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Clinical Development

LBH589 / Panobinostat / Farydak®

Oncology Clinical Protocol CLBH589DUS106 / NCT02720510

A Randomized, Phase II trial evaluating the efficacy and safety of lenalidomide, bortezomib and dexamethasone (RVD) with or without panobinostat in transplant eligible, newly diagnosed Multiple Myeloma

Authors	[redacted]
Document type	Oncology Clinical Study Protocol
EUDRACT number	Not applicable
Version number	00 (Original Protocol)
Development phase	II
Document status	Final
Release date	19-Jan-2016

Template version 19-Nov-2015

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ASCT	Autologus Stem Cell Transplant
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BTZ	Bortezomib
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
Dex	Dexamethasone
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
G-CSF	Granulocyte-Colony Stimulating Factor
HDAC	Histone Deacetylase
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
nCR	Near Compete Response
o.d.	omnia die/once a day
ORR	Overall Response Rate
p.o.	per os/by mouth/orally
PHI	Protected Health Information
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
REV	Revlimid
RP2D	Recommended Phase II Dose
RVD	Revlimid, Velcade, Dexamethasone
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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Protocol summary:

Title	A Randomized, Phase II trial evaluating the efficacy and safety of lenalidomide, bortezomib and dexamethasone (RVD) with or without panobinostat in transplant eligible, newly diagnosed Multiple Myeloma
Sponsor and Clinical Phase	Novartis Pharmaceuticals Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	In data presented at ASH 2015, the combination of RVD and panobinostat in newly diagnosed MM patients showed an ORR of 94%, with a 46% CR/nCR rate after 4 cycles. This marked improvement from historical data reporting CR/nCR rates of approximately 7% warrants further investigation of this combination in this population.
Primary Objective(s) and Key Secondary Objective	Primary Objective: To evaluate the efficacy of the combination of RVD + panobinostat compared to RVD alone Key Secondary Objective: To assess MRD negativity after 4 cycles of induction by next gen sequencing
Secondary Objectives	To assess best overall response rate (ORR) and MRD negativity after ASCT and maintenance To assess depth of response by IMWG criteria To assess the duration of response To assess overall survival and progression free survival at three years To assess the toxicity and tolerability
Study design	This is a multicenter, open-label, randomized phase II study which will enroll 112 newly diagnosed symptomatic multiple myeloma patients in a 1:1 fashion. Patients will be enrolled at approximately 20 centers in the United States. Patients will undergo stem cell mobilization with plerixafor plus G-CSF (according to investigator discretion) after 4 cycles of induction therapy. Study treatment interruption for stem cell collection may not exceed 30 days. All patients will receive one additional cycle of study treatment after stem cell collection and then proceed to autologous transplant using melphalan 200mg/m^2(140mg/m^2 for patients > 70 years), as conditioning. After ASCT, patients still on study will initiate maintenance therapy within the 60-120 day period following ASCT, provided they have adequate blood count and clinical recovery. Patients in the RVD arm will initiate maintenance therapy with lenalidomide alone, and patients in RVD-panobinostat arm will receive lenalidomide + panobinostat maintenance. Lenalidomide will be dosed orally at 10mg/day continuously in both arms, increasing to 15mg/day after the first 84 day cycle. Panobinostat will be dosed at 10mg three times a week, every other week. Total planned duration of maintenance therapy will be 3 years. Patients will remain on study treatment until they complete the maintenance phase, or until they experience disease progression, unacceptable toxicity, or at the discretion of the Investigator.
Population	Newly diagnosed Multiple Myeloma patients who plan to receive autologous stem cell transplantation.
Inclusion criteria	Patient must be newly diagnosed with multiple myeloma, based on IMWG 2014 definition (Rajkumar et al 2014) Patient must have measurable disease defined by at least 1 of the following conditions present at screening: • Serum M-protein by PEP ≥ 1.0 g/dL (≥ 10 g/L). • Urine M-protein by PEP ≥ 200 mg/24 hours.

