definitions (as per IMWG, Kyle, et al 2003)

Myeloma-related organ or tissue impairment (end organ damage) (ROTI) due to the plasma cell proliferative process.

• Calcium levels increased: serum calcium >0.25 mmol/l above the upper limit of normal or > 2.75 mmol/l

• Renal insufficiency: creatinine >173 mmol/l

• Anaemia: haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl

• Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)

• Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2

episodes in 12 months)

("CRAB": calcium, renal insufficiency, anaemia or bone lesions)

Symptomatic multiple myeloma:

• M-protein in serum and/or urine

• Bone marrow (clonal) plasma cells* or plasmacytoma

• Related organ or tissue impairment (end organ damage, including bone lesions)

*If flow cytometry is performed, most plasma cells (> 90%) will show a 'neoplastic' phenotype.

Some patients may have no symptoms but have related organ or tissue impairment.

Definitions for Measurable M protein/MM disease (per IMWG, Kyle 2003)

- Serum M-protein ≥1 g/dl (≥10 gm/l)[10 g/l]
- Urine M-protein ≥200 mg/24 h
- Serum FLC assay: Involved FLC level ≥10 mg/dl ((≥100 mg/l) provided serum FLC ratio is abnormal.

Treatments

Patients were assigned to one of the following 2 treatment arms in a ratio of 1:1:

• PAN + BTZ + Dex (investigational arm) or

• Placebo + BTZ + Dex (control arm)

Table 23: Treatment doses and regimens - D2308 study

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

Treatment phase 1 (TP1): In TP1 the duration of a treatment cycle was 21 days given to a total of 8 cycles. The first dose of oral panobinostat/placebo in Cycle 1 defined Day 1 of the treatment cycle.

Treatment phase 2 (TP2): TP2 started with Cycle 9. Only patients who had experienced a No Change (NC) or better and presented no toxicities (CTCAE ≥ grade 2) could enter TP2. The duration of a treatment cycle in TP2 was 42 days. In TP2, a maximum of 4 cycles was administered. The first dose of panobinostat/placebo in Cycle 9 defined Day 1 of the treatment cycle.

No cross-over was allowed.

Permitted dose adjustments and interruptions of study treatment

Patients unable to tolerate the minimum dose level of Dex could continue on the rest of their randomly assigned regimen without Dex.

Patients requiring discontinuation of BTZ due to peripheral neuropathy could continue on PAN/Placebo ± Dex. BTZ could be restarted at any time during treatment phases 1 and 2 if clinically indicated. Patients requiring permanent discontinuation of BTZ due to any other reason or permanent discontinuation of PAN/Placebo were to discontinue study treatment and be followed for progressive disease/relapse and survival.

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

The dose of PAN/PBO could be modified as per the table below during any cycle. Dose levels lower than 10 mg TIW in combination with a minimum of 0.7 mg/m2 BTZ, with or without Dex, were not permitted at any time. If a dose below 10 mg TIW in combination with the minimum dose of BTZ was required, the patient was to be discontinued from study treatment. Continuation of PAN/Placebo dosing without BTZ at any dose was not permitted in TP1 or TP2.

Table 24: Dose reductions for panobinostat/placebo- D2308 study

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

Patients receiving a reduced dose level of panobinostat/placebo due to toxicity could be considered for dose re-escalation if: either the study treatment-related AE had reverted in severity to grade ≤ 1 or baseline level, and at least nine scheduled doses at the reduced level had been administered and tolerated.

Growth factor support for anaemia and neutropenia, if initiated before study entry was allowed. Bisphosphonates were permitted only if treatment had begun prior to the start of screening.

Objectives

The primary objective of study CLBH589D2308 was to compare progression free survival (PFS) in patients treated with panobinostat in combination with bortezomib/dexamethasone vs. patients treated with placebo in combination with bortezomib/dexamethasone.

The key secondary objective was to compare overall survival (OS) between treatment arms. Other secondary objectives included: comparison of overall response rate (ORR) comprising complete response (CR), near CR (nCR) and partial response (PR), determination of nCR plus CR rate, determination of minimal response rate (MRR), determination of time to response (TTR), determination of time to progression (TTP), assessment of duration of response (DOR) from first occurrence of PR or better, assessment of safety of the combination therapy, assessment of health-related quality of life (QoL) and symptoms of multiple myeloma, and evaluation of the pharmacokinetics (PK) of panobinostat and bortezomib in a subset (at least 20) of Japanese patients.

Outcomes/endpoints

Primary endpoint

The primary endpoint was PFS based on modified European Society for Blood and Marrow Transplantation (mEBMT) criteria assessed by the Investigator.

Disease status categories according to EBMT, Modified EBMT

EBMT (Bladé et al., 1998)	Modified EBMT
NC	SD
MR	MR
PR	PR
-	nCR
CR	CR

NC: no change; SD: stable disease; MR: minor response; PR: partial response; VGPR: very good partial response; CR: complete response; nCR: near complete response; sCR: stringent complete response; mCR: molecular complete response.

PFS was defined as the time from the date of randomization to the date of the first documented PD or relapse or death due to any cause. If a patient had not progressed or was not known to have died by the date of the analysis cut-off or had started another antineoplastic therapy, or had PD/relapse or died after more than two

missing adequate assessments, PFS was censored at the date of the last adequate response assessment prior to the cut-off date or start of new antineoplastic therapy.

Secondary endpoints

Overall survival (OS) was defined as the time from date of randomization to the date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last contact.

The overall response rate (ORR) was based on the proportion of patients with CR, nCR or PR per investigator's assessment based on mEBMT criteria.

Time to response (TTR) was defined as the time between the dates of randomization until first documented response (CR, nCR or PR) per investigator's assessment based on mEBMT criteria.

Duration of response (DOR) was defined as the time from the first documented occurrence of response (PR or nCR or CR) until the date of the first documented PD or relapse or death due to MM per investigator's assessment based on mEBMT criteria.

Time to progression or relapse (TTP) was defined as the time from the date of randomization to the date of the first documented PD or relapse or death due to multiple myeloma per investigator's assessment based on mEBMT criteria.

HRQoL and multiple myeloma symptoms as measured by: EORTC QLQ-C30, EORTC QLQ-MY20, and FACT/GOG-NTX. Time to definitive deterioration in PRO was estimated according to the minimal important difference (MID). For EORTC QLQ-C30 global health status scores, a 5-point decrease or more in the score from baseline was considered as definitive deterioration (Osoba 1998, Dubois 2006). For EORTC QLQ-MY20 disease symptom scales, the MID (Osoba 1998, Dubois 2006) was defined by considering a 5-point increase or more in the score as definite deterioration. For FACT/GOG-NTX neurotoxicity subscale, the MID (Dubois 2006) was defined as a decrease of 3 points or more in the score which will be considered a definitive deterioration.

Sample size

In order to calculate the sample size, median PFS of PBO+ BTZ + DEX and PAN + BTZ + DEX arms were assumed to be 7.5 months and 10.2 months, respectively (HR=0.74). This assumption was based on a study comparing BTZ with DEX in patients with relapsed myeloma with an observed median TTP of 6.22 months (Richardson et al., 2005). Under the above assumption and using a 1:1 randomization to the two arms a total of 460 PFS events were required corresponding to an estimated 762 randomized patients.

Randomisation

The randomisation procedure pertained that at Visit 2 (Day 1 Cycle 1) all eligible patients were randomized via Interactive Voice Response System/Interactive Web Response System (IXRS) to one of the two treatment arms. A total of 768 eligible patients were randomized 1:1 to the panobinostat and control arms. Central randomization was stratified 1) by number of prior lines of anti-myeloma therapy: 1 vs 2 or 3 and 2) by prior use of bortezomib: yes vs no.

Blinding (masking)

This was a double blind study.

Statistical methods

Full Analysis Set (FAS) comprises all randomized patients. All efficacy analyses were performed on the FAS, following the intent-to-treat principle.

The Safety Set comprises all patients who received at least one dose of any component of study treatment. All safety analyses were performed on the Safety Set.

Per Protocol Set (PP Set) comprises all patients from the FAS who had received at least one dose of randomized study drug and had no major protocol deviations. Protocol deviations classified as major led to the exclusion of patients from the PP Set.

Interim analysis

Per the 3 look group sequential design, two interim analyses were planned after observing 33% and 80% of the required final number of 460 PFS events. These analyses allowed stopping for futility at the first interim analysis of PFS and for efficacy at the second interim analysis of PFS.

The second interim analysis, planned to occur after 80% of observed events, was not performed due to the time needed to implement amendment 5 to the protocol and the resulting overlap with the timing of the final analysis. Accordingly, the Applicant continued the study until the final number of 460 PFS events had accrued. There was no change in the group sequential design for the final analyses of PFS and OS; alpha was spent at each time point that an interim analysis had been planned.

Sensitivity analyses

A stratified log-rank test, the median with 95% CI and HR as derived from a Cox proportional hazards model including treatment arm and stratification factors, were repeated with the following alternative conventions (Table 25).

Table 25: Sensitivity analyses of PFS- D2308 study

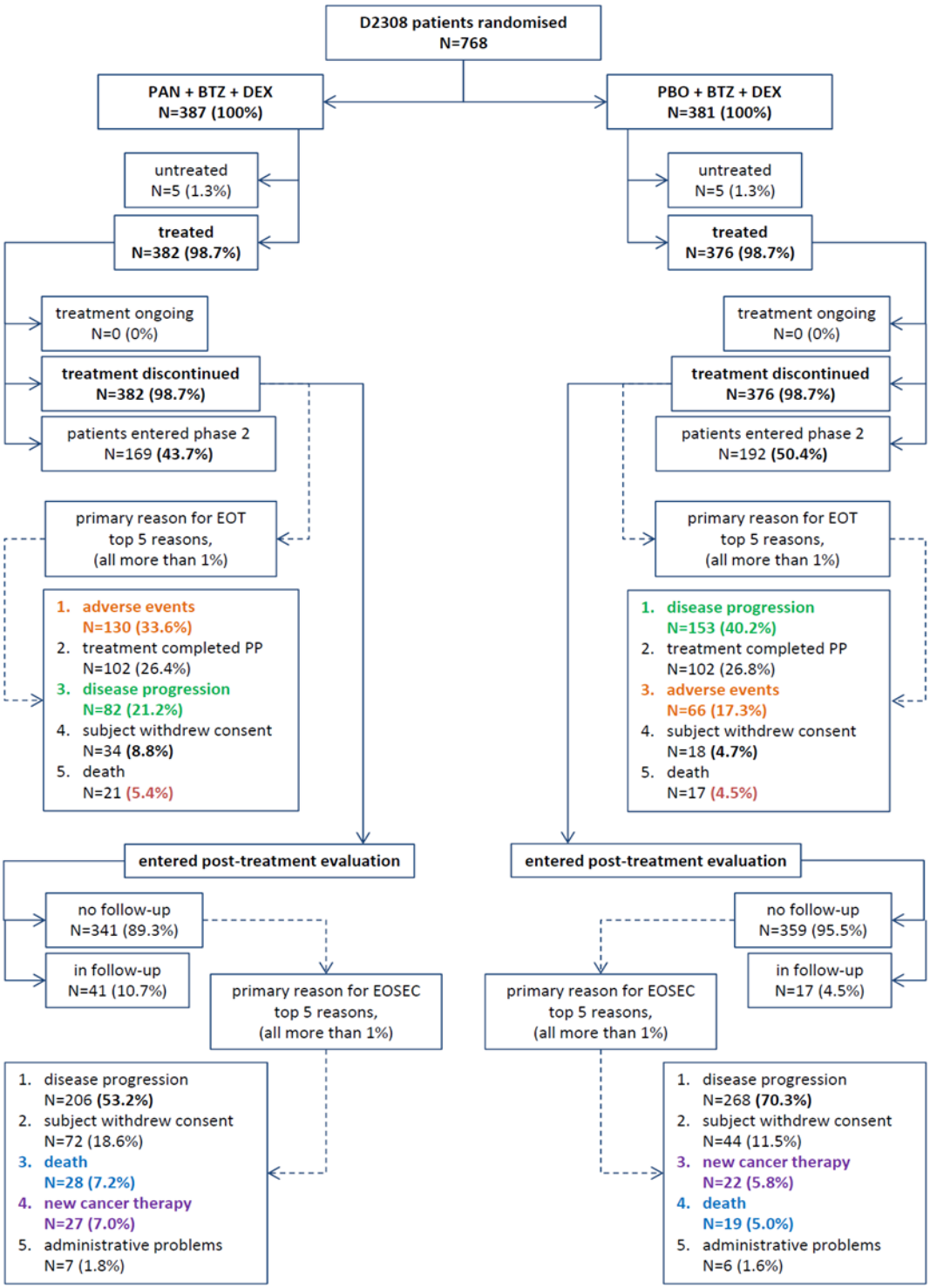
Analysis	Rules
Assess impact of missing response assessments (Actual event)	Regardless of the number of preceding missing assessments, the actual event date of progression, relapse or death was used as the PFS event date.
Assess impact of missing response assessments (Backdating event)	In case of a documented PFS event after 1 or more subsequent missing response assessments, PFS was considered to have occurred at the next scheduled response assessment after the date of the last adequate response assessment.
Assess impact of patients who are not followed any longer for disease assessments (Drop-out)	The following were considered as PFS events: All patients who were censored in the primary analysis due to inadequate or lack of documented disease progression/relapse/death while having progressive disease as the reason for End of Treatment/Study Evaluation Completion were considered as a PFS event. All patients who stopped disease follow-up due to new anti-cancer therapy. This applied for the following situations: (1) new anticancer therapy started (as documented on ANP CRF): The start date of new anticancer therapy was considered as a PFS event date. (2) Reason for End of Treatment /Study Evaluation Completion is the start of a new ANP: The date of documentation was considered as event date. All patients whose PFS censoring reason was PFS event after ≥ 2 missing adequate assessments was considered as a PFS event. The date of the PD/ relapse/ death assessment was used as the PFS event date. In case more than 1 criterion applies, the earliest date was used as the PFS event date.
Assess impact of using IRC assessment	• Use Independent Review Committee (IRC) assessment instead of Investigator's evaluation for all patients. • Use IRC assessment for patients without M-protein assessment by electrophoresis and investigator's evaluation for patients with M-protein measurements.
Investigator assessment as Per Protocol Set analysis	Include only the Per Protocol Set in the analysis.
IRC assessment as per protocol set analysis	Include only the Per Protocol Set in the analysis.
Assess impact of prognostic factors	Use multivariate Cox regression model including as prognostic factors: sex, age, race, renal impairment, prior stem cell transplantation, clinical staging of MM according to ISS (Stage I/Stage II and III), geographic region, prior use of IMiDs (defined as thalidomide or lenalidomide), prior use of IMiDs and BTZ, MM characteristics (relapsed/relapsed-and-refractory)

Supportive analyses

A multivariate cox model analysis was performed if the primary analysis of PFS was statistically significant. The following prognostic factors in the Cox proportional hazards model were included: sex, age (< 65 years/ ≥ 65 years), race (Caucasian/Asian/Other), renal impairment: yes/no, prior stem cell transplantation: yes/no, clinical staging of MM according to ISS (Stage I/Stage II and III), geographic region (Europe/South East Asia/Western Pacific/Africa/Americas/ Eastern Mediterranean), prior use of IMiDs (defined as thalidomide or lenalidomide): yes/no, prior use of IMiDs and BTZ: yes/no, MM characteristics (relapsed/relapsed-and-refractory).

Results

Participant flow



Recruitment

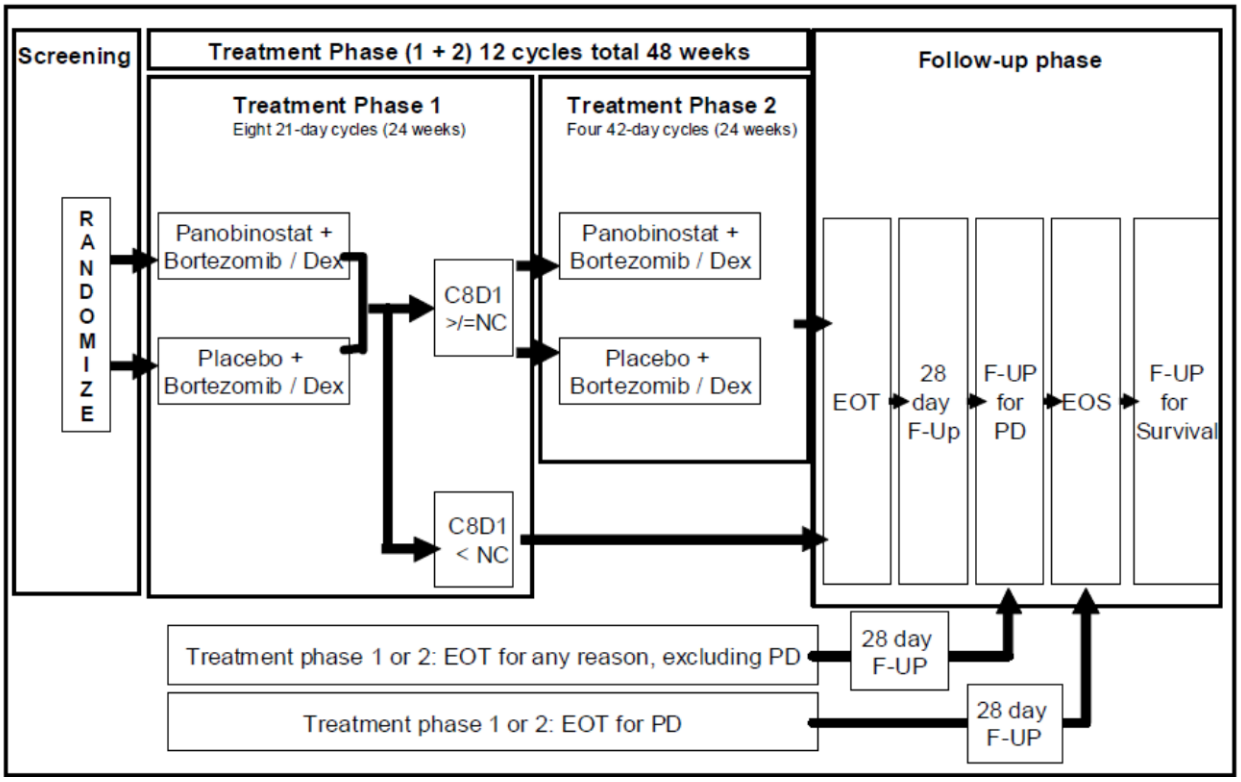
Between 29 January 2010 and 12 March 2012, 768 patients with relapsed or relapsed/refractory multiple myeloma were randomized into the trial from 194 centres in 34 countries.

The first patient was enrolled on 21 January 2010 and the last patient completed the study treatment on 1 March 2013.

Conduct of the study

The study design and planned conduct is presented in Table 26.

Table 26: The study design and planned conduct - D2308 study



Protocol amendments

The study protocol was amended five times. The key features of each amendment are given below.

Amendment 1 (issued on 30-Jun-2010): This amendment was a local, country-specific amendment for Japan whose main purpose was to include hospitalization of Japanese patients during the first cycle of treatment in order to comply with the local BTZ label. Secondly, this amendment included PK sampling on Cycle 1 Day 1 and Cycle 1 Day 8 in Japanese patients. Thirdly, this amendment added the commercially available dosage form of BTZ available in Japan as part of the global protocol. As of the release date of this amendment, 34 patients had been randomized worldwide.

Amendment 2 (issued on 22-Dec-2011): As of 17-Nov-2011, 668 patients had been randomized worldwide. This amendment was a global amendment to adjust the sample size to compensate for a higher than expected drop-out rate in the absence of any safety concerns. A review of blinded data concluded that the drop-out rate was higher than originally assumed. The main reason for the drop-out rate was that patients who discontinued treatment withdrew their consent to be followed for response assessment as per protocol. As a consequence,

the expected drop-out rate as written in the statistical section of the original protocol needed to be updated. The sample size was therefore recalculated in order to attain the targeted number of PFS events while maintaining the original statistical assumptions. In addition to the increased sample size, an operational action plan for new and ongoing patients was put into place to follow patients for disease assessment after treatment discontinuation. Under the original assumption of obtaining 460 PFS events based on 610 patients and a drop-out rate of 10%, the required sample size was 672. Based on review of blinded data, the drop-out rate was approximately 20%. As a result, the sample size was increased to 762 patients.

Amendment 3 (issued on 07-Mar-2012): As of 07-Feb-2012, 742 patients had been randomized worldwide, with 386 patients having discontinued treatment. This amendment was a global amendment to enhance robustness of the second interim analysis (IA2), in order to provide a more precise estimate of the treatment effect and to increase the probability of detecting a treatment effect. This amendment increased the PFS event fraction for IA2 from 67% to 80% (306 to 368 events). If the study were to be stopped at IA2, the higher fraction of planned PFS events would reduce the risk of an overestimation of the treatment effect. The treatment effect assumptions (HR 0.74) were unchanged. The power to detect a treatment effect and to stop the study at IA2 for efficacy was increased from 53% to 71%. The cumulative type I error was unchanged (less than 5 %, two-sided).

Based on the recommendation of the Study Steering Committee, an additional secondary objective was added: to compare nCR plus CR between treatment arms per mEBMT criteria.

The protocol was updated with current panobinostat guidance on the use of concomitant medications.

Amendment 4 (issued on 02-Oct-2012): As of 07-Sep-2012, there were 87 patients remaining on treatment. At the time of this amendment, the first interim analysis had been performed. The main aim of this global amendment was to clarify that the collection of serum calcium variables (ionized serum calcium and/or total serum calcium and serum albumin for the derivation of albumin-adjusted serum calcium) should continue after the end of treatment until the end of follow-up for disease evaluations. The collection of calcium data after the end of treatment is mandatory in order to identify hypercalcaemia, which is a criterion for progressive disease and relapse, both during the treatment phase and during post-treatment disease evaluation.

Amendment 5 (issued on 06-May-2013): The study completed enrolment in March 2012 with 768 randomized patients. Last patient last treatment (LPLT) occurred on 01-March-2013. For efficacy assessments, the study protocol required measurement of M-protein spikes by PEP in serum and urine as per mEBMT criteria. Accordingly, the objective of this protocol amendment was: to document PEP results without specific measurement of the M-protein spike, and to document use of measurement methods other than PEP (e.g. nephelometry).

Baseline data

Baseline demographic and disease characteristics are summarized in Table 27 and Table 28 respectively.

Table 27: Demographic and baseline summary by treatment (FAS) - D2308 study

Demographics	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	All N=768
Age (years)			
n	387	381	768
Mean	62.4	61.8	62.1
SD	9.34	9.43	9.38
Median	63.0	63.0	63.0
Minimum	28	32	28
Maximum	84	83	84
Age category (years) - n (%)			
<65	225 (58.1)	220 (57.7)	445 (57.9)
≥ 65	162 (41.9)	161 (42.3)	323 (42.1)
Sex - n (%)			
Male	202 (52.2)	205 (53.8)	407 (53.0)
Female	185 (47.8)	176 (46.2)	361 (47.0)
Race - n (%) [1]			
Caucasian	249 (64.3)	250 (65.6)	499 (65.0)
Asian	128 (33.1)	104 (27.3)	232 (30.2)
Black	5 (1.3)	17 (4.5)	22 (2.9)
Other	5 (1.3)	10 (2.6)	15 (2.0)
ECOG performance status - n (%)			
0	175 (45.2)	162 (42.5)	337 (43.9)
1	191 (49.4)	186 (48.8)	377 (49.1)
2	19 (4.9)	29 (7.6)	48 (6.3)
>2	0	1 (0.3)	1 (0.1)
Missing	2 (0.5)	3 (0.8)	5 (0.7)
Body weight (kg)			
n	386	381	767
Mean	71.46	72.80	72.12
SD	16.275	16.494	16.387
Median	70.05	72.00	71.00
Minimum	37.7	28.8	28.8
Maximum	144.0	132.0	144.0

[1] Categories for race will be displayed in the case of >2% for any treatment group. Otherwise, patients will be counted in the "other" category.

Table 28: Baseline disease characteristics (FAS) - D2308 study

	PAN+BTZ+Dex (N=387)	PBO+BTZ+Dex (N=381)	All (N=768)
Time since diagnosis (months)			
n	386	381	767
Mean	46.7	49.0	47.8
SD	38.02	34.78	36.44
Median	37.1	38.9	37.9
Minimum	2.4	2.4	2.4
Maximum	308.1	300.2	308.1
Time since diagnosis -n (%)			
<6 months	8 (2.1)	4 (1.0)	12 (1.6)
>=6 months <1 year	20 (5.2)	16 (4.2)	36 (4.7)
>=1 year <2 years	78 (20.2)	68 (17.8)	146 (19.0)
>=2 years <5 years	187 (48.3)	188 (49.3)	375 (48.8)
>=5 years	93 (24.0)	105 (27.6)	198 (25.8)
Missing	1 (0.3)	0	1 (0.1)
Immunoglobulin class -n (%)			
IgG	252 (65.1)	251 (65.9)	503 (65.5)
IgA	90 (23.3)	86 (22.6)	176 (22.9)
IgM	4 (1.0)	1 (0.3)	5 (0.7)
IgD	3 (0.8)	3 (0.8)	6 (0.8)
IgE	0 (0.0)	1 (0.3)	1 (0.1)
Indeterminate	32 (8.3)	30 (7.9)	62 (8.1)
Missing	6 (1.6)	9 (2.4)	15 (2.0)
Involved light chains at initial diagnosis -n (%)			
Kappa	241 (62.3)	219 (57.5)	460 (59.9)
Lambda	126 (32.6)	137 (36.0)	263 (34.2)
Indeterminate	14 (3.6)	16 (4.2)	30 (3.9)
Missing	6 (1.6)	9 (2.4)	15 (2.0)
Light chain MM -n (%)			
Yes	24 (6.2)	19 (5.0)	43 (5.6)
No	362 (93.5)	362 (95.0)	724 (94.3)
Missing	1 (0.3)	0	1 (0.1)
Renal function -n (%) [1]			
Renal function impairment	265 (68.5)	249 (65.4)	514 (66.9)
No renal function impairment	120 (31.0)	129 (33.9)	249 (32.4)
Missing	2 (0.5)	3 (0.8)	5 (0.7)

Patient who consented for exploratory biomarker protocol			
No	267 (69.0)	257 (67.5)	524 (68.2)
Yes	120 (31.0)	124 (32.5)	244 (31.8)
Cytogenetic risk group -n (%) [2]			
Patients evaluable for assessment	120	124	244
Normal risk	79 (65.8)	88 (71.0)	167 (68.4)
Poor risk	24 (20.0)	13 (10.5)	37 (15.2)
Unknown	1 (0.8)	0	1 (0.4)
Missing	16 (13.3)	23 (18.5)	39 (16.0)
Clinical staging according to ISS -n (%)			
Stage I	156 (40.3)	152 (39.9)	308 (40.1)
Stage II	104 (26.9)	92 (24.1)	196 (25.5)
Stage III	77 (19.9)	86 (22.6)	163 (21.2)
Not assessed	50 (12.9)	51 (13.4)	101 (13.2)
Serum M-protein measure by PEP [g/dL]			
n	330	317	647
Mean	2.4	2.6	2.5
SD	1.62	1.71	1.67
Median	2.2	2.5	2.3
Minimum	0.0	0.0	0.0
Maximum	8.3	8.4	8.4
Urine M-protein measure by PEP [mg/24 h]			
n	278	264	542
Mean	696.3	754.3	724.5
SD	2091.56	1815.05	1960.16
Median	10.5	0.0	0.1
Minimum	0.0	0.0	0.0
Maximum	21720	16050	21720
Bone marrow plasma cell count [%] [3]			
n	347	345	692
Mean	28.3	30.3	29.3
SD	24.15	23.87	24.01
Median	20.0	25.0	22.0
Minimum	0.0	0.0	0.0
Maximum	100.0	99.0	100.0

Soft tissue plasmacytoma -n (%)			
Present	21 (5.4)	19 (5.0)	40 (5.2)
Absent	363 (93.8)	356 (93.4)	719 (93.6)
Not assessed	3 (0.8)	6 (1.6)	9 (1.2)
Lytic bone lesions -n (%)			
Present	180 (46.5)	193 (50.7)	373 (48.6)
Absent	164 (42.4)	143 (37.5)	307 (40.0)
Not assessed	43 (11.1)	45 (11.8)	88 (11.5)

[1] Renal function impairment defined as a baseline CCr < 90 mL/min; No renal function impairment CCr>= 90 mL/min. These patients have a clearance between 60-90 mL/min (due to inclusion / exclusion criteria).
[2] Percentages are based on the number of patients who consented for biomarker protocol.
[3] Bone marrow plasma cell count as assessed by biopsy or aspirate.

The treatment history at baseline is presented in Table 29.

Table 29: Prior treatment of MM at baseline by treatment group in Study D2308 (FAS)

Prior anti-myeloma treatment	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	All N=768
Prior stem cell transplantation - n (%)			
No	172 (44.4)	157 (41.2)	329 (42.8)
Yes	215 (55.6)	224 (58.8)	439 (57.2)
Autologous[1]	215 (100.0)	224 (100.0)	439 (100.0)
Allogeneic[1]	6 (2.8)	4 (1.8)	10 (2.3)
Number of prior stem cell transplantations			
n	215	224	439
Mean	1.3	1.3	1.3
SD	0.48	0.53	0.50
Median	1.0	1.0	1.0
Minimum	1.0	1.0	1.0
Maximum	3.0	3.0	3.0
Best response to last prior stem cell transplantation - n (%)[1]			
Response	194 (90.2)	213 (95.1)	407 (92.7)
Stable disease	14 (6.5)	8 (3.6)	22 (5.0)
Progressive disease	3 (1.4)	1 (0.4)	4 (0.9)
Unknown	4 (1.9)	2 (0.9)	6 (1.4)

Prior anti-myeloma treatment	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	All N=768
Prior lines of antineoplastic medication with - n (%) [2]			
Bortezomib	169 (43.7)	161 (42.3)	330 (43.0)
Lenalidomide	72 (18.6)	85 (22.3)	157 (20.4)
Thalidomide	205 (53.0)	188 (49.3)	393 (51.2)
Melphalan	310 (80.1)	301 (79.0)	611 (79.6)
Combined bortezomib+lenalidomide	34 (8.8)	45 (11.8)	79 (10.3)
Combined bortezomib+IMiDs	94 (24.3)	99 (26.0)	193 (25.1)
Combined bortezomib+dexamethasone	147 (38.0)	143 (37.5)	290 (37.8)
Cyclophosphamide	182 (47.0)	166 (43.6)	348 (45.3)
Dexamethasone	308 (79.6)	315 (82.7)	623 (81.1)
Doxorubicin	129 (33.3)	138 (36.2)	267 (34.8)
Etoposide	33 (8.5)	41 (10.8)	74 (9.6)
Prednisolone	63 (16.3)	48 (12.6)	111 (14.5)
Prednisone	53 (13.7)	59 (15.5)	112 (14.6)
Vincristine	115 (29.7)	117 (30.7)	232 (30.2)
Other	106 (27.4)	117 (30.7)	223 (29.0)
Last prior line of antineoplastic medication with - n (%) [2]			
Bortezomib	139 (35.9)	124 (32.5)	263 (34.2)
Lenalidomide	62 (16.0)	76 (19.9)	138 (18.0)
Thalidomide	148 (38.2)	124 (32.5)	272 (35.4)
Melphalan	203 (52.5)	201 (52.8)	404 (52.6)
Combined bortezomib+lenalidomide	11 (2.8)	11 (2.9)	22 (2.9)
Combined bortezomib+IMiDs	42 (10.9)	31 (8.1)	73 (9.5)
Combined bortezomib+dexamethasone	109 (28.2)	98 (25.7)	207 (27.0)
Cyclophosphamide	134 (34.6)	111 (29.1)	245 (31.9)
Dexamethasone	272 (70.3)	272 (71.4)	544 (70.8)
Doxorubicin	59 (15.2)	60 (15.7)	119 (15.5)
Prednisolone	45 (11.6)	32 (8.4)	77 (10.0)

Vincristine	50 (12.9)	47 (12.3)	97 (12.6)
Other	101 (26.1)	106 (27.8)	207 (27.0)
Number of prior lines of antineoplastic therapy [3]			
n	386	381	767
Mean	1.7	1.7	1.7
SD	0.76	0.78	0.77
Median	1.0	1.0	1.0
Minimum	1.0	1.0	1.0
Maximum	4.0	3.0	4.0

Prior anti-myeloma treatment	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	All N=768
Number of prior lines of antineoplastic therapy - n (%)			
0	1 (0.3)	0 (0.0)	1 (0.1)
1	197 (50.9)	198 (52.0)	395 (51.4)
2	124 (32.0)	108 (28.3)	232 (30.2)
3	64 (16.5)	75 (19.7)	139 (18.1)
>3	1 (0.3)	0 (0.0)	1 (0.1)
Best response to last prior line of antineoplastic medication - n (%)			
Response	343 (88.6)	327 (85.8)	670 (87.2)
Stable disease	24 (6.2)	24 (6.3)	48 (6.3)
Progressive disease	15 (3.9)	16 (4.2)	31 (4.0)
Unknown	4 (1.0)	14 (3.7)	18 (2.3)
Missing	1 (0.3)	0 (0.0)	1 (0.1)
Prior total body radiotherapy - n (%)			
Yes	1 (1.1)	2 (2.7)	3 (1.8)
No	92 (98.9)	71 (97.3)	163 (98.2)
Prior radiotherapy - n (%)			
Yes	93 (24.0)	73 (19.2)	166 (21.6)
No	294 (76.0)	308 (80.8)	602 (78.4)
Multiple myeloma definition – n (%)			
Relapsed and refractory [4]	134 (34.6)	141 (37.0)	275 (35.8)
Progression under last line	92 (23.8)	88 (23.1)	180 (23.4)
Progression within 60 days of last line	105 (27.1)	113 (29.7)	218 (28.4)
Stable disease as best response in last line	22 (5.7)	27 (7.1)	49 (6.4)
Relapsed	247 (63.8)	235 (61.7)	482 (62.8)
Other	6 (1.6)	5 (1.3)	11 (1.4)

[1] Percentages are based on the number of patients with prior stem cell transplantation.
[2] Drugs with ≥ 10% of patients and drugs and combinations of interest. Combinations include at least the 2 drugs but combinations with any additional 3rd drug or more is included in the row
[3] n is the number of patients with at least one prior line of therapy.
[4] Patients who are primary refractory are excluded.

Numbers analysed

Analysis sets are presented by treatment arm and by stratification factor in Table 30.

Table 30: Analysis sets (all randomised patients - D2308 study)

Analysis set	Stratification factor		PAN+BTZ+Dex N=387 n (%)	PBO+BTZ+Dex N=381 n (%)	All N=768 n (%)
Full Analysis Set	All		387 (100.0)	381 (100.0)	768 (100.0)
	Number of prior lines with anti-MM therapy	1	178 (45.99)	174 (45.67)	352 (45.83)
		2 or 3	209 (54.01)	207 (54.33)	416 (54.17)
	Prior treatment with BTZ	Yes	169 (43.67)	167 (43.83)	336 (43.75)
		No	218 (56.33)	214 (56.17)	432 (56.25)
Per-Protocol Set	All		289 (74.68)	274 (71.92)	563 (73.31)
	Number of prior lines with anti-MM therapy	1	136 (35.14)	131 (34.38)	267 (34.77)
		2 or 3	153 (39.53)	143 (37.53)	296 (38.54)
	Prior treatment with BTZ	Yes	127 (32.82)	117 (30.71)	244 (31.77)
		No	162 (41.86)	157 (41.21)	319 (41.54)
Safety Set	All		381 (98.4)	377 (99)	758 (98.7)

Outcomes and estimation

Primary endpoint: Progression Free Survival (PFS)

Results are summarised in the following Table31 and Figure 10.

Table 31: Progression-free survival in Study D2308 (FAS, investigator and IRC assessments) (cut-off date 10 September 2013)

	Investigator assessment		IRC assessment	
	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381
PFS events - n (%)	207 (53.5%)	260 (68.2%)	241 (62.3%)	283 (74.3%)
Disease progression	164 (42.4%)	231 (60.6%)	193 (49.9%)	244 (64.0%)
Relapse from CR	20 (5.2%)	15 (3.9%)	24 (6.2%)	26 (6.8%)
Death	23 (5.9%)	14 (3.7%)	24 (6.2%)	13 (3.4%)
Number censored - n (%)	180 (46.5%)	121 (31.8%)	146 (37.7%)	98 (25.7%)
Median PFS (months)	11.99	8.08	9.95	7.66
95% CI	10.32, 12.94	7.56, 9.23	8.31, 11.30	6.93, 8.54
Hazard ratio (95% CI)	0.63 (0.52,0.76)		0.69 (0.58,0.83)	
p-value	<0.0001		<0.0001	

Figure 10: Kaplan-Meier plot of PFS (FAS, investigator assessment, Study D2308)

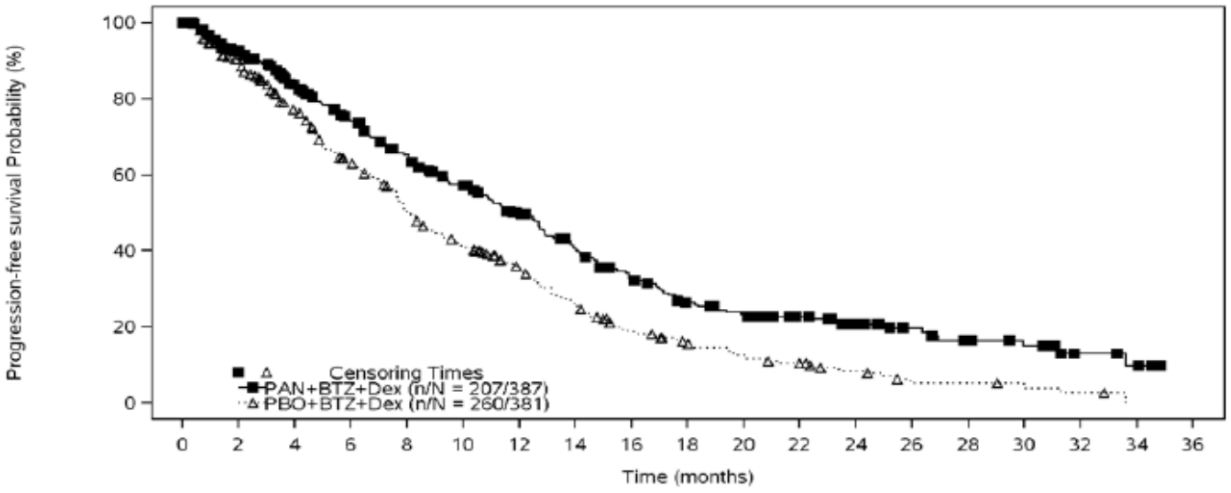
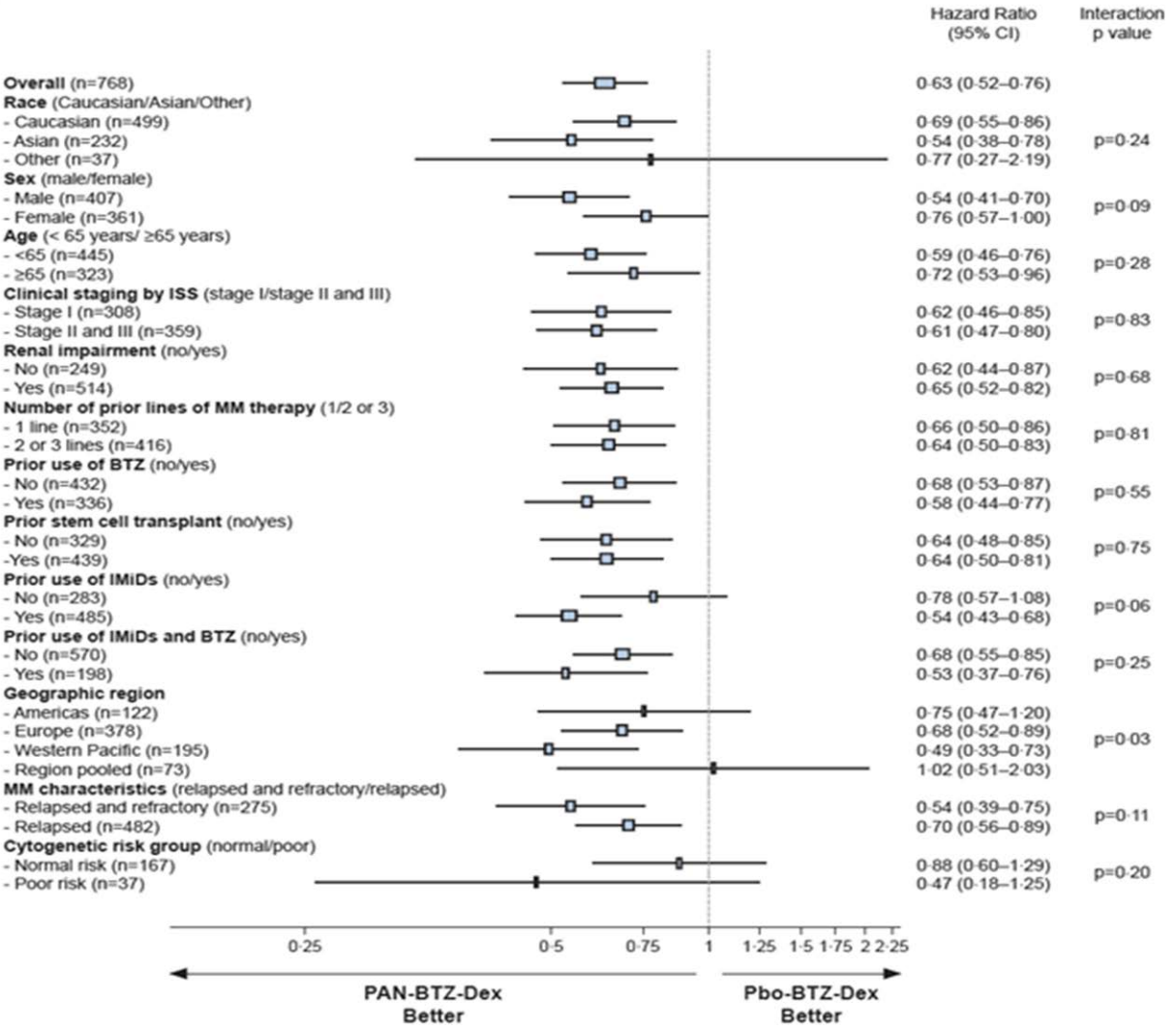


Table 32: Forest plot of PFS by subgroup, based on investigator assessment (mEBMT criteria) – Study D2308 (FAS)



Investigator-based PFS benefit of PAN + BTZ + DEX was consistent across the series of pre-planned analyses in clinically relevant subgroups for the patient population including number of prior lines of treatment: one vs two or three and prior use of bortezomib: yes vs no. However,(after database lock) the cytogenetic risk factor was removed from the multivariate cox model for PFS and OS analyses as the FISH assessment has only been done for 244 out of 768 patients who consented for the biomarker companion protocol. Thus efficacy in relation to cytogenetic risk factor cannot be evaluated.