[redacted]

	• Involved serum free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal. Patient has an ECOG performance status (PS) ≤ 2 Patient has the following laboratory values within 3 weeks before starting study drug: • Absolute neutrophil count (ANC) ≥ 1.0 x 109 /L • Platelet count ≥ 75 x 109 /L • Calculated creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula)
Exclusion criteria	Patient received prior treatment with DAC inhibitors including Panobinostat Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period) Patient who received: • prior anti-myeloma chemotherapy or medication • 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. Patient has not recovered from all therapy-related toxicities associated with above listed treatments to < grade 2 CTCAE. Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 month prior to screening), such as: • History of angina pectoris, symptomatic pericarditis, or myocardial infarction • Left Ventricular Ejection Fraction (LVEF) < 45% as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA) • History or presence of any cardiac arrhythmias, e.g. ventricular, supraventricular, nodal arrhythmias, or conduction abnormality • Complete left bundle branch block (LBBB), bifascicular block • Corrected QT (QTcF) ≥ 450 ms for males and females using Fridericia's correction on screening ECG (as average of triplicate ECGs) • History of documented congestive heart failure (New York Heart Association functional classification III-IV)
Investigational and reference therapy	Arm 1 – Lenalidomide, bortezomib, dexamethasone, panobinostat Arm 2 – Lenalidomide, bortezomib, dexamethasone
Efficacy assessments	• Serum and urine sample collection for central and local M-protein assessment by PEP, and IF • Serum sample collection for FLC assessment • Cytogenetics in bone marrow by local assessment • Plasma cell count in bone marrow by local assessment • Additional central response assessments in bone marrow (MRD) • Assessment of soft tissue plasmacytoma • Imaging assessment by CT/MRI/PET • Full body skeletal survey • Response assessment by Investigator
Safety assessments	• Physical examination • Vital signs • Height and weight • Performance status • Laboratory evaluations

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	• Hematology • Chemistry • Electrolytes • Thyroid • Coagulation • Troponin I • Creatinine Clearance • Pregnancy and assessments of fertility • Electrocardiogram • MUGA/ECHO
Data analysis	The sample size of the study is based on the assumption that in the RVD alone arm the nCR/CR rate will be 7% and adding Pano to RVD will improve the nCR/CR rate to 25%. For one sided alpha=0.05, fifty patients in each arm will have 81% power to detect this improvement. The primary endpoint will be analyzed based on nCR/CR rate of the combination of panobinostat with bortezomib, lenalidomide and dexamethasone (P-RVD) vs RVD in newly diagnosed multiple myeloma patients after 4 cycles of therapy. The analysis will be based on Investigator assessment of response.
Key words	Myeloma, bortezomib, lenalidomide, dexamethasone, newly-diagnosed, panobinostat

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Multiple myeloma (MM) is a malignant proliferation of plasma cells which accounts for 10% to 15% of all hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow in adults. Approximately 24,000 people in the US will receive a new diagnosis of MM in 2014 (Howlader et al 2014). Despite a survival that improved from 45 to 60 months after the introduction of newer therapies (particularly proteasome inhibitors and immunomodulatory drugs, commonly called "IMiDs", often used in combination with dexamethasone), all patients ultimately progress and the disease remains incurable (Kumar et al 2014).

MM is characterized by excessive proliferation of plasma cells resulting in production of monoclonal proteins, which can lead to end-organ damage. The hallmarks of MM are bone marrow failure, renal failure, and bone disease. Symptoms related to bone marrow dysfunction include anemia, decreased white blood cells leading to increased susceptibility to infection, and decreased platelet counts leading to increased susceptibility to bleeding (Rajkumar 2013). Patients with MM suffer from bone pain and fractures as a result of osteolytic lesions. They also suffer from the symptoms and complications of renal failure which further contribute to worsening anemia. These signs and symptoms are commonly denoted as CRAB (Calcium elevation, Renal dysfunction, Anemia, Bone destruction) (Rajkumar 2013).

A feature of MM that is thought to contribute to recurrent relapses and disease persistence is the presence of multiple malignant clones from the time of initial diagnosis onwards (Egan et al 2012). Such clonal heterogeneity has been demonstrated with several methods including whole genome sequencing (WGS) on patient tumor samples followed longitudinally from the point of initial diagnosis (Egan et al 2012).

Overall Goals of Therapy of Induction Therapy in NDMM

Given the clonal heterogeneity of MM in its initial stages, standard therapy for newly diagnosed MM (NDMM) has traditionally employed combination therapy with multiple drugs having different mechanisms of action, with the intent to maximally cytoreduce the disease, and achieve deep responses to induction therapy (Rosinol et al 2014). The preferred therapeutic program for NDMM involves combination induction therapy followed by autologous stem cell transplantation (ASCT), followed by prolonged maintenance therapy to maintain disease control and prolong remissions (Rajkumar 2013). The overall goal of induction therapy and ASCT in NDMM is to achieve maximal reduction of tumor burden, as measured by both M-protein reduction and plasma cell clearance in the marrow (Lonial et al 2014). Additional more sensitive tools to measure depth of response include minimal residual disease (MRD) assessment using multi-color flow cytometry and ASO-PCR (Lonial et al 2014).