Key secondary endpoint: Overall Survival (OS)

The first interim analysis of OS was based on 286 (68.9%) OS events: 134 (34.6%) in the panobinostat group and 152 (39.9%) in the placebo group. Median OS in the PAN arm was 33.64 months) compared to 30. 39 months in the PBO arm (HR 0.87; CI:0.69,1.10; p=0.2586) (data not shown).

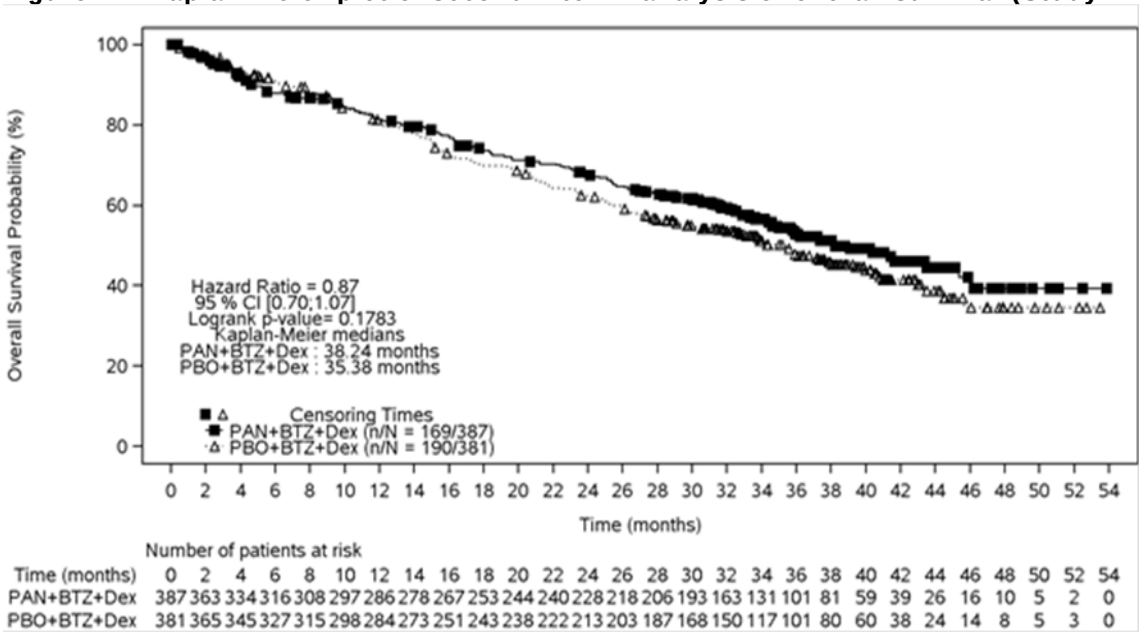
The second interim analysis of OS (cut-off date August 2014) was based on 359 (86.5%) OS events: 169 (43.7%) in the panobinostat group and 190 (49.9%) in the placebo group. Median OS was 38.24 months and 35.38 months, in the PAN+BTZ+Dex and PBO+BTZ+Dex arms, respectively (HR 0.87; 95% CI: 0.70, 1.07; p=0.18). The results are presented in Table 33 and Figure 11.

Table 33: Second interim analysis of overall survival (Study D2308, FAS, cut-off date August 2014)

	PAN+BTZ+Dex	**PBO+BTZ+Dex**	**HR (95% CI)**	**p-value**
	N=387	**N=381**		
Number of OS events – n (%)	169 (43.7)	190 (49.9)	0.87 (0.70, 1.07)	0.1783
Number censored – n (%)	218 (56.3)	191 (50.1)		
Kaplan-Meier estimates – months (95% CI)				
25th percentile	16.49 (14.55, 21.26)	15.18 (13.08, 17.48)		
Median	38.24 (34.63, 45.37)	35.38 (29.37, 39.92)		
75th percentile	NE	NE		

CI: confidence interval; HR: hazard ratio; NE: not estimable; OS: overall survival
Hazard ratio (HR) is obtained from a stratified Cox model.
2-sided p-value is obtained from a stratified log-rank test.

Figure 11: Kaplan-Meier plot of second interim analysis of overall survival (Study D2308, FAS)



Other secondary endpoints

The results for secondary and exploratory endpoints of Study D2308 are presented in Table 34.

Table 34 : Efficacy results for other secondary and exploratory endpoints (Study D2308, FAS)

	PAN+BTZ+Dex N=387	PBO+BTZ+Dex N=381	p-value [2]
Other Secondary Endpoints [1]			
ORR	235 (60.7%)	208 (54.6%)	0.0873
CR	42 (10.9%)	22 (5.8%)	
nCR	65 (16.8%)	38 (10.0%)	
PR	128 (33.1%)	148 (38.8%)	
MRR	23 (5.9%)	42 (11.0%)	
nCR/CR rate (nCR and CR)	107 (27.6%)	60 (15.7%)	
Med. TTR (months) (95% CI) [3]	1.51 (1.41, 1.64)	2.00 (1.61, 2.79)	
Med. DOR (months) (95% CI) [3]	13.14 (11.76, 14.92)	10.87 (9.23, 11.76)	
Med. TTP (months) (95% CI) [3]	12.71 (11.30, 14.06)	8.54 (7.66, 9.72)	
Exploratory Endpoints			
sCR (IMWG)	5 (1.3%)	0 (0.0%)	
VGPR (IMWG)	105 (27.1%)	78 (20.5%)	

[1] Investigator assessed responses.

[2] 2-sided p-value that was generated by Cochran-Mantel-Haenszel test.

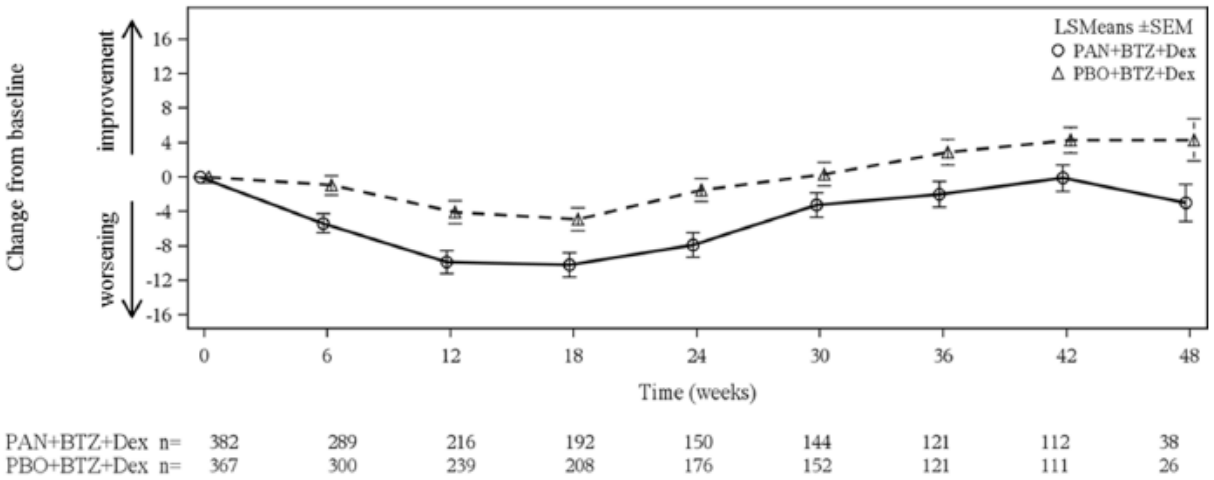
[3] Derived using Kaplan-Meier method and its 95% CI according to Brookmeyer & Crowley.

ORR, overall response rate; CR, complete response; nCR, near complete response; PR, partial response; MRR, minimal response rate; TTR, time to response; TTP, time to progression; DOR, duration of response; sCR, stringent complete response; VGPR, very good partial response; IMWG, International Myeloma Working Group.

Patient-Reported Outcomes

Global health status/QOL scores of the QLQ-C30 initially declined in both treatment arms over the study treatment period, before returning back to baseline levels after Week 18 in both the PAN+BTZ+Dex and PBO+BTZ+Dex arms, as illustrated in Figure 12.

Figure 12 : EORTC QLQ-C30 Global Health Status/ QoL Score: Change from baseline by treatment group (FAS)



Mean (SD) baseline global health status/QOL scores from the EORTC QLQ-C30 for the PAN+BTZ+Dex and PBO+BTZ+Dex arms were 60.86 (21.153) and 58.27 (23.250), respectively.

The decline in mean change from baseline global health status/QOL scores at Week 12, Week 24, and Week 48 were –9.853, –7.867, and –2.986 in the PAN+BTZ+Dex arm, and –4.044, –1.518, and 4.345 in the PBO+BTZ+Dex arm, respectively. The difference in the median time to definitive deterioration in global health status/QOL between the PAN+BTZ+Dex and the PBO+BTZ+Dex arms was 2 weeks. The median (95% CI) time to definitive deterioration was 2.33 months (1.97, 2.79) in the PAN+BTZ+Dex arm and 2.83 months (2.76, 3.02) in the PBO+BTZ+Dex arm, with a HR of 1.26 (1.05, 1.50) in favour of the PBO+BTZ+Dex arm.

Mean changes from baseline in diarrhoea scores were numerically positive and high (>10 point change) in both treatment arms; changes in diarrhoea scores were higher in the PAN+BTZ+Dex arm (data not shown).

Mean baseline disease symptoms scores from the myeloma specific module, EORTC QLQMY20,were 24.90 for the PAN+BTZ+Dex and 26.23 for the PBO+BTZ+Dex arm. Mean change from baseline disease symptoms scores indicated a trending improvement from baseline in both treatment arms but were not different between treatment arms (data not shown).

The mean baseline neurotoxicity subscales of the FACT/GOG-NTX were 36.11 and 36.05 for the PAN+BTZ+Dex and PBO+BTZ+Dex arms respectively. Mean changes from baseline in the neurotoxicity subscale initially declined in both treatment arms before recovering to some extent over time, but was not different between treatment arms (data not shown).

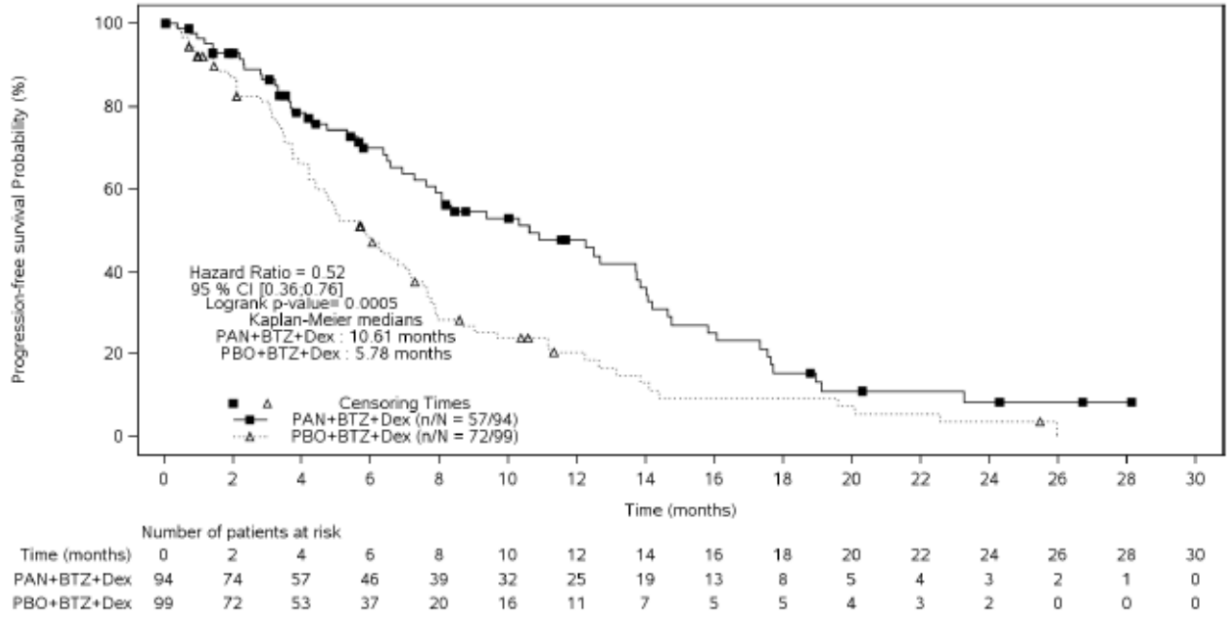
Subgroup of patients with prior BTZ and IMiD

For the subgroup of patients with prior BTZ and IMiDs the results of the primary and secondary endpoints are presented in Table 35 and Figures 13 and 14.

Table 35 : Patients with prior BTZ and IMiDs: summary of efficacy (D2308 study)

	Overall study population		Prior BTZ and IMiD	
	N=768		N=193	
	PAN+BTZ+Dex	PBO+BTZ+Dex	PAN+BTZ+Dex	PBO+BTZ+Dex
Efficacy	**N=387**	**N=381**	**N=94**	**N=99**
PFS (Investigator), median (months)	12.0	8.1	10.6	5.8
Δ median PFS (months) HR (95% CI)	3.9 0.63 (0.52,0.76)		4.8 0.52 (0.36, 0.76)	
OS, median (months)	38.2	35.4	28.0	24.7
ORR (EBMT) %	60.7	54.6	58.5	41.4
CR/nCR (EBMT) %	27.6	15.7	22.3	9.1

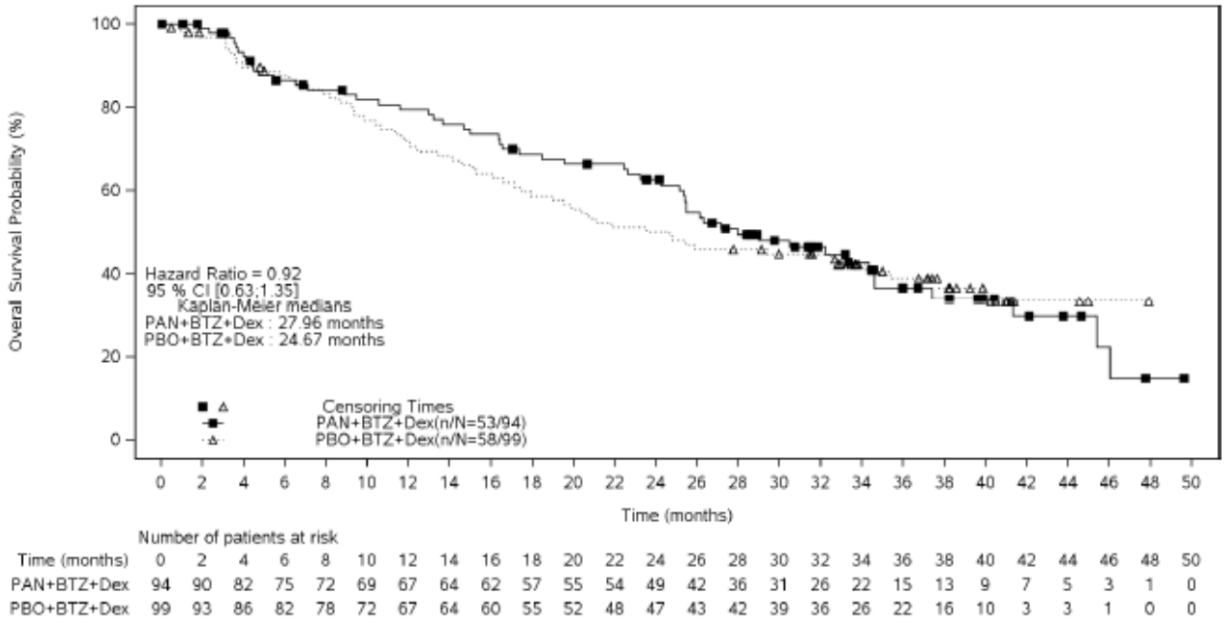
Figure 13: Kaplan-Meier plot of PFS in patients with prior BTZ and IMiDs (Study D2308, FAS)



Number of patients at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
PAN+BTZ+Dex	94	74	57	46	39	32	25	19	13	8	5	4	3	2	1	0
PBO+BTZ+Dex	99	72	53	37	20	16	11	7	5	5	4	3	2	0	0	0

Figure14: Kaplan-Meier plot of OS in patients with prior BTZ and IMiDs (Study D2308, FAS)



Number of patients at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
PAN+BTZ+Dex	94	90	82	75	72	69	67	64	62	57	55	54	49	42	36	31	26	22	15	13	9	7	5	3	1	0
PBO+BTZ+Dex	99	93	86	82	78	72	67	64	60	55	52	48	47	43	42	39	36	26	22	16	10	3	3	1	0	0

Subgroup of patients who received at least two prior regimens including bortezomib and an immunomodulatory agent

In their response to the CHMP request for further discussion on the benefit/risk assessment in patients with multiple myeloma who have received bortezomib and an immunomodulatory agent, the Applicant provided data on the subgroup of patients with prior BTZ and IMiDs and ⩾2 prior regimens. Results of the primary and secondary endpoints in this subgroup are presented in Tables 36 and 37 and Figures 15.

Table 36: Progression-free survival in patients who received at least two prior regimens including bortezomib and an immunomodulating agent

	Farydak bortezomib and dexamethasone N=73	Placebo bortezomib and dexamethasone N=74
Progression-free survival		
Median, months [95% CI]	12.5 [7.26, 14.03]	4.7 [3.71, 6.05]
Hazard ratio [95% CI][1]	0.47 (0.31, 0.72)	

[1] Hazard ratio obtained from stratified Cox model

Figure 15: Kaplan-Meier plot of progression-free survival in patients with multiple myeloma who received at least two prior regimens including bortezomib and an immunomodulatory agent

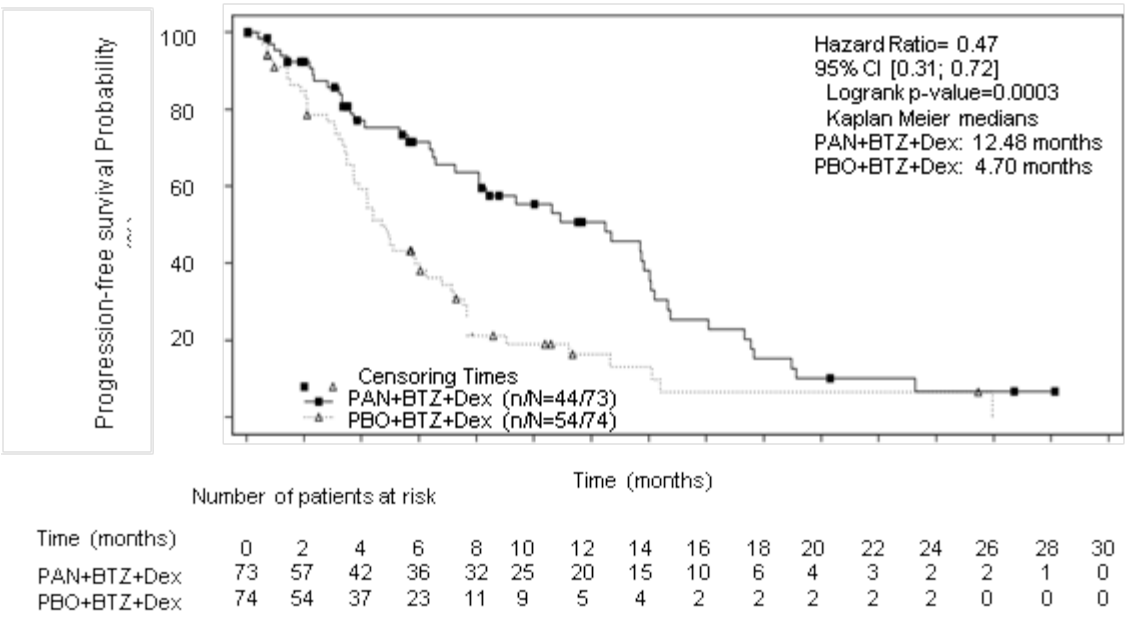


Table 37: Response rates in patients with multiple myeloma who received at least two prior regimens including bortezomib and an immunomodulatory agent

	Farydak bortezomib and dexamethasone N=73	**Placebo bortezomib and dexamethasone N=74**
Overall response	43 (59%)	29 (39%)
[95% CI]	(46.8, 70.3)	(28.0, 51.2)
Complete response	6 (8%)	0
Near complete response	10 (14%)	6 (8%)
Partial response	27 (37%)	23 (31%)

Ancillary analyses

N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of Efficacy for D2308 study

Title: A multicentre, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.			
Study identifier	CLBH589D2308, 2009-015507-52		
Design	randomised, double-blind, placebo-controlled		
	Duration of main phase:	2 years and 11 months	
Hypothesis	superiority		
Treatments groups	PAN + BTZ + DEX 387 patients randomised	Treatment schedule: 2 weeks on/1 week off. - PAN (20mg) or PBO (20 mg) TIW - BTZ 1.3 mg/m2 (iv) twice weekly - DEX oral 20 mg/day, 4 days/week. Maximum duration of the study treatment period was 48 weeks and consisted of two treatment phases. Treatment phase 1 (TP1): 24 weeks of combined treatment. Treatment phase 2 (TP2): For those with clinical benefit, further 24 weeks of combined treatment with reduced frequency of BTZ and DEX .	
	PBO + BTZ +DEX 381 patients randomised		
Endpoints and definitions	Primary endpoints	Progression Free Survival (PFS) (Inv)	Time from the date of randomization to the date of the first documented PD or relapse or death due to any cause as assessed by the investigator based on mEBMT criteria.
	Key secondary endpoint	Overall Survival (OS)	Time from date of randomization to the date of death due to any cause.
	Other secondary endpoints	Overall Response Rate (ORR)	The proportion of patients with CR, nCR or PR per investigator's assessment based on mEBMT criteria.
Database lock	10-Sept-2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analyses set (all randomised patients)		
Descriptive statistics and estimate variability	Treatment group	PAN + BTZ + DEX	PBO + BTZ + DEX
	Number of subjects	387	381
	Median PFS (months)	12.0	8.1
	95% CI	10.3, 12.9	7.6, 9.2
OS from second interim analysis cut-off date August 2014	Median OS (months)	38.2	35.4
	95% CI	34.6, 45.4	29.4, 39.9
	ORR (n (%))	235 (60.7%)	208 (54.6%)
	95% CI (%)	55.7, 65.6	49.4, 59.7
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.63

		95% CI	0.52, 0.76
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.87
		95% CI	0.70, 1.07
		P-value	0.1783
	Secondary endpoint ORR	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		Difference (%)	6.1
		P-value	0.0873

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Subgroup of in patients with prior BTZ and IMiDs		
Descriptive statistics and estimate variability OS analysis for this subgroup is for cut-off date August 2014	Treatment group	PAN + BTZ + DEX	PBO + BTZ + DEX
	Number of subjects	94	99
	Median PFS - Inv (months)	10.6	5.8
	95% CI	7.6, 13.8	4.4, 7.1
	Median OS (months)	28	24.7
	95% CI	25.1, 34.6	17.5, 35.4
	ORR (n (%))	55 (58.5%)	41 (41.44%)
	95% CI (%)	47.9, 686	31.6, 51.8
	nCR (n (%))	13 (13.8%)	7(7.1%)
	CR	8 (8.5%)	2 (2%)
	PR	34 (36.2%)	32 (32.3%)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.52
		95% CI	0.36, 0.76
		Logrank P-value	0.0005
	Secondary endpoint OS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.92
		95% CI	0.63, 1.35
		P-value	Not calculated
	Secondary endpoint ORR	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		Difference (%)	17.1
		P-value	0.019
Notes	Stratification factors: by number of prior lines of anti-myeloma therapy: 1 vs 2 or 3 and by prior use of bortezomib: yes vs no.		

Analysis description	Primary Analysis		
Analysis population and time point description	Subgroup of in patients with prior BTZ and IMiDs and ≥2 prior lines		
Descriptive statistics and estimate variability OS analysis for this subgroup is for cut-off date August 2014	Treatment group	PAN + BTZ + DEX	PBO + BTZ + DEX
	Number of subjects	73	74
	Median PFS - Inv (months)	12.5	4.7
	95% CI	Not provided	
	Median OS (months)	26.1	19.5
	95% CI	Not provided	
	ORR (n (%))	59%	39%
	95% CI (%)	Not provided	
	OR/nCR (n (%))	22%	8%
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.47
		95% CI	0.31, 0.72
		Logrank P-value	0.0003
	Secondary endpoint OS	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		HR	0.84
		95% CI	0.55, 1.27
		P-value	Not provided
	Secondary endpoint ORR	Comparison groups	PAN + BTZ + DEX vs PBO + BTZ + DEX
		Difference (%)	20%
		P-value	Not provided
Notes	Only limited descriptive statistics available		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No studies in special populations have been submitted (see discussion on clinical pharmacology and discussion on clinical safety).

Supportive studies

Phase II study DUS71 (Panorama II)

Study DUS71 was a two stage, single arm, open label multicentre phase II study of oral panobinostat (20 mg) in combination with bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) in 55 patients with relapsed and refractory multiple myeloma, who were bortezomib refractory and had received at least two prior lines of therapy. Patients had to be exposed to an IMiD (lenalidomide or thalidomide). Refractoriness to bortezomib was defined as disease progression on or within 60 days of the last bortezomib containing line of therapy. The

primary endpoint of the study was to assess overall response rate (ORR) after 8 cycles of therapy as per mEBMT criteria (see SmPC section 5.1).

Patients were heavily pre treated and had received multiple prior regimens (median: 4; range: 2-11). All 55 patients were previously treated with bortezomib and at least one IMiD (lenaolidomide: 98.2%, thalidomide: 69.1%). The majority of patients had received prior transplant (63.6%) (see SmPC section 5.1).

The median duration of exposure to study treatment was 4.6 months (range: 0.1 24.1 months). Patients achieved an ORR (≥PR (partial response)) of 34.5% and 52.7% (≥ MR (minimal response)). The median time to response was 1.4 months and the median duration of response was 6.0 months. The median OS was 17.5 months (95% CI 329, 767 days) and the median PFS was 5.4 months (95% CI 107, 204 days) (see SmPC section 5.1).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The defined study objectives fit the overall aim of the pivotal study to investigate whether the combination of PAN + BTZ + DEX would improve PFS results as compared to PBO + BTZ + DEX in patients with relapsed or relapsed and refractory multiple myeloma requiring re-treatment. Indeed, the comparator in the Phase III study D2308, i.e. placebo + BTZ + DEX, is considered appropriate for the study population. The baseline characteristics regarding the age, sex, race and ECOG performance status were well balanced between the two arms. The median age of the studied patients was 62.1 years with approximately half of the patients being male. Most of the patients were of Caucasian origin followed by Asian subjects and the utmost of the patients, i.e. 93%, had an ECOG status of 0 or 1. The median time since diagnosis was 37.1 months in the PAN + BTZ + DEX arm and 38.9 months in the PBO + BTZ + DEX arm. Furthermore, all of the included patients had a creatinine clearance between 60 and 90 mL/min based on inclusion/exclusion criteria. In addition, most patients in both treatment arms entered the study with International Staging System (ISS) Stage I or Stage II disease. The disease history was also well balanced between the two treatment arms. Regarding the MM treatment history, all but one patient in the study had received at least 1 line of antineoplastic therapy with the median number of prior lines being one for both study arms. In this respect, the percentage of patients who had received one prior line of anti-MM therapy was 50.9% in the PAN + BTZ + DEX arm and 52.0% in the PBO + BTZ + DEX arm. The percentage of patients with 2 or 3 prior lines of anti-MM therapy was 48.5% in the PAN + BTZ + DEX arm and 48.0% in the PBO + BTZ + DEX arm. Stem cell transplantation was applied in 55.6% of the patients in the experimental arm and 58.8% of the patients in the control arm. Of these, nearly all were in the autologous setting with 10 patients in total having received allogeneic stem cell transplantation. Of the patients that had undergonestem cell transplantation, 90.2% and 95.1% responded to this treatment in the experimental and control arm, respectively. Finally, irrespective of the type of last treatment, the majority of patients in both arms (88.6% in the PAN + BTZ + DEX arm, 85.8% in the PBO + BTZ + DEX arm) responded to their last prior line of therapy. At presentation, the majority of patients in both arms had relapsed disease; 63.8% in the PAN + BTZ + DEX arm and 61.7% in the PBO + BTZ + DEX arm. Primary refractory patients were excluded. Together, this study population overall represents the expected patient population as defined by the inclusion/exclusion criteria and the study arms were well balanced regarding patient and disease characteristics as well the type and number of prior treatments. In addition, this patient population studied well represents the patient population requiring at least 2nd line therapy for MM in the clinical practise.

Patients were randomized 1:1 to the PAN + BTZ + DEX or to the PBO + BTZ + DEX arm and stratified by a number of prior lines of therapy (1 vs 2 or 3) and prior use of BTZ (yes vs no) which in a more or less equal

number of patients in each study arm, i.e. 387 patients vs 381 patients, respectively, and in well-balanced treatment arms regarding the number of prior lines of therapy as well as prior BTZ treatment in both FAS and the PP set.

Treatment arms were also balanced with regard to the number of major protocol deviations. Furthermore, most classes of major protocol deviations were reported in small percentages of patients (≤ 3.4%). However, the percentage of patients with missing efficacy baseline assessment is remarkable i.e. 19.9% in the experimental arm and 22.6% in the control arm, but may be dominated by missing laboratory values. Finally, it is considered that the amendments as implemented by the Applicant were not likely to have had negative impact on the conduct of the study, the performed (statistical) analyses and/or the results.

Efficacy data and additional analyses

The results of the pivotal D2308 study showed that the median PFS (investigator based) was prolonged by 3.9 months in patients receiving PAN+BTZ+Dex treatment as compared to the PBO+BTZ+Dex control arm, with a 37% relative risk reduction in the hazard rate of progression/death (HR = 0.63, 95% CI [0.52; 0.76]; p-value < 0.0001). The PFS results for the PBO+BTZ+Dex arm (8.1 months) were consistent with prior Phase III trials using a BTZ backbone in the same patient population and represent an adequate comparator for the target population at hand, i.e. relapsed multiple myeloma. Furthermore, the data are consistent between the pre-specified subgroups analyses.

In addition, all sensitivity analyses yielded a similar HR in favour of PAN and provided consistent support for the robustness of the primary analysis results.

The final number of OS events has not been reached yet. At the time of a second OS interim analysis after 359 (86.5%) of the target 415 OS events required for the final OS analysis had been observed, the median OS was 38.24 months in the PAN+BTZ+Dex arm and 35.38 months in the PBO+BTZ+Dex arm.

During the initial evaluation, the CHMP raised a major objection about the indication needing to be further discussed, with reference to patients who have received prior bortezomib and an immunomodulatory agent, a population who formed a pre-specified subgroup in pivotal Study D2308, as having a high unmet medical need considering the current limited treatment options for this population.

Higher efficacy benefits in PFS, and ORR and CR/nCR relative to BTZ+Dex were seen in subjects with prior BTZ and IMiD treatment and the data showed that these benefits relative to BTZ+Dex are driven by the lower efficacy in the PBO+BTZ+Dex arm. The median PFS (investigator based) was prolonged by 4.8 months in patients receiving PAN+BTZ+Dex treatment as compared to the PBO+BTZ+Dex control arm, with a 48% relative risk reduction in the hazard rate of progression/death (HR: 0.52; 95% CI [0.36, 0.76], log-rank p-value = 0.0005). The absolute duration of 10.6 months median PFS as seen in subjects who have received prior BTZ and IMiD treatment is considered of clinical relevance in a population with limited treatment options.

In subjects who have received prior BTZ and IMiD treatment the overall response rate using modified EBMT criteria was 59% in the PAN+BTZ+Dex arm and 41% in the PBO+BTZ+Dex arm.

The additional analysis in patients who had received at least two prior regimens including BTZ and IMiD showed a similar pattern, but with a larger median PFS benefit of 7.8 months with PAN+BTZ+Dex vs PBO+BTZ+Dex with a 53% relative risk reduction in the hazard rate of progression/death (HR: 0.47; 95% CI [0.31, 0.72], log-rank p value = 0.0003) as compared to the subgroup with prior BTZ and IMiD.

However, the benefit in PFS has not been translated into a similar relative benefit in OS which was improved by only 3.3 months (HR: 0.92) in the PAN+BTZ+Dex arm compared to the PBO+BTZ+Dex in this prior BTZ and

IMiD subgroup. A larger median OS benefit of 6.6 months was observed in the subgroup of patients who had received at least two prior regimens including BTZ and IMiD, however, the final OS analysis is awaited. To further support the PFS benefit, the Applicant will submit the final overall survival analysis for study D2308, including a tabulated summary of deaths within 8 months of first dose. Subgroups OS analyses in patients who have received at least two prior regimens including BTZ and IMiD agent will also be provided (see conclusions on clinical efficacy).

The results from the EORTC QLQ-C30 captured a consistently negative effect by the experimental regimen compared to the control arm with mean changes from baseline in global health status/QOL exceeding the threshold defined as a minimal important change (e.g. <5 points).

Several biomarker assessments were planned for studies B2207 and D2308. Specifically, bone marrow aspirate samples were taken at baseline in patients participating in the dose expansion phase of this trial in order to perform gene expression analysis to identify potential predictive markers. The CHMP recommended the applicant to provide the results for the currently planned or upcoming biomarker studies.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 4 May 2015 to provide advice on the following list of questions:

1. Remaining uncertainty concerning the clinical benefit

The SAG is asked to discuss whether the observed benefit of the PAN+BTZ+Dex combination in terms of PFS - in the absence of a significant effect on OS - in MM patients, who had received at least one prior therapy, is sufficient to justify exposing these patients to the severe adverse event profile of the drug.

Based on the final analysis of the pivotal study D2308, PAN + BTZ + DEX was associated with a statistically significant difference in progression-free survival (PFS) (increase in median IRC-based PFS of 3.6 months compared to PBO+BTZ+DEX; HR 0.63; 95% CI: 0.52, 0.76; p<0.0001). The HR for OS (secondary endpoint as determined by the second interim analysis) was 0.87 and not statistically significant (95% CI: 0.70, 1.07; p=0.18) compared to PBO+BTZ+DEX). The proportion of patients in whom a complete or near complete response (CR/nCR) was observed was 27.6% vs 15.7%, for PAN *v*. PBO, respectively).

Concerning unfavourable effects, PAN + BTZ + DEX was associated with significant worsening in quality of life during the treatment period. In the PAN+BTZ+DEX arm vs. PBO+BZT+DEX arm there were consistently more grade 3/4 AEs (96% vs. 82%), SAEs (60% vs. 42%), AEs leading to treatment discontinuation (36% vs. 20%), and AEs leading to dose adjustment or temporarily dose interruption (89 % vs. 76 %). More patients required hospitalization due to AEs in the PAN+BTZ+Dex group (55 % *v.* 37 %). The main reported AEs were thrombocytopenia (G3-4: 67.4% *v*. 31. 3) with associated haemorrhage (33.3% *v.* 10.3% of patients received at least one platelet transfusion). Other important unfavourable effects included neutropenia (G 3: 34.5% *v*. 11.4%; G 4: 6.6% *v*. 2.4%), severe infections (G3-4: 20.5% *v*. 15.6%), and diarrhoea (G3-4: 25.5% *v*. 8. 2%).

The SAG discussed the observed benefits, risks and remaining uncertainties and disagreed on the balance of benefits and risks.

According to some experts, albeit with some uncertainty, the clinical benefit (although moderate) was considered established. The observed effect in terms of PFS was considered clinically important. Based on the OS data, it is possible to rule out a detriment in OS based on visual exploration. The lack of a statistically

significant difference in OS could actually be due to the relatively long post-PD survival. Transient deterioration of QoL during treatment was expected in view of the toxicity profile. The high CR/nCR rate was also considered as important and potentially enabling stem cell transplant (SCT). Although pomalidomide and other agents could be used in this indication, relapsed/refractory MM remains a setting with very few therapeutic options and poor prospect of cure. Panobinostat provides an additional option with a new mechanism of action that can be of benefit when all other therapeutic options have failed or when it is preferable to reserve the few available options for later lines of treatment. Adequate toxicity management is paramount and expected to improve with further experience. Furthermore, future studies will aim to improve the BTZ schedule to decrease toxicity of the combination. Given the benefit observed, the small number of alternative treatment options and the high unmet medical need, the toxicity profile (although significant) was considered acceptable. According to some of the experts and patient representatives, the availability of a new treatment, even if associated with modest benefits and significant toxicity is of value for patients. The likelihood of experiencing unfavourable side effects and the likelihood of benefit should be clearly described to allow informed treatment choice by physicians and patients, considering the available therapeutic options.

According to a different view, the clinical benefit cannot be considered established. The observed effect in terms of PFS cannot be considered clinically relevant in the absence of improved QoL, symptoms or OS. OS did not improve by addition of panobinostat. There was no evidence that treatment with panobinostat was associated with a higher access to SCT. Based on the available evidence, although there are signs of antitumor activity, it is impossible to conclude that a clinical benefit has been established. The B/R was considered negative in view of lack of OS benefit, lack of increased access to stem cell transplants and because of the severe toxicity profile including increased death rate caused by the addition of panobinostat. MM is a disease of the elderly. The significantly higher toxicity, including a higher number of treatment-related deaths associated with panobinostat, especially in elderly patients, makes it impossible to conclude that a positive benefit-risk balance has been established. There are other treatments available for relapsed/refractory MM, including pomalidomide. Availability of a new agent with a new mechanism of action cannot be considered of benefit unless clinical benefits have been established. In order to establish efficacy and that there is a clinical benefit, further data should be provided to show at least an improvement of QoL or symptoms in the post-treatment phase, or duration of OS, or improved access to SCT. In addition, concerning the risks, further data are needed to establish that toxicity can be actively managed and improved without loss of activity, and that different schedules of BTZ can improve the tolerability without adversely impacting the presumed efficacy.

2. Implications of the observed toxicity

The SAG is asked to discuss the implications of the observed toxicity of the PAN+BTZ+Dex combination on its clinical use, especially in elderly patients. Issues that should be addressed in particular are the feasibility of the proposed dose regimen and the management of the toxicity profile by dose-reductions and/or delays, transfusions, hospitalizations and bone marrow support by G-CSF.

The toxicity was considered significant especially in elderly patients. Dose-reductions were needed in a high proportion of patients and there were concerns on whether such reductions might be associated with lower antitumor activity in view of the apparent synergistic or additive effect of the combination. Further data to assess the impact of dose-reduction on antitumor activity and tolerability was considered essential to address these concerns.

According to some experts, the proposed dose regimen was feasible and the toxicity manageable and expected to improve based on clinical experience, active management of elderly patients according to current guidelines,

and less intensive doses of BTZ+Dex. According to a different view, the feasibility and tolerability of the current regimen was questionable (see answers to question No. 1).

3. Identification of a suitable population where the B/R is considered positive

The SAG is asked to discuss whether the B/R of PAN+BTZ+Dex could be deemed positive in a subset of more advanced patients within the scope of the applicant's proposed indication; e.g. for MM patients with relapsed/refractory disease who have received at least 2, 3 or more prior lines of therapy (including BTZ and immunomodulatory drugs).

Exploratory efficacy subgroup analyses (e.g., by number of prior lines of treatment) did not allow identifying a population most likely to respond.

However, the SAG identified a subpopulation in which the unmet need is higher, in view of the poor prognosis and few available treatment options. This subpopulation corresponds to MM patients with relapsed/refractory disease who have received at least 2 lines of therapy, including BTZ and immunomodulatory drugs. (The SAG was uncertain whether this indication could be further generalised, e.g., to proteasome inhibitors as data are lacking to rule out important pharmacodynamic differences between different agents.)

The SAG did not agree on whether a positive benefit-risk balance has been established in this population. According to one view, the observed benefit and toxicity were acceptable in this high unmet need situation, despite the existing uncertainty about the clinical relevance of the observed effect and the possibility to actively manage toxicity in clinical practice. According to an opposite view, even in this high unmet need situation, the lack of clearly established benefits did not outweigh the observed risks, despite the few available treatment options (see answers to question No. 1).

4. Role of panobinostat in patients resistant or refractory to bortezomib

The SAG is asked to discuss whether the activity data for panabinostat in patients with bortezomib resistant/refractory disease are sufficient to support an indication that does not exclude these patients. Patients with bortezomib resistant/refractory disease were excluded from the pivotal trial, but were enrolled in the single arm study DUS71 and data may be supported by non-clinical data.