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Achieving deep responses (defined as nCR/CR by mEBMT criteria and >VGPR by IMWG criteria) strongly correlated with PFS and overall survival in several randomized studies of frontline therapy in NDMM (Lahuerta et al, Gertz et al, Moreau et al, Alegre et al). The incorporation of ASCT in the era of conventional chemotherapy increased the rates of CR in patients with NDMM, which translated into improved PFS in most randomized studies (Cavo et al 2010, Kumar et al 2012, Wang et al 2010, Ladetto et al 2010), but these regimens were limited to younger more fit patients who were eligible for high dose therapy. In a meta-analysis of 21 studies in NDMM (10 prospective and 11 retrospective) totaling 4,990 patients, highly significant associations between maximal response and outcomes were noted. Specifically, maximal response post-ASCT was associated with prolonged OS (P<0.0001), and prolonged TTP/PFS/EFS (P<0.00001) (Channan Khan et al 2010) Furthermore, durability of deep responses is also an important predictor of overall survival. In a retrospective analysis by Barlogie et al of patients enrolled in a total therapy 2 (TT2) study, median OS was significantly longer (not reached) in patients who sustained CR for > 36 months compared to the non-CR group (5.6 years) and those who lost CR before 36 months (1.6 years) (Barlogie et al 1999).

Prior to the advent of novel therapies in multiple myeloma, achieving deep responses with induction therapy alone was not common, and therefore, meaningful measurements of the impact of depth of response on outcomes were available primarily in patients undergoing ASCT (Lonial et al 2014). However, there were trends toward improved survival in those patients who achieved deep responses to pre-transplant induction therapy alone, although the association was less robust. In subsequent studies of induction therapies employing novel agents, the association between quality of response and PFS/OS continued to hold, even in older patients who were able to better tolerate the novel agents compared to traditional chemotherapy. In a meta-analysis of phase 3 bortezomib trials totaling 2086 transplant-eligible patients, the improved quality of responses with bortezomib regimens (> VGPR and CR) corresponded to improvements in PFS and OS (Nooka et al 2011).

An additional important factor with induction therapy that impacts survival outcomes is time to achieving CR. Compelling evidence has emerged from several randomized studies that improved outcomes are associated with response quality at each treatment stage (post-induction, post-transplant, post-consolidation, etc). In a large phase 3 study (IFM 2005-01), in which 482 patients were randomized to bortezomib vs. non-bortezomib based induction therapy, PFS was significantly longer for patients achieving VGPR post-induction compared to post-transplant (median 41.1 months vs. 31.1 months) (Moreau et al 2011). Importantly, achieving < VGPR overall and post-induction were negative prognostic factors in the multivariate analysis. Table 1-3 shows the differences in outcomes based on quality of response post- induction therapy across various studies comparing induction regimens for transplant-eligible patients with NDMM. In a meta-analysis of 21 studies in NDMM patients undergoing ASCT, post-induction response was strongly associated with OS (P=0.0015) and TTP/PFS/EFS (P<0.00001) (Channan Khan et al 2010). Together, these data demonstrate the importance of achieving deep responses early with induction therapy, in order to allow subsequent treatment stages to further deepen and maintain the response, and maximize PFS and OS.

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Table 1-1 Prognostic impact of response level post induction in patients with newly diagnosed multiple myeloma undergoing autologous transplant

Reference	Treatment	Response	N	PFS/EFS	OS
Lahuerta et al	GEM2000→ASCT →IFN+prednisone	CR nCR PR SD	101 96 346 63	53% (5 yr EFS) 49% 34% 33%	78% (5 yr) 65% 63% 56% (p 0.02 CR vs. SD)
Dytfeld et al	VDD ± ASCT	≥VGPR < VGPR	16 14	77.8% (4 yr PFS) 53.8% (p<0.05)	92.9% (4yr) 64.3% (p : 0.027)
Gertz et al	T or R regimen→ASCT	PR <PR	232 54	22.1 mo (mPFS) 13.1 mo (p<0.001)	73.5 mo (mos) 30.4 mo (p<0.001)
Moreau et al	VD or VAD ± DCEP →ASCT	≥VGPR <VGPR	125 357	41.2 mo (mes) 29 mo (p<0.0001)	---
Allègre et al	HD-ASCT ± IFN main	CR PR SD	56 153 25	35 mo. (MPs) 28 mos. 20 mo (p<0.001 CR/PR vs. SD)	39 36 24 (p<0.001 CR/PR vs. SD)
Galli et al	Total therapy 1	CR ≥VGPR PR/SD SD	17 29 81 18	65% (5yr EFS) 54% 24% 27% (p : 0.025 CR vs.< CR)	63% 63% 47% 56% (p : 0.31 CR vs < CR)