The SAG agreed that the antitumor activity appeared to be similar between these subgroups based on indirect comparisons of results from the phase 3 and phase 2 studies. Nevertheless, the activity has to be seen in the light of the known toxicity of the product (see answer to question No. 1).

2.5.4. Conclusions on the clinical efficacy

Study D2308 has provided convincing evidence of clinical efficacy of panobinostat in terms of the primary endpoint PFS, in a subpopulation in which the unmet need is higher, in view of the poor prognosis and few available treatment options. This subpopulation corresponds to MM patients with relapsed and/or refractory disease who have received at least 2 lines of therapy, including BTZ and immunomodulatory drugs. The addition of panobinostat to bortezomib and dexamethasone combination resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS compared to the placebo + bortezomib + dexamethasone combination in the above mentioned subgroup (see Discussion on the benefit-risk balance).

The CHMP considers the following measures necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): The Applicant shall submit the final survival analysis for study D2308, including a tabulated summary of deaths within 8 months of first dose. Subgroups OS analyses in the patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent shall also be provided. This post authorisation measure is included in the Annex II.

2.6. Clinical safety

The main safety data has been obtained from the randomised, placebo controlled pivotal Study D2308 in relapsed or relapsed-and-refractory MM patients in which PAN + BTZ + DEX (n=381) was compared with PBO + BTZ + DEX (n=377). Additional safety data concerning the treatment of MM patients with PAN + BTZ + DEX became available from the expansion phase of the single arm dose escalation Phase Ib Study B2207 (n=15) and from the single arm Phase II Study DUS71 (n=55) in BTZ refractory patients.

The safety data of panobinostat have been assessed from a total of 451 patients with multiple myeloma treated with panobinostat in combination with bortezomib and dexamethasone and 38 patients with multiple myeloma treated with panobinostat as a single agent (see SmPC section 4.8).

In addition, data from 5 studies including a total of 240 patients with other haematological malignancies and solid tumours (Table 39) were included to provide additional information for single agent panobinostat 20 mg administered once daily, three times a week (tiw), every week or every other week.

Table 39: Summary of studies included in the safety assessment

Safety pool	Studies included in the safety pool	N of patients receiving 20 mg panobinostat
MM combination studies		**Total pool: N=451**
Patients from studies with same panobinostat dose, administration, combination and treatment schedule:	[Study D2308]	n=381
	[Study DUS71]	n=55
20 mg panobinostat (2 weeks on/1 week off) + 1.3 mg/m^2 BTZ + 20 mg Dex	[Study B2207] expansion phase	n=15
Single agent studies		**Total pool: N=278**
Patients from studies with single agent 20 mg panobinostat administered orally with different schedules	[Study B2203]	n=38 (MM)
	[Study B2202]	n=29 (CML)
	[Study B2211]	n=27 (CML)
	[Study B2201]	n=139 (CTCL, mycosis fungoides or Sézary syndrome)
	[Study B2101]	n=36 (21 adv. solid tumors, 10 CTCL, 1 lymphoma, 4 melanoma)
	[Study B2102]	n=9 (6 AML, 1 ALL, 1 MM, 1 MDS)

MM, multiple myeloma; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphoma; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome.

Patient exposure

Study treatment exposure in patients enrolled in the pivotal Study D2308 and the supportive studies Study DUS71 and Study B2207 is summarized in Table 40.

Table 40: Duration of exposure to study treatment in patients with multiple myeloma (MM combination studies Safety set)

	Study B2207 (expansion cohort)	Study DUS71	Study D2308		Pooled data
Study start	18 Oct 2007	22 Jun 2010	21 Dec 2009		
Data cut-off	10 Aug 2011	04 Dec 2012	10 Sep 2013		
	PAN+BTZ+Dex N=15	**PAN+BTZ+Dex** N=55	**PAN+BTZ+Dex** N=381	**PBO+BTZ+Dex** N=377	**PAN+BTZ+Dex** N=451
Exposure (months)	N (%)	N (%)	N (%)	N (%)	N (%)
<1	0 (0.0)	8 (14.5)	37 (9.7)	30 (8.0)	45 (10.0)
>=1 and <3	2 (13.3)	15 (27.3)	84 (22.0)	69 (18.3)	101 (22.4)
>=3 and <6	8 (53.3)	12 (21.8)	90 (23.6)	87 (23.1)	110 (24.4)
>=6 and <9	2 (13.3)	7 (12.7)	45 (11.8)	62 (16.4)	54 (12.0)
>=9 and <12	3 (20.0)	9 (16.4)	108 (28.3)	122 (32.4)	120 (26.6)
>=12	0 (0.0)	4 (7.3)	17 (4.5)	7 (1.9)	21 (4.7)
Duration of exposure (days)					
Mean	178.3	168.8	183.5	195.0	181.5
SD	92.30	146.07	125.75	118.33	127.29
Median	159.0 (5.2 months)	139.0 (4.6 months)	152.0 (5.0 months)	187.0 (6.1 months)	152.0 (5.0 months)
Minimum	45	2	3	3	2
Maximum	353	735	411	443	735

A patient is counted only once in each category. n is the number of patients. Duration of exposure (days) = [(Last dosing date of any study treatment component – date of first administration of any study treatment component) + 1].

In Study D2308 for panobinostat the median overall relative dose intensity (RDI: overall actual dose intensity / overall planned dose intensity x100) was 80.7% for panobinostat, it decreased to 75.0% at cycle 4 and remained stable through the remainder of the trial. For bortezomib the median overall RDI in Study D2308 was 75.7%.

The total cumulative exposure in Study DUS71 was 305 months and in Study D2308 it was 2297 months. The exposure adjusted rate of any AE in Studies DUS71 and D2308, was respectively 17.7 versus 16.5 per 100 person treatment months and the exposure adjusted rates of grade 3/4 AEs was respectively 16.1 versus 15.8 per 100 person treatment months. In study D2308, 50.9% of patients had at least one dose change compared to 63.6% in Study Dus71 and this confounds the evaluation of the exposure adjusted rate of AEs as it was apparently based on any study treatment component.

Adverse events

An overview of adverse events is presented in Table 41.

Table 41: Summary of patients with at least one adverse event in any category (D2308 Safety Set)

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

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
Categories are not mutually exclusive.
[1] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized
[2] Clinically notable adverse events are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.

The AEs suspected to be related to study treatment by severity (with an incidence of 10% or greater in either group) in study D2308 are presented in Table 42.

Table 42: AEs suspected to be related to study treatment by primary SOC and PT (with an incidence of 10% or greater in either group) (D2308 Safety Set)

	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
Study treatment-related AEs by SOC and PT	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
-Any primary system organ class				
-Total	345 (90.6)	293(76.9)	284 (75.3)	193(51.2)
Blood and lymphatic system disorders				
-Total	242 (63.5)	201 (52.8)	139 (36.9)	97 (25.7)
Thrombocytopenia	193 (50.7)	166 (43.6)	108 (28.6)	67 (17.8)
Anaemia	97 (25.5)	30 (7.9)	60 (15.9)	26 (6.9)
Neutropenia	83 (21.8)	63 (16.5)	27 (7.2)	18 (4.8)
Leukopenia	40 (10.5)	21 (5.5)	21 (5.6)	8 (2.1)
Lymphopenia	38 (10.0)	31 (8.1)	21 (5.6)	13 (3.4)
Gastrointestinal disorders				
-Total	262 (68.8)	99 (26.0)	170 (45.1)	35 (9.3)
Diarrhoea	194 (50.9)	72 (18.9)	95 (25.2)	23 (6.1)
Nausea	89 (23.4)	17 (4.5)	46 (12.2)	2 (0.5)
Vomiting	62 (16.3)	21 (5.5)	23 (6.1)	5 (1.3)
Constipation	46 (12.1)	3 (0.8)	52 (13.8)	3 (0.8)
General disorders and administration site conditions				
-Total	187 (49.1)	78 (20.5)	125 (33.2)	42 (11.1)
Fatigue	118 (31.0)	56 (14.7)	82 (21.8)	29 (7.7)
Asthenia	50 (13.1)	21 (5.5)	24 (6.4)	4 (1.1)
Metabolism and nutrition disorders				
-Total	118 (31.0)	61 (16.0)	64 (17.0)	26 (6.9)
Decreased appetite	60 (15.7)	10 (2.6)	26 (6.9)	2 (0.5)
Hypokalaemia	41 (10.8)	30 (7.9)	11 (2.9)	4 (1.1)
Nervous system disorders				
-Total	148 (38.8)	46 (12.1)	144 (38.2)	25 (6.6)
Neuropathy peripheral	53 (13.9)	12 (3.1)	61 (16.2)	11 (2.9)

Adverse Drug Reactions (ADRs)

Adverse drug reactions from the phase III study (Panorama 1) are shown in Table 43. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 43: Adverse drug reactions observed in multiple myeloma patients in the phase III study

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection, pneumonia
	Common	Septic shock, urinary tract infection, viral infection, oral herpes, *Clostridium difficile* colitis, otitis media, cellulitis, sepsis, gastroenteritis, lower respiratory tract infection, candidiasis
	Uncommon	Pneumonia fungal, hepatitis B, aspergillosis
Blood and lymphatic system disorders [a]	Very common	Pancytopenia, thrombocytopenia, anaemia, leukopenia, neutropenia, lymphopenia
Endocrine disorders	Common	Hypothyroidism
Metabolism and nutrition disorders	Very common	Decreased appetite, hypophosphataemia [a], hyponatraemia [a], hypokalaemia [a]
	Common	Hyperglycaemia, dehydration, hypoalbuminaemia, fluid retention, hyperuricaemia, hypocalcaemia, hypomagnesaemia
Psychiatric disorders	Very common	Insomnia
Nervous system disorders	Very common	Dizziness, headache
	Common	Haemorrhage intracranial, syncope, tremor, dysgeusia
Eye disorders	Common	Conjunctival haemorrhage
Cardiac disorders	Common	Bradycardia, atrial fibrillation, sinus tachycardia, tachycardia, palpitation
	Uncommon	Myocardial infarction
Vascular disorders	Very common	Hypotension
	Common	Hypertension, haematoma, orthostatic hypotension
	Uncommon	Shock haemorrhagic
Respiratory, thoracic and mediastinal disorders	Very common	Cough, dyspnoea
	Common	Respiratory failure, rales, wheezing, epistaxis
	Uncommon	Pulmonary haemorrhage, haemoptysis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, vomiting, abdominal pain, dyspepsia
	Common	Gastrointestinal haemorrhage, haematochezia, gastritis, cheilitis, abdominal distension, dry mouth, flatulence
	Uncommon	Colitis, haematemesis, gastrointestinal pain
Hepatobiliary disorders	Common	Hepatic function abnormal, hyperbilirubinaemia [a]
Skin and subcutaneous disorders	Common	Skin lesions, rash, erythema
	Uncommon	Petechiae
Musculoskeletal and connective tissue disorders	Common	Joint swelling
Renal and urinary disorders	Common	Renal failure, haematuria, urinary incontinence
General disorders and administration site conditions	Very common	Fatigue, oedema peripheral, pyrexia, asthenia
	Common	Chills, malaise

Investigations	Very common	Weight decreased
	Common	Blood urea increased, glomerular filtration rate decreased, blood alkaline phosphatase increased, electrocardiogram QT prolonged, blood creatinine increased [a], SGPT alanine transaminase (ALT) increased [a], SGOT aspartate transaminase (AST) increased [a]

[a] Frequency is based on laboratory values

Clinically notable adverse events

Clinically notable AEs (CNAE) are selected categories of risks consisting of pooled AEs that are similar in nature and for which there is a specific clinical interest in connection with the mechanism of action of panobinostat (DAC inhibitors), non-clinical studies and signals observed during the conduct of the clinical development program. Based on these criteria, 17 groups of CNAEs were identified and analysed.

These 17 groups of CNAEs are: QT prolongation, myelosuppression, haemorrhage, severe infections, hepatic dysfunction, renal dysfunction, diarrhoea, cardiac failure, ischaemic heart disease, tachyarrythmia, venous thromboembolism, ischaemic colitis, interstitial lung disease, hypothyroidism, pericardial effusion, acute pancreatitis and hepatitis B reactivation. The most frequently observed CNAEs were diarrhoea, neutropenia associated with infections and thrombocytopenia associated with haemorrhage.

Thrombocytopenia

In Study D2308, thrombocytopenia was a common safety finding in both treatment arms with a higher incidence of the adverse event thrombocytopenia reported in the PAN + BTZ + DEX arm compared to the PBO + BTZ + DEX arm (64.6% vs 40.8%). Most of these events were of Grade 3/4 severity (57.0% vs 24.9%). The AE thrombocytopenia was present in 65.0% of the patients of the pooled PAN + BTZ + DEX data set and for 58.1% it was a Grade 3/4 event.

Based on laboratory data on platelet count, the number of patients in Study D2308 with thrombocytopenia was much higher. In the PAN + BTZ + DEX arm vs the PBO + BTZ + DEX arm, any grade thrombocytopenia was reported in 97.6% vs 88.1% of patients, Grade 3 thrombocytopenia was reported for 32.5% vs 19.6% and Grade 4 for 34.6% vs 12.2%.

The median time to recovery to Grade 0, 1, or 2 from first reported Grade 3 or 4 thrombocytopenia was the same (12 days or 0.39 months) for the two treatment groups. Following an initial decrease in median platelet counts in the first two weeks of treatment, a return to baseline was observed by Day 1 of the subsequent cycle in both treatment arms.

Haemorrhage

Haemorrhages were observed in both treatment arms in Study D2308. The rate of haemorrhages of any grade was 20.7% for patients in the PAN + BTZ + DEX arm and 11.7% for patients in the PBO + BTZ + DEX arm. Grade 3/4 haemorrhages were 4.2% vs 2.4% respectively.

In study D2308, reported haemorrhage events (≥ 1%), (PAN + BTZ + DEX arm vs PBO + BTZ + DEX arm) included epistaxis (4.7% vs 4.0%), haematoma (2.6% vs 1.1%), contusion (2.4% vs 2.1%), conjunctival haemorrhage (2.1% vs 0.5%), GI haemorrhage (1.3% vs 0.8%), gingival bleeding (1.0% vs 1.1%), haematochezia (1.0% vs 0.5%), and haematuria (1.0% vs 0.0%). Grade 3/4 severity haemorrhage reported in 2 or more patients included GI haemorrhage (0.8% vs 0.8%), gastric haemorrhage (0.5% vs 0.0%), hematemesis (0.5% vs 0.0%), cerebral haemorrhage (0.0% vs 0.5%) and contusion (0.0% vs 0.5%). Five

patients in the PAN + BTZ + DEX arm died of events associated with haemorrhage (2 gastrointestinal, 2 pulmonary, and 1 cerebral haemorrhage).

In the combination pooled data set, 95 patients (21.1%) experienced haemorrhagic events with only a low number (4.0%) of patients experiencing events of Grade 3/4 severity.

Severe infections

In Study D2308 the incidence of severe infections in the PAN + BTZ + DEX-treated patients was 20.5 % vs 21.5 % in the PBO + BTZ + DEX treated patients. Incidence of Grade 3/4 events was 20.5% vs 15.6%. Severe infections were reported in 121 patients (26.8%) in the combination pooled data set and 20.8% were of Grade 3/4 severity.

Pneumonia and sepsis

In study D2308, adverse events falling within the grouping of pneumonia were reported more frequently in the PAN + BTZ+ DEX arm than in the PBO + BTZ + DEX arm (23.9% vs 18.6%) with Grade 3/4 reported in 15.7 vs 12.7 respectively. The single AE of “pneumonia” was also were more frequently reported in the PAN + BTZ + DEX arm than in the PBO + BTZ + DEX arm (17.1% vs 12.7% with Grade 3/4 frequency 12.6% vs 10.4%.)

In Study D2308, AEs in the grouping sepsis were reported for 6.6% of patients in the PAN + BTZ + DEX arm and in 4.0% of patients in the PBO + BTZ + DEX arm. In the combination pooled data set AEs in the grouping sepsis were reported for 7.3 % of patients.

Neutropenia

In Study D2308, neutropenia (based on laboratory data) was reported in 75.0% of patients treated with PAN + BTZ + DEX and in 35.5% of those treated with PBO + BTZ + DEX (Grade 3/4 neutropenia was also more frequently reported in the PAN + BTZ + DEX arm than in the PBO + BTZ + DEX arm (34.5% of patients vs 11.4%) as was Grade 4 neutropenia (6.6% vs 2.4%). Febrile neutropenia as a Grade 3/4 adverse event was reported in 1.0% of the patients in the PAN + BTZ + DEX arm, 0.5% in the PBO + BTZ + DEX arm, and in 1.3% in the pooled PAN + BTZ + DEX data set. Furthermore, 13.1% of patients in the PAN + BTZ + DEX arm received granulocyte colony stimulating factors vs 4.2% in the PBO + BTZ + DEX arm.

Diarrhoea

In the Phase III Study D2308, diarrhoea was reported in 68.2% of patients treated with PAN + BTZ + DEX (Grade 3/4; 25.5%), as compared with 41.6% (Grade 3/4; 8.0%) in patients treated with PBO + BTZ+ DEX. Among the patients reporting diarrhoea of Grade 3 or 4 in the PAN + BTZ + DEX arm, the vast majority (24.1%) had Grade 3 events and 1.3% of patients had diarrhoea of Grade 4.

Cardiac related events

Cardiac events (most frequently atrial fibrillation, tachycardia, palpitation and sinus tachycardia) were reported in 17.6% of panobinostat + bortezomib + dexamethasone-treated patients versus 9.8% of placebo + bortezomib + dexamethasone-treated patients and syncope events were reported in 6.0% versus 2.4% respectively (see SmPC section 4.8).

In Study D2308, ischemic heart disease was reported in 14 patients (3.7%) in the PAN + BTZ + DEX arm and in 5 patients (1.3%) in the PBO + BTZ + DEX arm. For 8 patients (2.1%) in the PAN + BTZ + DEX arm and for 1 patient (0.3%) in the PBO + BTZ + DEX arm this was a Grade 3/4 event. The most frequently occurring AE in the PAN + BTZ +DEX arm was angina pectoris (6 patients, 1.6%).

In PAN + BTZ + DEX-treated patients compared to PBO + BTZ + DEX-treated patients there is a general trend towards a higher frequency of increased pulse rate (4.6% vs 3.0%) and a higher frequency of lower blood pressure (systolic pressure 5.7% vs 4.3% and diastolic pressure 2.2% vs 0.2%).

The frequency of reporting of the adverse event of sinus tachycardia was 2.4% in the PAN + BTZ + DEX arm vs 0.3%) in the PBO + BTZ + DEX arm.

No episodes of QTcF prolongation >500 msec were reported with the dose of 20 mg panobinostatin the phase III clinical study, in combination with bortezomib and dexamethasone. A >60 ms change from baseline in QTcF interval was seen in 3 patients (0.8%) and four patients (1.1%), respectively. An absolute QTcF interval of >450 ms and ≤ 480 ms was observed in 40 patients (10.8%) in the PAN + BTZ + DEX arm and 26 patients (7.1%) in the PBO + BTZ + DEX arm. A change from baseline of >30 ms and ≤60 msec in QTcF interval was seen in 55 patients (14.5%) and 41 patients (10.9%), respectively. In Study DUS71, there were two patients (3.7%) with an absolute QTcF interval of >450 ms and ≤ 480 and three patients (5.5%) with an increase from baseline in QTcF interval >30 ms. In Study B2207, none of the patients experienced a notable QTcF value.

Pooled clinical data from over 500 patients treated with panobinostat alone in multiple indications and at different dose levels have shown that the incidence of CTC grade 3 QTc prolongation (QTcF >500 msec) was approximately 1% overall and 5% or more at a dose of 60 mg or higher; no episodes of torsades de pointes were observed.

Concomitant medications with known risks of QT prolongation (e.g. azithromycin, clarithromycin, and moxifloxacin) were received by 35.7% in the PAN + BTZ + DEX arm and 27.9% in the PBO + BTZ + DEX arm). For both treatment groups in the 3 studies, the vast majority (>90%) of the patients who took such medications did not experience QTcF prolongation >60 ms from baseline or QTcF >480 ms. In addition, among those few patients who did experience such low grade QTcF interval prolongation, no apparent difference in frequency was observed between those who took concomitant medications with potential impact on QTc intervals and those who did not.

In study D2308 the percentage of patients with newly occurring qualitative ECG abnormalities was 63.5% in the PAN + BTZ + DEX arm vs 42.2% in the PBO + BTZ + DEX arm.

Sinus tachycardia was also observed more frequently in the PAN + BTZ + DEX arm (15.5% in PAN + BTZ + DEX vs 6.8% in PBO +BTZ + DEX).

T-wave changes were reported in 39.6% of patients in the PAN + BTZ + DEX arm and in 18.3% of those in the PBO + BTZ + DEX arm, but no cases were reported as SAEs or as causes for treatment discontinuation. ST-T segment changes, primarily involving ST-T depression were reported in 21.7% of patients in the PAN + BTZ + DEX arm and in 3.6% in the PBO + BTZ + DEX arm.

Regardless of events chronology, syncope was reported in 9% of patients with ST-T depression and 7.2% of patients with T wave change and 4.9% of patients with neither of these ECG abnormalities. Likewise ischaemic heart disease (including myocardial infarction and ischaemia) were reported in 4.5% of patients with ST-T depression and 4.5% of patients with T wave change and 2.7% of patients with neither of these ECG abnormalities.

Renal dysfunction

In Study D2308, events related to renal dysfunction were reported in 72 patients (18.9%) of the PAN + BTZ + DEX arm and 41 patients (10.9%) of the PBO + BTZ+ DEX arm. A low number of 5.0% and 4.5% of these patients, respectively experienced events of Grade 3/4 severity. The most frequently occurring AEs (≥ 2%) in the PAN + BTZ + DEX arm vs PBO + BTZ + DEX were blood creatinine increased (10.0% vs 5.8%), blood urea

increased (5.2% vs 2.7%), renal failure acute (3.1% vs 3.2%) and renal failure (2.6% vs 1.9%). None of the patients in the PAN + BTZ + DEX arm had renal dysfunction AEs that led to study treatment discontinuation. The pattern for the combination pooled dataset is nearly the same as observed in Study D2308.

Hepatic dysfunction

Events related to hepatic dysfunction were reported in 63 of the PAN + BTZ + DEX-treated patients (16.5%) and 46 of the PBO + BTZ + DEX-treated patients (12.2%) in Study D2308 with 4.2% and 3.4%, respectively with Grade 3/4 severity. The most frequent occurring AEs (≥ 2%) in the PAN + BTZ + DEX arm were ALT increased (6.0%), hypoalbuminaemia (5.5%), aspartate AST increased (4.5%), blood alkaline phosphatase increased (2.9%), gamma-glutamyltransferase increased (2.4%) and hyperbilirubinaemia (2.4%). In the pooled dataset, the numbers were almost identical to those of the PAN + BTZ + DEX-treated patients in Study D2308.

Second Primary Malignancy

A total of five (1.3%) patients in the experimental arm vs. 11 (2.9%) for the control arm reported AEs in the SOC of neoplasms. One case each of basal cell carcinoma, endometrial cancer, and thyroid neoplasm (benign goiter, grade 1/2) were reported in the experimental arm with the remaining two involving cancer pain and tumour pain. Among the 11 patients in the control arm, eight cases reported different types of neoplasms including two cases of small cell lung cancer and one case each of lipoma, melanocytic naevus, prostate neoplasm, skin neoplasm, prostate cancer, and rectal cancer.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

In the Phase III Study D2308, SAEs regardless of study drug relationship were reported more frequently in patients treated in the PAN + BTZ + DEX arm compared with those in the PBO + BTZ + DEX arm (59.8% vs 41.6%) (Table 44).

Table 44: SAEs by primary SOC and PT irrespective of causality (with at least 5.0% incidence by PT in either group) (D2308 Safety Set)

	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
SAEs by SOC and PT	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
-Total	228 (59.8)	214 (56.2)	157 (41.6)	141 (37.4)
Blood and lymphatic system disorders	42 (11.0)	38 (10.0)	15 (4.0)	13 (3.4)
Thrombocytopenia	28 (7.3)	26 (6.8)	8 (2.1)	8 (2.1)
Gastrointestinal disorders				
-Total	71(18.6)	57(15.0)	23(6.1)	21(5.6)
Diarrhoea	43 (11.3)	35 (9.2)	9 (2.4)	8 (2.1)
Infections and infestations				
-Total	120 (31.5)	105 (27.6)	75 (19.9)	68 (18.0)
Pneumonia	56 (14.7)	47 (12.3)	40 (10.6)	36 (9.5)

In the pooled data set, SAEs regardless of study relationship were frequently reported (≥ 10%) in the SOCs of infections and infestations (30.6%), gastrointestinal disorders (17.7%), blood and lymphatic disorders (14.4%) and general disorders and administration site conditions (11.8%). Similarly, thrombocytopenia (10.6%), diarrhoea (10.2%), and pneumonia (14.2%) were more commonly reported.

In the Phase III Study D2308, SAEs suspected to be study drug related were reported more frequently in patients treated in the PAN + BTZ + DEX arm as compared with those in the PBO + BTZ + DEX arm (34.9% vs

15.1%). The more common drug-related SAEs were thrombocytopenia (5.8% vs 1.6%), diarrhoea (7.9% vs 1.6%) and pneumonia (8.1% vs 3.4%). In the pooled data set, SAEs suspected to be study drug related were frequently reported (≥ 10%) in the SOCs of Infections and infestations (12.4%), gastrointestinal disorders (11.5%) and blood and lymphatic disorders (11.1%). The more common drug-related SAEs were thrombocytopenia (8.9%), diarrhoea (7.3%) and pneumonia (7.5%).

Deaths

On-treatment deaths were defined as deaths occurring on treatment and up to 28 days after discontinuation of study treatment.

In the pivotal Study D2308, a total of 48 deaths occurred on treatment (death that occurred within 28 days of the last dose of study drug); 30 (7.9%) in the PAN + BTZ + DEX arm vs 18 (4.8%) in the PBO + BTZ + DEX arm. The main causes of on-treatment deaths by SOC were infections and infestations (1.8% vs 1.3% in PBO + BTZ + DEX), respiratory, thoracic and mediastinal disorders (1.6% vs 0.5% in PBO + BTZ + DEX), and cardiac disorders (1.0% vs 0.8% in PBO + BTZ + DEX) and Study indication (1.0% vs 1.6% in PBO + BTZ + DEX) (Table 45).

Table 45: On-treatment deaths in Study D2308

Primary System Organ Class **Principal cause of death**	**PAN+BTZ+Dex** **N=381 n (%)**	**PBO+BTZ+Dex** **N=377 n (%)**
Total number of deaths	**30 (7.9)**	**18 (4.8)**
Due to Study indication	4 (1.0)	6 (1.6)
Due to other causes	26 (6.8)	12 (3.2)
Cardiac disorders	**4 (1.0)**	**3 (0.8)**
Myocardial infarction	2 (0.5)	0
Cardiac arrest	1 (0.3)	1 (0.3)
Myocardial ischaemia	1 (0.3)	0
Cardio-respiratory arrest	0	1 (0.3)
Cardiopulmonary failure	0	1 (0.3)
Gastrointestinal disorders	**2 (0.5)**	**0**
Gastrointestinal haemorrhage	1 (0.3)	0
Intestinal ischaemia	1 (0.3)	0
General disorders and administration site conditions	**1 (0.3)**	**0**
Death	1 (0.3)	0
Infections and infestations	**7 (1.8)**	**5 (1.3)**
Septic shock	3 (0.8)	0
Bronchopneumonia	1 (0.3)	0
Lung infection	1 (0.3)	0
Pneumonia	1 (0.3)	3 (0.8)
Pulmonary tuberculosis	1 (0.3)	0
Necrotising fasciitis	0	1 (0.3)
Neutropenic sepsis	0	1 (0.3)
Injury, poisoning and procedural complications	**1 (0.3)**	**0**
Toxicity to various agents	1 (0.3)	0
Nervous system disorders	**2 (0.5)**	**2 (0.5)**
Cerebral haemorrhage	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Brain injury	0	1 (0.3)
Haemorrhage intracranial	0	1 (0.3)

Renal and urinary disorders	**2 (0.5)**	**0**
Renal failure acute	2 (0.5)	0
Respiratory, thoracic and mediastinal disorders	**6 (1.6)**	**2 (0.5)**
Respiratory failure	2 (0.5)	0
Acute respiratory failure	1 (0.3)	1 (0.3)
Lung disorder	1 (0.3)	0
Pulmonary haemorrhage	1 (0.3)	0
Pulmonary oedema	1 (0.3)	0
Pulmonary embolism	0	1 (0.3)
Vascular disorders	**1 (0.3)**	**0**
Shock haemorrhagic	1 (0.3)	0

In the pooled data set, 36 deaths (8.0%) occurred on treatment; 7 deaths (1.6%) due to study indication and 29 (6.4%) due to other causes. About the same percentage was seen in the individual studies for the PAN + BTZ + DEX-treated patients. In Study B2207, two deaths (13.3%) were on-treatment and in Study DUS71 there were four on-treatment deaths (7.3%). The most notable causes of death in the PAN + BTZ + DEX-treated patients were infection and haemorrhage.

Laboratory findings

The most common haematological and biochemical abnormalities in the pivotal D2308 study are summarised in the following Tables.

Table 46: Patients with newly occurring or worsening haematologic abnormalities (D2308 Safety Set)

Hematology laboratory parameter	Worsening from Basline to	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
		Total	n (%)	Total	n (%)
Haemoglobin	Grade 3	372	56 (15.1)	361	63 (17.5)
	Grade 4	379	11 (2.9)	377	9 (2.4)
	Any Grade	379	235 (62.0)	377	197 (52.3)
	Grade 3/4	379	67 (17.7)	377	72 (19.1)
Platelet count (direct)	Grade 3	380	124 (32.6)	375	73 (19.5)
	Grade 4	380	132 (34.7)	376	45 (12.0)
	Any Grade	380	371 (97.6)	376	314 (83.5)

	Grade 3/4	380	256 (67.4)	376	118 (31.4)
WBC (total)	Grade 3	379	78 (20.6)	375	26 (6.9)
	Grade 4	380	10 (2.6)	377	5 (1.3)
	Any Grade	380	308 (81.1)	377	180 (47.7)
	Grade 3/4	380	88 (23.2)	377	31 (8.2)
Absolute neutrophils (Seg. + Bands)	Grade 3	379	106 (28.0)	375	34 (9.1)
	Grade 4	380	25 (6.6)	377	9 (2.4)
	Any Grade	380	285 (75.0)	377	134 (35.5)
	Grade 3/4	380	131 (34.5)	377	43 (11.4)
Absolute lymphocytes	Grade 3	374	157 (42.0)	368	123 (33.4)
	Grade 4	380	45 (11.8)	377	27 (7.2)
	Any Grade	380	314 (82.6)	377	278 (73.7)
	Grade 3/4	380	202 (53.2)	377	150 (39.8)

Total = number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the lab parameter.

n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.

Table 47: Patients with newly occurring or worsening biochemistry abnormalities (D2308 Safety Set)

	PAN+BTZ+Dex N=381			PBO+BTZ+Dex N=377		
Chemistry laboratory parameter	Total	Any grade n (%)	Grade 3/4 n (%)	Total	Any grade n (%)	Grade 3/4 n (%)
Decreased calcium	363	257 (70.8)	20 (5.5)	362	206 (56.9)	8 (2.2)
Decreased Phosphate	374	240 (64.2)	76 (20.3)	370	171 (46.2)	45 (12.2)
Increased Albumin	378	241 (63.8)	7 (1.9)	375	145 (38.7)	7 (1.9)
Increased glucose	377	226 (59.9)	22 (5.8)	374	205 (54.8)	29 (7.8)
Decreased potassium	379	200 (52.8)	69 (18.2)	376	137 (36.4)	26 (6.9)
Decreased sodium	379	185 (48.8)	51 (13.5)	376	134 (35.6)	26 (6.9)
Increased Creatinine	379	157 (41.4)	4 (1.1)	376	85 (22.6)	7 (1.9)
Increased SGOT (AST)	379	118 (31.1)	6 (1.6)	376	106 (28.2)	5 (1.3)
Increased SGPT (ALT)	379	117 (30.9)	7 (1.8)	375	144 (38.4)	5 (1.3)
Increased Alkaline phosphatase (serum)	379	109 (28.8)	7 (1.8)	375	74 (19.7)	1 (0.3)
Increased magnesium	369	103 (27.9)	19 (5.1)	369	53 (14.4)	5 (1.4)
Decreased magnesium	369	92 (24.9)	0	369	79 (21.4)	2 (0.5)
Bilirubin (total)	379	79 (20.8)	3 (0.8)	376	48 (12.8)	1 (0.3)
Decreased glucose	377	78 (20.7)	2 (0.5)	374	80 (21.4)	3 (0.8)
Increased potassium	379	76 (20.1)	15 (4.0)	376	61 (16.2)	6 (1.6)
Increased sodium	379	43 (11.3)	0	376	52 (13.8)	1 (0.3)
Increased calcium	362	17 (4.7)	1 (0.3)	361	30 (8.3)	4 (1.1)

Electrolyte abnormalities

There was a generally higher frequency of electrolyte abnormalities with PAN + BTZ + DEX compared to PBO + BTZ + DEX, in particular of hypokalemia, for which 5% of patients required dose adjustment or interruption and led to discontinuation in 0.8% (3 patients).

Thyroid function

Based on pre-clinical findings, hypothyroidism is considered a potential safety risk monitored in the panobinostat clinical development program. Accordingly, shifts in thyroid stimulating hormone (TSH) and free thyroxine (T4) values from baseline to extreme post-baselines values were assessed. Of those patients with normal T4 levels at baseline, shifts to a higher value occurred in 4.2% of patients in both arms. Shifts to lower values were slightly higher for the experimental arm (6.3%) than the control arm (2.4%).

Safety in special populations

All 221 patients <65 years and 159 of the 160 patients ≥ 65 years in the experimental arm experienced at least one AE. In general the incidence of AEs was lower in the patients <65 years in the following SOCs: Blood and lymphatic system disorders, 74.7% of the patients <65 years had an AE and 86.9% of the patients ≥ 65 years with thrombocytopenia (58.8% vs. 72.5%); Gastrointestinal disorders 84.6% vs.91.9% with diarrhoea (63.3% vs. 75.0%); General disorders and administration site conditions 72.4% vs. 80.0% with fatigue (36.7% vs. 47.5%). For Infections and infestations it was 73.3% vs. 62.5% with pneumonia (16.7% vs. 17.5%). A similar pattern was seen for the control arm. Furthermore, 125 of the 126 patients aged ≥ 65 to <75 years and all 34 patients ≥ 75 years experienced at least one AE. In the control arm the corresponding numbers were 132 and 28 patients, respectively. In general the incidence of AEs was lower in the patients aged ≥ 65 to <75 years than for patients ≥ 75 years in the experimental arm, for example thrombocytopenia (71.4% vs. 76.5%), diarrhoea (71.4% vs. 88.2%) and fatigue (45.2% vs. 55.9%). Similarly, the main difference with higher frequency in patients ≥ 75 years was seen for the common AEs reported such as thrombocytopenia, diarrhoea, fatigue/asthenia, and hypotension.

In the experimental arm, all 201 males experienced at least one AE, as did 179 of the 180 (99.4%) females. In the control arm the number and frequency of male or female patients with AEs was 204/205 (99.5%) and 172/172(100.0%), respectively. The frequencies for the AEs with notable differences in the experimental arm are as follows for men vs. women respectively: anaemia (39.8% vs. 43.3%), thrombocytopenia (59.7% vs. 70.0%), neutropenia (24.4% vs. 36.1%), diarrhoea (67.2% vs. 69.4%), nausea (29.9% vs. 43.3%), vomiting (18.9% vs. 33.3%), fatigue (38.3% vs. 44.4%), pneumonia (23.4% vs. 10%), and muscle spasms (10.0% vs. 1.7%).

In the experimental arm, there were 244 Caucasian patients, 127 Asian and 10 Other. Almost all of them experienced AEs during the study. In the control arm the number of Caucasian, Asian and Other race patients was 247, 103 and 27, respectively, and the AE frequency was 99.6%, 100.0%, and 100.0%, respectively. The notable AEs in the experimental arm are as follows for Caucasian vs. Asian: thrombocytopenia (60.7% vs. 70.1%), diarrhoea (66.4% vs. 71.7%), fatigue (48.4% vs. 26.8%), hypokalemia (18.4% vs. 44.9%), decreased appetite (20.9% vs. 43.3%), pneumonia (12.7% vs. 26.0%), hypoesthesia (3.7% vs. 15.0%), hepatic function abnormal (0.0% vs. 3.9%), gastroenteritis (2.5% vs. 4.7%), and herpes zoster (2.9% vs. 8.7%).

In addition, events related to hepatic dysfunction were reported in 63 of the PAN + BTZ + DEX-treated patients (16.5%) and 46 of the PBO + BTZ + DEX-treated patients (12.2%) in Study D2308 with 4.2% and 3.4%, respectively with Grade 3/4 severity. The most frequent occurring AEs (≥ 2%) in the PAN + BTZ + DEX arm were ALT increased (6.0%), hypoalbuminaemia (5.5%), aspartate AST increased (4.5%), blood alkaline

phosphatase increased (2.9%), gamma-glutamyltransferase increased (2.4%) and hyperbilirubinaemia (2.4%).

In the pooled dataset, the numbers were almost identical to those of the PAN + BTZ + DEX-treated patients in Study D2308. In the study LBH589X2101hepatic impairment increased the plasma exposure of panobinostat by 43%, moderate impairment increased the plasma exposure by 105%.

In the PAN+BTZ+Dex arm of Study D2308, 84.5% of patients had normal baseline hepatic function vs. 55 (14.4%) with mild hepatic impairment and in the PBO+BTZ+Dex arm, these percentages were 86.7% and 13.0% respectively.

In the PAN + BTZ + DEX arm of Study D2308 the results are as follows for renal impairment and no renal impairment, respectively: thrombocytopenia (67.7% vs 57.6%), diarrhoea (70.0% vs 64.4%) and fatigue (39.5% vs 44.9%). Additional analysis was performed of the frequency of AEs according to the degree of renal impairment. It must be noted that there were only 11 patients in each arm with severe renal impairment.

In the PAN+BTZ+Dex arm the rates of SAEs in patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment respectively were 45%, 61%, 72%, and 91%. In the PBO+BTZ+Dex arm the corresponding rates of SAEs were 33%, 44%, 51% and 46% respectively.

The Applicant has presented the age distribution of patients with renal impairment at baseline (Study D2308, FAS) and it can be seen that in the PAN+BTZ+Dex arm the median age for normal renal function was 56 years, for mild renal impairment it was 65 years, for moderate 68 years and for severe its was 74 years. The median age and age ranges for the categories of renal function were almost the same in the PBO+BTZ+Dex arm.

Safety related to drug-drug interactions and other interactions

Please refer to pharmacokinetic drug interactions and the discussion on clinical pharmacology.

Discontinuation due to adverse events

In the Phase III Study D2308, study treatment discontinuation due to AEs was 36.2% (138 patients), in the PAN + BTZ + DEX combination therapy arm and 20.4% (77 patients) in the PBO + BTZ + DEX arm. The SOCs with the highest percentage (≥ 1%) of AEs leading to discontinuation of study drug for the PAN + BTZ + DEX arm were nervous system disorders (8.1%) with peripheral neuropathy (3.7% vs 1.9% for PBO + BTZ + DEX), gastrointestinal disorders (7.3%) with diarrhoea (4.5% vs 1.6% for PBO + BTZ + DEX), general disorders and administration site conditions (7.3%) with asthenia (2.9% vs 0% for PBO +BTZ + DEX) and fatigue (2.9% for both treatment groups), and infections and infestations (5.0%) with pneumonia (1.3% vs 2.1% for PBO + BTZ + DEX).In the pooled data set, 153 patients (33.9%) discontinued treatment due to AE. Most frequent AEs (≥ 1%) leading to discontinuation in the pooled data set were diarrhoea (4.2%), peripheral neuropathy (3.8%), fatigue (3.5%), asthenia (3.1%), pneumonia (1.6%), and thrombocytopenia (1.3%).

In the Phase III Study D2308, the overall incidence of AEs requiring dose adjustments was 88.7% in the PAN + BTZ + DEX vs 75.6% in the PBO + BTZ + DEX treatment arms. The AEs requiring dose adjustments reported more frequently in the PAN + BTZ + DEX arm of study D2308 (with a ≥ 5% difference between the treatment arms) were thrombocytopenia (31.0% vs 10.9% for PBO + BTZ + DEX), diarrhoea (26.0% vs 9.0% for PBO +BTZ + DEX), neutropenia (10.2% vs 2.4% for PBO + BTZ + DEX) and fatigue (16.3% vs 7.2% for PBO + BTZ + DEX).In the pooled data set, 397 patients (88.0%) experienced AEs that required dose adjustments or interruptions. The AEs requiring dose adjustments were (with a ≥ 10% occurrence) thrombocytopenia (32.2%), diarrhoea (24.6%), fatigue (17.1%), peripheral neuropathy (12.2%) and neutropenia (10.2%).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety data reported are based on the phase III clinical study (Panorama 1) in 381 patients with multiple myeloma treated with 20 mg panobinostat once a day three times per week, on a 2 weeks on and 1 week off dosing regimen in combination with bortezomib and dexamethasone. The median duration of study treatment exposure (any component) was longer in the control arm compared to the experimental arm (6.7 months and 5.4 months respectively). In the control arm 54 % of the patients endured treatment ≥ 6 months compared to 47 % in the experimental arm. The mean relative dose intensity was overall higher in the control arm for all three compounds. It is concluded that the add-on by panobinostat to bortezomib and dexamethasone unfavourably affects the tolerability for all three compounds.

There are no major differences in the safety profile between the prior BTZ and IMiD subgroup and the overall population. There are also no major differences in the safety profile between the subgroups according to number of prior lines of treatment and the overall population or amongst these subgroups. There are no additional safety factors with regard to adverse events in these subgroups that need to be taken into account when considering the B/R in any subgroup.

Notably, there is an overlap in toxicity profiles of panobinostat and bortezomib in the context of primarily GI disorders (diarrhoea, nausea, vomiting), haematology (thrombocytopenia, anaemia, neutropenia) and fatigue.

Although it is recognized that a similar proportion of patients between the two treatment-arms reported least one AE, there was consistently a higher proportion of grade 3/4 AEs (96% vs. 82%), SAEs (60% vs. 42%), AEs leading to treatment discontinuation (36% vs. 20%), AEs leading to dose adjustment or temporarily dose interruption (89 % vs. 76 %) and on-treatment deaths (8 % vs.5 %) in the experimental compared to the control arm.

As may be anticipated given the overlapping toxicity profiles, the most frequent AEs suspected to be drug-related included blood disorders (primarily thrombocytopenia [51%, all grades] neutropenia [22%, all grades] and anaemia (25%, all grades), GI toxicities (primarily diarrhoea [51%, all grades], nausea [23%, all grades] and vomiting [16 %, all grades]), and constitutional disorders such as fatigue (31 %, all grades).

A quite substantial proportion of patients discontinued treatment due to an AE in the experimental arm compared to the control arm (36 % vs.20 %). The single most frequent AEs leading to treatment discontinuations were diarrhoea (4.5% and 1.6%, respectively), fatigue (2.9% both arms), asthenia (2.9% and 0, respectively), and peripheral neuropathy (3.7% and 1.9%, respectively). The most frequent according to SOCs leading to discontinuations in the experimental arm were Nervous system disorders (8.1%), Gastrointestinal disorders (7.3%), General disorders and administration site conditions (7.3%), Infections (5.0%).

Consistent with the findings in regard to discontinuations, more patients in the experimental arm were in need of study drug interruption or dose adjustment (89 %) compared to the control arm (76 %). The main causes pertained to thrombocytopenia (31 % vs. 11 %), diarrhoea (26 % vs. 9 %), fatigue (16 % vs. 7 %) and pneumonia (11 % vs. 8 %).

In study D2308 in the overall population (n=758) the rate of deaths on-treatment, but not due to the study indication of MM, was twice as high in the PAN + BTZ + DEX arm (6.8%) compared to the PBO + BTZ + DEX arm

(3.2%) and in the subpopulation of patients having received prior BTZ and IMIDs and ≥ 2 prior lines of therapy these rates were 6.9% and 4.1% respectively. For comparison, the rate of on-treatment deaths due to the disease was 1.0% in the PAN + BTZ + DEX arm compared to 1.6% the PBO + BTZ + DEX arm and in the subpopulation of patients having received prior BTZ and IMIDs and ≥ 2 prior lines of therapy these rates were 0% and 2.7% respectively.

As part of a post authorisation measure which is included in the Annex II, the Applicant shall submit the final survival analysis for study D2308, including a tabulated summary of deaths within 8 months of first dose and also an analysis in the patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

The SmPC contains recommendations for patient monitoring and for dose modifications, interruption or discontinuation in case of adverse events (see below).

Due to the nature of multiple myeloma and the known haematotoxicity for panobinostat and its combination agent bortezomib, thrombocytopenia, often severe, has been frequently observed. CTC grade 3 or 4 thrombocytopenia occurred in 256 patients, with a median onset time of one month. However, thrombocytopenia is reversible (median time to recovery of 12 days) and can usually be managed by dose adjustment and interruption with or without platelet transfusion (see section 4.4). 33.3% patients in the panobinostat + bortezomib + dexamethasone arm and 10.3% patients in the placebo + bortezomib + dexamethasone arm received platelet transfusions during treatment (See SmPC section 4.8).

Thrombocytopenia rarely leads to treatment discontinuation (1.6% of patients). Most patients with thrombocytopenia did not experience haemorrhage. 20.7% of patients experienced haemorrhage, most frequently epistaxis (4.7%), haematoma (2.6%), and conjunctival haemorrhage (2.1%). CTC grade 3 or 4 haemorrhage was reported in 4.2% of patients, mostly commonly involving gastrointestinal haemorrhage. Five patients (1.3%) died of events associated with haemorrhage. Amongst the patients who died of haemorrhage, one patient had thrombocytopenia grade 4, three patients had thrombocytopenia grade 3 and 1 patient had thrombocytopenia grade 1 (See SmPC section 4.8).

Therefore, physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for haemorrhage, especially in patients with coagulation disorders or in those who are receiving chronic anti coagulation therapy (See SmPC section 4.4). Interaction with warfarin has been classified as a potential risk in the Risk Management Plan.

Dose modification recommendations, monitoring of blood counts including platelet count (in particular before each injection of bortezomib), recommendation of platelet transfusion in case of thrombocytopenia is provided in section 4.2 of the SmPC. Severe haemorrhage and myelosuppression have been classified as identified risks in the Risk Management Plan.

Relapsed or refractory multiple myeloma patients are at risk of infections. Potential contributing factors may include prior history of chemotherapy, stem cell transplant, the nature of the disease and neutropenia or lymphopenia associated with Farydak treatment (see SmPC section 4.8).

Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including hepatitis B virus and herpes simplex, have been reported in patients taking panobinostat. Some of these infections (e.g. pneumonia) have been severe (e.g. leading to sepsis, or respiratory or multi organ failure) and have had fatal outcomes. Of note, whereas grade 3 and grade 4 neutropenia were observed in 28% and 7% of patients, respectively, febrile neutropenia was observed in 1% of patients (see SmPC section 4.4).

The most frequently reported infections include upper respiratory tract infection, pneumonia and nasopharyngitis. Fatalities involving either pneumonia or sepsis were reported. Treatment discontinuation due to infections was reported in 5% of patients (see SmPC section 4.8). Severe infections (including sepsis/ pneumonia) have been classified as an identified risk in the Risk Management Plan and Reactivation of Hepatitis B Infection has been classified as a potential risk in the Risk Management Plan.

Physicians and patients should be aware of the increased risk of infection with panobinostat. Farydak treatment should not be initiated in patients with active infections. Pre-existing infections should be treated prior to initiation of the therapy. Patients should be monitored for signs and symptoms of infections during treatment with panobinostat; if a diagnosis of infection is made, appropriate anti-infective treatment should be instituted promptly and interruption or discontinuation of Farydak considered. If a diagnosis of invasive systemic fungal infection is made, panobinostat should be discontinued and appropriate anti-fungal therapy instituted (see SmPC section 4.4).

Neutropenia was frequently reported on the basis of laboratory findings determined during the study (all grades: 75%). Most newly occurring severe neutropenia was grade 3 (28%), with considerably fewer cases of grade 4 (6.6%). While many patients developed neutropenia, febrile neutropenia only occurred in a fraction of treated patients (1.0%, both for CTC all grades and for grades 3 and 4). Patients with neutropenia are prone to infection, mostly upper respiratory tract infection or pneumonia. Only 0.3% of the patients were discontinued from the treatment due to neutropenia (See SmPC section 4.8).

Neutropenia may require temporary or permanent dose reduction. In the event of grade 3 or 4 neutropenia, physicians should consider the use of growth factors (e.g. G CSF) according to local guidelines. Discontinuation of treatment may be considered if neutropenia does not improve despite the dose modifications and/or despite the addition of granulocyte colony stimulating factor therapy according to local medical practice and treatment guidelines, and/or in the event of severe secondary infections. Instructions for dose interruptions and reductions for panobinostat are described in Table 5 in section 4.2 of the SmPC.

Severe nausea, diarrhea, constipation and vomiting, sometimes requiring the use of anti emetic and anti diarrhoeal medicinal products, have been reported in patients treated with Farydak. However, treatment discontinuation due to these reactions was reported in a relatively small proportion of patients, with diarrhea at 4.5% and nausea and vomiting at 0.5% each (see SmPC section 4.8). Patients should be advised to contact their physician if severe gastrointestinal toxicity occurs and dose adjustment or discontinuation may be required (see SmPC section 4.4). Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances (see SmPC section 4.2). Prophylactic anti emetics (e.g. prochlorperezine) may be considered at the discretion of the physician and in accordance with local medical practice. Anti-emetic medicinal products with a known risk of QT prolongation such as dolasetron, granisetron, ondansetron and tropisetron should be used with caution (see SmPC section 4.5).

At the first sign of abdominal cramping, loose stools or onset of diarrhoea, it is recommended that the patient be treated with anti-diarrheal medicinal product (e.g. loperamide) or any additional treatment in accordance with local treatment guidelines. Replacement intravenous fluids and electrolytes may be used as appropriate. Medicinal products with laxative properties should be used with caution because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss the use of any laxative product (see SmPC section 4.4). Severe diarrhoea has been classified as an identified risk in the Risk Management Plan.

The incidence of the important AEs thrombocytopenia, diarrhoea, raised creatinine and dehydration was increased markedly already in patients ≥ 65 years in PAN + BTZ + DEX-treated patients as compared to the PBO + BTZ + DEX arm. The increase in frequency once patients were ≥ 75 years was less marked. This suggested that the increased susceptibility to these adverse events may start already at the relatively younger age of 65 years. On the other hand, it is also noted that the rate at which AEs led to discontinuation in patients ≥ 65 years was approximately 1.5 times that in in patients < 65 years in both PAN + BTZ + DEX-treated patients (45.0% vs 29.9%) and in PBO + BTZ + DEX-treated patients (25.6% vs 16.6%). In addition, it should also be considered that the rate of on-treatment deaths not due to disease progression was relatively higher in PAN + BTZ + DEX-treated patients ≥ 65 years (8.8% vs 5.4%), but was fairly similar in PBO + BTZ + DEX-treated patients (5.6% for age ≥ 65 years vs 2.8% for age <65 years). Increased toxicity in elderly patients (aged 65 years or above) has been classified as an identified risk in the Risk Management Plan.

In addition, sections 4.2 and 4.4 of the SmPC provides recommendations on more frequent monitoring of patients over 65 years of age, especially for thrombocytopenia and gastrointestinal toxicity and consideration of dose adjustment of panobinostat, bortezomib and/or dexamethasone in elderly patients above 75 years of age.

Hepatic dysfunction, primarily mild transient elevations in aminotransferases and total bilirubin, have been reported in patients during treatment with panobinostat. Liver function should be monitored prior to treatment and regularly during treatment. If results of liver function tests show abnormalities according to the NCI CTEP classification, dose adjustments for patients with mild and moderate hepatic impairment are recommended and the patient should be followed until values return to normal or pretreatment levels. Panobinostat should not be administered in patients with severe hepatic impairment due to lack of experience and safety data in this population. Adjustment of bortezomib dose should also be considered (see SmPC section 4.4). Hepatic dysfunction and use in patients with hepatic impairment have been classified as potential risks in the Risk Management Plan.

Hypothyroidism events were reported in 8 of 381 patients treated with panobinostat + bortezomib + dexamethasone in Study D2308, of whom 2 required treatment. Thyroid and pituitary function should be monitored by measuring hormone levels (e.g. free T4 and TSH) as clinically indicated (see SmPC section 4.4). Hypothyroidism has been classified as a potential risk in the Risk Management Plan.

Panobinostat may prolong cardiac ventricular repolarisation (QT interval) (see SmPC section 5.3). The risk of QTc prolongation does not increase over time. QTcF should be <480 msec prior to initiation of treatment with Farydak. Appropriate monitoring of electrolytes (e.g. potassium, magnesium and phosphorus) and ECG should be performed at baseline and periodically during treatment, particularly in patients with severe gastrointestinal adverse drug reaction. Farydak should be used with caution in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients: with long QT syndrome and with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia (see smPC section 4.2).

Concomitant use of anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol) and other substances that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended. Anti-emetic medicinal products with a known risk of QT prolongation such as dolasetron, granisetron, ondansetron and tropisetron should be used with caution (see SmPC section 4.5). QTc Prolongation has been classified as an identified risk in the Risk Management Plan and ischemic heart disease and tachyarrhythmias have been classified as potential risks.

Data about use in patients with cardiac diseases is missing. These have been adequately reflected in the SmPC (see section 4.2, 4.4, 4.5 and 5.3) and are reflected in the Risk Management Plan.

At this point the risk of second primary malignancies raises no concern. However, based on the non-clinical observations where it is concluded that panobinostat is mutagenic and hence have carcinogenic potential, it is concluded that the risk of second primary malignancies may be subject to close monitoring and has been classified as potential risk in the Risk Management Plan.

Plasma exposure of panobinostat is not altered in cancer patients with mild to severe renal impairment. Therefore, starting dose adjustments are not necessary. Panobinostat has not been studied in patients with end stage renal disease (ESRD) or patients on dialysis (see SmPC section 4.2). There seems to be a trend towards higher risk of AEs, including important AEs such as thrombocytopenia, diarrhoea, vomiting and atrial fibrillation in patients with impaired renal function defined as creatinine clearance <90 mL/min at baseline. Frequencies of AEs with increasing degree of renal impairment are confounded by the fact that renal function also decreases with increasing age which has been shown to correlate with a disimprovement in the safety profile. It can also be expected that there may be some degree of renal impairment with more severe disease which may lead to a higher rate of reporting of some AEs. However, the age range per category of renal function is very wide and furthermore, it is not clear if the increasing frequency of AE with age is related to increasing renal impairment or vice versa. The risk of renal dysfunction has been classified as a potential risk in the Risk Management Plan and a non-interventional study of panobinostat use in relapsed and/or refractory multiple myeloma patients observational study is planning to address this safety issue.

Colitis is included as ADR in Section 4.8 of the SmPC. Patients should be advised to contact their physician if severe gastrointestinal toxicity occurs and dose adjustment or discontinuation may be required. Ischaemic colitis has been classified as a potential risk in the Risk Management Plan.

Currently available data do not support inclusion of venous thromboembolism in the SmPC. The risk of venous thromboembolism has been classified as potential risk in the Risk Management Plan.

Limited experience with overdose has been reported during clinical studies. Adverse reactions observed were consistent with the safety profile, with events primarily involving haematological and gastrointestinal disorders such as thrombocytopenia, pancytopenia, diarrhoea, nausea, vomiting and anorexia. Cardiac monitoring and assessment of electrolytes and platelet counts should be undertaken and supportive care given as necessary in the event of overdose. It is not known whether panobinostat is dialysable (see SmPC section 4.9).

An additional risk minimisation measure (educational material with the compliance card provided for the patients) has been introduced to help minimise the potential for medication errors based on the complicated posology regimen which had been classified as potential risk in the Risk Management Plan. The Applicant will continue to monitor the below safety concerns in a non-interventional observational study (LBH589D2408A) of panobinostat use in relapsed and/or refractory multiple myeloma patients (in the real world setting): severe haemorrhage, severe infections (including sepsis and pneumonia), severe diarrhoea, use in elderly patients (aged 65 years or above), ischaemic heart disease, venous thromboembolism, carcinogenicity/ second primary malignancy, medication errors, use in patients with hepatic impairment and use in patients with renal impairment.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile is dominated by the (S)AEs of diarrhoea, thrombocytopenia, haemorrhage, neutropenia and infections. There was a transient decrease in QoL in the PAN + BTZ + DEX-treated patients as compared to those in the control arm in TP1 during treatment. However, the deterioration in QoL during treatment was transient and expected in view of the toxicity profile.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice and PRAC Assessment Reports.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	QTc Prolongation Myelosuppression Severe haemorrhage Severe infections (including sepsis/ pneumonia) Severe diarrhoea Increased toxicity in elderly patients (aged 65 years or above)
Important potential risks	Ischemic Heart Disease Tachyarrhythmias Venous Thromboembolism Ischemic Colitis Hypothyroidism

Summary of safety concerns	
	Reactivation of Hepatitis B Infection Hepatic dysfunction Renal dysfunction Developmental toxicity Carcinogenicity/ Second primary malignancy Reduced fertility in males Use in patients with hepatic impairment Medication errors Interaction with strong CYP3A4 inhibitors Interaction with CYP2D6 substrates Interaction with strong CYP3A inducers Interaction with sensitive CYP3A4 substrates Interaction with warfarin Interaction with drugs that may prolong the QT interval
Missing information	Use in patients with cardiac diseases Use in patients with renal impairment

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
LBH589D2408 (PASS Study) Non-interventional study of panobinostat use in relapsed and/or refractory multiple myeloma patients observational study (category 3)	The primary objective is to document safety of panobinostat in patients with Relapsed and/or Refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory	Severe haemorrhage, severe infections (including sepsis and pneumonia), Severe diarrhea, Increased toxicity in elderly patients (aged 65 years or above), Ischemic heart disease,	Planned	To be confirmed

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events.	Venous thromboembolism, Carcinogenicity/ Second primary malignancy, Medication errors, Use in patients with hepatic impairment, Use in patients with renal impairment		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
QTc prolongation	Dose modification recommendations, guidelines on periodic monitoring of ECGs and electrolytes, correction of electrolytes if clinically indicated in SmPC Section 4.2 posology and method of administration. Special warning and precautions for use in SmPC Section 4.4 provides guidelines on periodic monitoring of ECGs and electrolytes, particularly in patients with severe gastrointestinal side effects. Panobinostat should be used with caution in patients who already have QTc prolongation or who are at significant risk of developing QTc prolongation. Caution of use with concomitant administration of medicinal products that are known to cause QTc prolongation. Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Concomitant use of anti-arrhythmic medicines and other drugs that are known to prolong the QT interval are not recommended. Anti-emetic medicinal products with a known risk of QT prolongation should be used with caution. Syncope and Electrocardiogram QT prolonged are included as	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	ADRs in SmPC Section 4.8 Undesirable effects. This section also provides details on the frequency and severity of QT prolongation. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Myelosuppression	Dose modification recommendations, monitoring of blood counts including platelet count (in particular before each injection of bortezomib), recommendation of platelet transfusion in case of thrombocytopenia is provided in SmPC section 4.2 posology and method of administration. Recommendation to perform complete blood count before initiating therapy with panobinostat, frequent monitoring of blood cell count (in particular before each injection of bortezomib), recommendation of platelet transfusion in case of thrombocytopenia provided in Special warning and precautions for use in SmPC Section 4.4. Pancytopenia, thrombocytopenia, anaemia, neutropenia, leukopenia, lymphopenia are included as ADRs in SmPC Section 4.8 Undesirable effects. This section also provides details on the frequency and severity of treatment emergent haematologic toxicities. Overdosage in SmPC Section 4.9: Limited experience with overdose has been reported during clinical studies. Platelet counts monitoring and supportive care is recommended in the event of overdose. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Severe haemorrhage	Dose modification recommendations provided in SmPC Section 4.2 posology and method of administration. Special warning and precautions for use in SmPC Section 4.4 details that physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for hemorrhage, especially in patients with coagulation disorders who are receiving chronic anti-coagulation therapy. It also provides dose modification and platelet transfusion recommendations in case of thrombocytopenia. Epistaxis, haematoma, conjunctival haemorrhage, haematochezia, petechiae, gastrointestinal haemorrhage, haematuria, haemoptysis, haematemesis, haemorrhage intracranial, pulmonary haemorrhage, and shock haemorrhagic are included as ADRs in SmPC Section 4.8 Undesirable effects.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC Section 4.9: Limited experience with overdose has been reported during clinical studies. Adverse reactions observed were consistent with the safety profile, with events primarily involving haematological disorders such as thrombocytopenia and pancytopenia. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Severe Infections (including sepsis/pneumonia)	Dose modification recommendations in SmPC Section 4.2 posology and method of administration. Dose modification, recommendations, description of frequency and severity of events, guidelines on monitoring of signs and symptoms of infection are provided in Special warning and precautions for use in SmPC Section 4.4. Panobinostat treatment should not be initiated in patients with active infections. If a diagnosis of invasive systemic fungal infection is made, panobinostat should be discontinued and appropriate antifungal therapy instituted. Pneumonia, septic shock, sepsis, lower respiratory tract infection, hepatitis B, and pneumonia fungal are included as ADRs in SmPC Section 4.8 Undesirable effects. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Severe diarrhea	SmPC Section 4.2 Posology and method of administration states that gastrointestinal toxicity is very common in patients treated with panobinostat. Patients who experience diarrhoea and nausea or vomiting may require temporary dose discontinuation or dose reduction. Dose modification recommendations for panobinostat and bortezomib are provided in the event of diarrhoea. At the first sign of abdominal cramping, loose stools or onset of diarrhoea, it is recommended that the patient be treated with an antidiarrhoeal medicinal product (e.g. loperamide). Special warning and precautions for use in SmPC Section 4.4 details that fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances. At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medicinal product (e.g. loperamide) or any	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	additional treatment in accordance with local treatment guidelines. Replacement intravenous fluids and electrolytes may be used as appropriate. Medicinal products 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 the use of any laxative product. Caution should be exercised when medicinal products with laxative properties is used because of the potential for exacerbation of diarrhoea. Diarrhoea is included as an ADR in SmPC Section 4.8 Undesirable effects. This section also details frequency and severity of GI toxicity including diarrhea and advises patients to contact their physician for dose modifications. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Increased toxicity in elderly patients (aged 65 years or above)	SmPC Section 4.2 Posology and method of administration provides recommendations on monitoring patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicity; recommendations on dose adjustment of the starting doses or schedule of the components of the combination regimen for patients >75 years of age. Section 4.4 Special warnings and precautions for use provides recommendations on more frequent monitoring of patients over 65 years of age and consideration of dose adjustment of panobinostat, bortezomib and/or dexamethasone in elderly patients above 75 years of age. Section 4.8 Undesirable effects provides incidence of deaths and ADRs in patients <65 years and ≥ 65 years of age. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Important Potential Risks		
Ischaemic heart disease	Myocardial infarction is included as an ADR in SmPC Section 4.8 Undesirable effects. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products	None
Tachyarrhythmias	Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Concomitant use of anti-arrhythmic medicines and other substances that are known to prolong the QT interval is not recommended.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Atrial fibrillation, tachycardia, sinus tachycardia, and palpitation are included as ADRs in SmPC Section 4.8 Undesirable effects SmPC Section 4.9 Overdose: Cardiac monitoring and assessment of electrolytes should be undertaken and supportive care given as necessary in the event of overdose. Limited experience with overdose has been reported during clinical studies. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Venous thromboembolism	Currently available data do not support inclusion in the SmPC. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Ischaemic colitis	Gastrointestinal haemorrhage, haematochezia, and colitis are included as ADRs in SmPC Section 4.8 Undesirable effects. Patients should be advised to contact their physician if severe gastrointestinal toxicity occurs and dose adjustment or discontinuation may be required. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Hypothyroidism	SmPC Section 4.2 provides recommendations on monitoring for thyroid and pituitary function (free T4 and TSH). Hypothyroidism is listed as an ADR in SmPC Section 4.8. Preclinical safety data in SmPC Section 5.3 details on thyroid hormone changes, histopathological and functional changes of the thyroid in rats and dogs. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Reactivation of Hepatitis B infection	Special warning and precautions for use in SmPC Section 4.4 provides recommendation on dose modification and monitoring of signs and symptoms of infections. If a diagnosis of infection is made, appropriate anti-infective treatment should be instituted promptly. Panobinostat treatment should not be initiated in patients with active infections. Physicians and patients should be aware of the increased risk of infection with panobinostat. Hepatitis is Included as an ADR in SmPC Section 4.8 Undesirable effects. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	products.	
Hepatic dysfunction	Special warning and precautions for use in SmPC Section 4.4 provides recommendation on dose modification and liver function monitoring prior to treatment and during treatment with panobinostat. Hepatic function abnormal, hyperbilirubinemia, ALT increased, and AST increased are included as ADRs in SmPC Section 4.8 Undesirable effects. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Renal dysfunction	Blood creatinine increased, renal failure, blood urea increased, and glomerular filtration rate decreased are included as ADRs in SmPC Section 4.8 Undesirable effects. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Developmental toxicity	SmPC Section 4.3 contraindicates breast feeding during treatment with panobinostat. SmPC Section 4.4 recommends using highly effective contraception during treatment and for three months after stopping treatment. SmPC Section 4.5: Panobinostat may reduce the effectiveness of hormonal contraceptives. Women using hormonal contraceptives should add a second barrier method. SmPC Section 4.6 Fertility, pregnancy, and lactation advises use of a highly effective method of contraception during treatment and for at least three months after the last dose of panobinostat, and use of second barrier method in women using oral contraceptives. It also states that there are no clinical studies on the use of panobinostat in pregnant patients and that panobinostat should only be used during pregnancy only if the expected benefits outweigh the potential risks to the foetus. Sexually active men taking panobinostat and their female partners should use a highly effective method of contraception during the man's treatment and for six months after his last dose of panobinostat. Breast-feeding is contraindicated during treatment with panobinostat. SmPC Section 5.3 Preclinical safety data describes that based on animal data, the likelihood of panobinostat increasing the risk of foetal death and developmental skeletal abnormalities is predicted to be high. Embryofoetal lethality and increases in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	skeletal anomalies were seen above exposures corresponding to 0.25 of the human clinical AUC. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Carcinogenicity/ Second primary malignancy	SmPC Section 5.3 Preclinical safety data states that carcinogenicity studies have not been performed with panobinostat; however, it has demonstrated mutagenic potential in the Ames assay. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Reduced fertility in males	SmPC Section 4.6 details that based on nonclinical findings panobinostat can influence quality of sperm formed during treatment. SmPC Section 5.3 Preclinical safety data details that in 4- and 13-week repeated dose oral toxicity studies in dogs, prostatic atrophy accompanied by reduced secretory granules and testicular degeneration, oligospermia and increased epididymal debris were observed that were not completely reversible following a 4-week recovery period. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Use in patients with hepatic impairment	SmPC Section 4.2 posology and method of administration provides dose adjustment guidelines in patients with mild and moderate hepatic impairment, and monitoring of liver function tests prior to treatment and regularly as clinically indicated frequent monitoring during treatment. Panobinostat should not be used in patients with severe hepatic impairment. Panobinostat should be avoided in patients with hepatic impairment requiring concomitant use of strong CYP3A4 inhibitors. Section 4.4 Special warnings and precautions provides recommendations for dose adjustment in patients with mild and moderate hepatic impairment. Panobinostat should not be administered in patients with severe hepatic impairment. Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Panobinostat treatment should be avoided in patients with hepatic impairment receiving concomitant strong CYP3A4 inhibitors. Pharmacokinetic properties in SmPC Section 5.2 details PK	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	information. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Medication errors	SmPC Section 4.2 provides clear guidance on the dosing schedule of panobinostat in combination with bortezomib and dexamethasone in a tabular format for better visual representation. Package leaflet provides similar guidance on the dosing schedule of the combination treatment, and a representation of the blister pack demonstrating how the blister is intended to be used. The pack design (blister pack) presents empty blister compartments corresponding to the Day of the Cycle on which panobinostat should not be taken. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	Educational material which consists of Compliance card for patients
Interaction with strong CYP3A4 inhibitors	SmPC Section 4.2: Recommends dose reduction of panobinostat in patients taking concomitant strong CYP3A4 inhibitors. Panobinostat treatment should be avoided in patients with hepatic impairment receiving concomitant strong CYP3A4 inhibitors. CYP3A4 inhibitors should not be started if patients are on reduced dose of panobinostat, and if cannot be avoided, then the patient should be closely monitored. SmPC Section 4.4 states that dose adjustment is required in patients with panobinostat treatment taking concomitant strong CYP3A4 inhibitors. Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5 states that concomitant administration of strong CYP3A inhibitor increases Cmax and AUC of panobinostat. It also provides recommendation on dose adjustment of panobinostat when coadministered with strong CYP3A inhibitors. CYP3A4 inhibitors should not be started if patients are on reduced dose of panobinostat, and if cannot be avoided, then the patient should be closely monitored. Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice, as these are known to inhibit cytochrome P450 3A enzymes and may increase the bioavailability of panobinostat. Prescription only medicine, should be initiated and supervised by	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	a physician experienced in the use of anti-cancer medicinal products.	
Interaction with CYP2D6 substrates	Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Avoid panobinostat in patients taking sensitive CYP2D6 substrates with a narrow therapeutic index. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Interaction with strong CYP3A inducers	SmPC Section 4.4 recommends avoiding concomitant use of CYP3A4 inducers. Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Provides instruction on avoiding concomitant use of strong CYP3A4 inducers. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Interaction with sensitive CYP3A4 substrates	Interaction with other medicinal products and other forms of interaction in SmPC Section 4.5: Medicinal products that can influence the CYP3A4 enzyme activity may alter the pharmacokinetics of panobinostat. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Interaction with warfarin	Special warning and precautions for use in SmPC Section 4.4: Physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for hemorrhage, especially in patients with coagulation disorders who are receiving chronic anticoagulation therapy. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Interaction with drugs that may prolong the QT intervale	Special warning and precaution for use in SmPC Section 4.4: Concomitant administration of medicinal products that are known to cause QTc prolongation is not recommended. SmPC Section 4.5: Concomitant use of antiarrhythmic medicines and other substance that are known to prolong the QT interval are not recommended. Anti-emetic medicinal products with a known risk of QT prolongation should be used with caution. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing Information		
Use in patients with cardiac diseases	Special warning and precautions for use in SmPC Section 4.4 details that panobinostat should be used with caution in patients with uncontrolled or significant cardiac disease. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None
Use in patients with renal impairment	SmPC Section 4.2 Posology and method of administration details that plasma exposure of panobinostat is not altered in cancer patients with mild to severe renal impairment and therefore starting dose adjustments are not necessary. SmPC Section 5.2 details that mild, moderate and severe renal impairment based on baseline urinary creatinine clearance did not increase the panobinostat plasma exposure. Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

A user testing of the blister and the compliance card will be submitted by the Applicant before the launch of the product and at the latest within 1 month after the CD.

3. Benefit-Risk Balance

Beneficial effects

The study pivotal to this application, CLBH589D2308, was a multicenter, randomized, double-blind, placebo-controlled study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma. To qualify, patients needed to have received at least one prior line of therapy.

In the full population of this study, the investigator-based PFS (primary endpoint) was 12 months for the experimental arm and 8 months for the control arm, thus an improvement in PFS of 4 months (HR: 0.63 (95% CI: 0.52, 0.76). The median OS (key secondary endpoint in the pivotal study) in the PAN + BTZ + DEX arm, as

determined by the second interim analysis, is 38 months and 35 months, in the PAN+BTZ+Dex and PBO+BTZ+Dex arms, respectively (HR 0.87; 95% CI: 0.70, 1.07; p=0.18).

Due to the less favourable safety profile, a group of patients with limited treatment options was retrospectively identified, in which panabinostat was considered to have a positive benefit risk (see below).

In the subgroup of patients who had received at least two prior regimens including BTZ and IMiD the median PFS (investigator based) was prolonged by 7.8 months in patients receiving PAN+BTZ+Dex treatment as compared to the PBO+BTZ+Dex control arm, with a 52% relative risk reduction in the hazard rate of progression/death (HR: 0.48; 95% CI [0.31, 0.72], log-rank p value = 0.0003) which is considered to be of clinical significance. The median OS was 26.1 months in the PAN+BTZ+DEX treated patients vs 19.5 months in PBO+BTZ+DEX treated patients (HR 0.84 (95% CI 0.55; 1.27).

The other secondary endpoints including, overall response rate (59% in the panobinostat + bortezomib + dexamethasone arm vs 39% in the placebo + bortezomib + dexamethasone arm) and nCR (14% in the panobinostat + bortezomib + dexamethasone arm vs 8% in the placebo + bortezomib + dexamethasone arm) supported the primary efficacy endpoint and favored the panobinostat arm.

The superior treatment effect of the experimental arm was consistent across performed sensitivity analyses, strata (prior lines of therapy 1 vs 2 or 3; previous exposure to bortezomib, yes/no), and most subgroups. Thus available data do not indicate that there is a loss of efficacy in patients with limited treatment options.

Results from the supportive DUS71 Study, that included BTZ-refractory patients (excluded from the main study) showed that the ORR (i.e. a response more than a PR) was 35%. This is higher as compared to the 22% ORR to the last prior treatment before study entry. In the high-risk cytogenetic subgroup (del[17p], t[4;14], t[14;16]), ORR was 43%. For the total population, median OS was 17.5 months, the median PFS and TTP were both 5.4 months, and the median DoR was 6.0 months. Therefore, these results from DUS71 showed a similar anti-tumour activity as in the pivotal trial and compared well to historical data.

Overall, the efficacy results from the Phase Ib and the Phase II study are considered supportive for the pivotal study.

Uncertainty in the knowledge about the beneficial effects

Due to long survival post progression and subsequent therapy the treatment benefit in terms of HR for survival is diluted. The MAH will submit the results of the final OS analysis post approval, but the results are expected to be stable. Thus, a precise estimate of effects on survival cannot be expected.

Risks

Unfavourable effects

The most frequently occurring AEs in PAN + BTZ + DEX treated patients in study D2308, were thrombocytopenia (any grade 97.6%; Grade 3/4, 67.6%), neutropenia (any grade 75.0%; Grade 3/4, 34.5%), anaemia (any grade 62.0%; Grade 3/4, 17.7%), infections and infestations (69.8%),(mostly due to AEs of upper respiratory tract infections (20.0%) and pneumonia (16.4%)), fatigue (45.5%), peripheral oedema (29.9%) and pyrexia (25.9%), peripheral neuropathy (30.8%), hypokalemia (27.1%).

In the PAN + BTZ + DEX arm, the rate of haemorrhages was approximately twice that of the rate in the PBO + BTZ + DEX arm at 20.7% vs 11.7% for any grade haemorrhages and 4.2% vs. 2.4% for Grade 3/4 haemorrhages.

Diarrhoea was also more frequent in patients treated with PAN + BTZ + DEX compared to those treated with PBO + BTZ + DEX (68% vs 41.6%), with Grade 3/4 severity being three times more frequent in the experimental arm (25.5% vs 8.0%).

The safety profile also included qualitative ECG abnormalities, such as T-wave changes and ST-T segment depression (63.5% of patients in the PAN + BTZ + DEX arm vs 42.2% in the PBO + BTZ + DEX arm) and sinus tachycardia (15.5% in the PAN + BTZ + DEX arm vs 6.8% in PBO +BTZ + DEX). The great majority of patients with ECG abnormalities did not experience a cardiac event subsequent to an ECG abnormality.

A high proportion of patients discontinued treatment due to an AE in the experimental arm compared to the control arm (36 % vs 20 %). More patients in the experimental arm were in need of study drug interruption or dose adjustment (89 %) compared to the control arm (76 %). The rate of death on-treatment, but not due to the study indication of MM, was twice as high in the PAN + BTZ + DEX arm (6.8%) compared to the PBO + BTZ + DEX arm (3.2%). The rate of on-treatment deaths due to the disease was 1.0% in the PAN + BTZ + DEX arm compared to 1.6% the PBO + BTZ + DEX arm which is expected given the disease and stage.

The QoL in the PAN + BTX + DEX arm decreased to a higher extent than in the control arm, crossing the threshold of the minimal important difference. However, the deterioration in QoL during treatment was transient and expected in view of the toxicity profile.

Uncertainty in the knowledge about the unfavourable effects

Due to the limited safety database, a number of uncertainties were identified during the assessment, including, use in elderly patients (aged 65 years or above) patients with ischemic heart disease. hepatic impairment and renal impairment which were satisfactorily addressed (see discussion on clinical safety) and have been adequately reflected in the SmPC and in the Risk Management Plan.. In addition, the Applicant will continue to monitor the above safety concerns in a non-interventional observational study of panobinostat use in relapsed and/or refractory multiple myeloma patients LBH589D2408 (see Risk Management Plan).

Balance

Importance of favourable and unfavourable effects

The relative PFS benefit of 4 months in the overall group of patients with relapsed multiple myeloma following at least one prior therapy receiving PAN+BTZ+Dex treatment as compared to the PBO+BTZ+Dex control arm is considered clinically relevant. This benefit was further extended to almost 8 months in the retrospectively established subgroup of patients who had received at least two prior regimens including BTZ and IMiD. No significant effect on the key overall survival was observed but this should be considered in the context of the long survival post progression and subsequent therapy. Overall, the effect on the secondary endpoints is consistent between subgroups and similar across various sensitivity analyses.

The limiting factor in the use of panobinostat is its toxicity. The safety profile is dominated by the (S)AEs of diarrhoea, thrombocytopenia, haemorrhage, neutropenia and infections with a high proportion of patients discontinuing treatment due to an AE in the experimental arm and an increased rate of deaths on-treatment. ECG abnormalities have been observed but their implications are unclear. There was a transient decrease in QoL in the PAN + BTZ + DEX-treated patients as compared to those in the control arm in TP1 during treatment.

Benefit-risk balance

The benefit-risk balance of panobinostat for the broad indication of patients with relapsed multiple myeloma following at least one prior therapy has been questioned due to the severity of the toxicity and alternative treatment options. For this reason it is considered that panobinostat is not indicated for patients that may still accrue a benefit from either BTZ or IMiD based therapy. Thus, the benefit-risk balance for panobinostat is considered to be only positive in the subgroup of adult patients with relapsed and /or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent. In these patients there is still an unmet medical need with a benefit of panobinostat that outweighs its toxicity, as will be discussed further below.

Bortezomib refractory patients were excluded from D2308, but the supportive evidence from DUS71 provides the evidence needed not to exclude these patients from the labelling.

Discussion on the benefit-risk balance

There are still uncertainties on the optimal dose. The impact of adverse events may be lessened by close monitoring and timely interventions and the SmPC contains recommendations for patient monitoring and for dose modifications, interruption or discontinuation in case of adverse events. Recommendations also include platelet transfusion in case of thrombocytopenia, administration of granulocyte colony stimulating factor therapy in case of neutropenia, according to local medical practice and treatment guidelines, and/or in the event of severe secondary infections and use of anti-diarrhoeal agents.

For patients with relapsed and/or refractory MM, treatment strategy is complex depending on the type of prior treatments, response to prior therapy, treatment tolerability, and patient characteristics and there is no standard recommended therapy. Previous treatments may be retried depending on the response to that treatment, second autologous stem cell transplantation depending on the response to the first SCT and on patient eligibility (or even a first SCT) may be an option for some patients. One of the current approaches in the treatment of relapsed and/or refractory MM is to change to an agent from a different class. The availability of a therapy with a different mechanism of action would provide another option to be used in this approach. Patients refractory to both an IMiD and bortezomib have a poorer prognosis and limited further treatment options. Overall, the efficacy of PAN+BTZ+DEX is considered to be of clinical significance in the perspective of current treatment strategies and to outweigh the risk associated with therapy, in such patients.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Farydak is not similar to Thalidomide Celgene, Revlimid and Imnovid within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of Farydak in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to address the risk of medication error.

The MAH shall ensure that in each Member State where Farydak is marketed, all patients/carers who are expected to use Farydak have access to/are provided with the following educational package:

- Patient information pack

The patient information pack should contain:

- Patient information leaflet
- A patient compliance card

- **The patients compliance card** shall contain instructions on the following key messages:
  - How to become familiar with the compliance card: this section provides a general overview of the compliance card and its purpose.
  - How to compile the compliance card: this section provides a general overview on how to use the compliance card
  - How to take medication according to the prescription: this section provides guidance on how to fill in the compliance card.
  - Recommendation to bring compliance card to each visit: this section reminds the patient to bring the compliance card to the HCP at each visit.
  - A table describing the treatment regimen for each day of the cycle with space for the patient to note what medication they took.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

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

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Panobinostat (as lactate anhydrous) is qualified as a new active substance.

REFERENCES

1. Bladé J, Samson D, Reece D, et al (1998). Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and hematopoietic stem cell transplantation. Br J Haematol; 102(5):1115-23.

2. Corso A, Varettoni M, Mangiacavalli S, et al (2009). Bortezomib plus dexamethasone is highly effective in relapsed and refractory myeloma patients but responses are short-lived. Eur J Haematol; 83(5):449-54.

3. Davies FE, Wu P, Jenner M, et al (2007). The combination of cyclophosphamide, velcade and dexamethasone (CVD) induces high response rates with comparable toxicity to velcade alone (V) and velcade plus dexamethasone (VD). Haematologica; 92:1149-50.

4. Dubois D1, Dhawan R, van de Velde H, Esseltine D, Gupta S, Viala M, de la Loge C. Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. J Clin Oncol. 2006 Feb 20;24(6):976-82. Epub 2006 Jan 23.

5. Jagannath S, Richardson PG, Barlogie B, et al (2006). Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica; 91(7):929-34.

6. Kyle RA, Gertz, MA, Witzig TE et al (2003a). Review of 1027 patients with newl diagnosed multiple myeloma. Mayo Clin Proc; 78:21-33.

7. Kyle RA, and the International Myeloma Working Group (2003b). The International Myeloma Working Group Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol; 121:749-57.

8. Lin R, Hu J, Paul S, et al (2009). Characteristics of thrombocytopenia in patients treated with oral panobinostat (LBH589). Blood (ASH Annual Meeting Abstracts); 114:2740.

9. Maiso P, Carvajal-Vergera X, Ocio EM et al (2006). The histone deacetylast inhibitor LBH589 is a potent antimyeloma agent that overcomes drug resistance. Cancer Res; 66(11):5781-5789.

10. Ocio EM, Villanova D, Atadja P, et al (2010). In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. Haematologica; 95(5):794-803.

11. Neymark N1, Kiebert W, Torfs K, Davies L, Fayers P, Hillner B, Gelber R, Guyatt G, Kind P, Machin D, Nord E, Osoba D, Revicki D, Schulman K, Simpson K. Eur J Cancer. 1998 Aug;34(9):1317-33.

12. Osoba D1, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.

13. Richardson PG, Sonneveld P, Schuster MW, et al. (2005). Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med; 352:2487-98.