Minimal residual disease (MRD) assessment

As quality of response to induction therapy improve with combination regimens employing novel agents, more sensitive tools to measure minimal residual disease (MRD) have evolved. These further stratify CR into immunophenotypic CR (iCR) and molecular CR (mCR) (Lonial et al 2014). Immunophenotypic CR assessment employs multiparametric flow cytometry with fluorescent antibodies against multiple plasma cell proteins to characterize and quantify plasma cell burden in the bone marrow with high sensitivity, ranging from 10^{-4} to 10^{-6} (Paiva et al 2011). Molecular CR is assessed with allele specific oligonucleotide PCR, using primers directed against the variable heavy chain gene sequence specific to the tumor cells (Martinez-Sanchez et al 2008), providing the ability to assess MRD with very high sensitivity using peripheral blood samples (Martinez-Sanchez et al 2008). More recently, next generation sequencing based platforms have also been used to molecularly quantify MRD (Mahindra et al 2012, Munshi et al 2013).

The prognostic utility of MRD measurement with these tools has been demonstrated in several studies in NDMM. In a prospective analysis of nearly 300 NDMM patients treated with the GEM2000 protocol, assessment of iCR (sensitivity 10^{-4}) was done at day 100 post-transplantation. 147 patients had achieved CR, with 58% MRD positive and 42% MRD negative (iCR). Both PFS and OS were significantly longer for the MRD negative patients; median PFS 71 vs. 31 months (p<0.001) and 5 year OS 80% vs. 62% (p=0.002), respectively (Paiva et al 2008). The benefit was independent of immunofixation status (nCR/CR). However, patients who had both CR (IFE negative) and iCR (MRD negative) had a 5 year PFS and OS rate of 62% and 87% respectively. In contrast, MRD positive patients in CR had

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corresponding 5 year PFS and OS rates of 30% and 59%, respectively. Another study, IFM, in which patients with NDMM received RVD induction, ASCT, followed by RVD consolidation, iCR rates were assessed using 7 color flow cytometry (sensitivity 10^{-5}) at the completion of each stage of therapy. Estimated 3 year PFS for those patients who achieved iCR was 100%, compared to 77% for all patients (Roussel et al 2014).

MRD assessment by nested PCR has also been shown to be a reliable predictor of PFS in some studies. In a study of consolidation therapy with bortezomib, thalidomide, and dexamethasone (VTD) in patients with NDMM who completed ASCT, 39 patients who achieved $\geq$VGPR with ASCT were analyzed by nested PCR (sensitivity 10^{-5}) to evaluate mCR in addition to CR (Ladetto et al 2010). After VTD consolidation therapy, CR and mCR improved to 49% and 18%, from 15% and 3% before consolidation, respectively. All patients who achieved mCR were relapse free after a median follow up of 42 months, while 11 patients with MRD positivity relapsed (Ladetto et al 2010). Recently, MRD assessment using a commercially available next generation sequencing (NGS) platform (ClonoSEQ™ assay, Adaptive Biotechnologies) was evaluated in several studies (Faham et al 2012, Martinez-Lopez et al 2014). MRD negativity by NGS was prognostic of both time to progression (median 80 vs. 31 months, $p<0.0001$) and OS (median not reached vs. 81 months, $p=0.02$) (Martinez-Lopez et al 2014). Together, these data demonstrate the role of MRD negativity (as defined by iCR and mCR), as a clinically meaningful endpoint in NDMM, in light of very compelling evidence of its utility as a surrogate marker for PFS, TTP, and OS.

Evolution of Induction Therapy for Myeloma

Induction therapy for patients with newly diagnosed myeloma has changed dramatically over the past 20 years. After the initial observation that melphalan and prednisone was an active combination for patients with myeloma, further combinations were tested incorporating agents such as BCNU, vincristine, doxorubicin, and cyclophosphamide. While it was determined in small phase II studies that these more aggressive combination regimens had a higher response rate, the incidence of true CR, using our current definitions, were quite low (Figure 1-1) and toxicity associated with these combinations was quite high (Myeloma Trialists collaborative Group 1998). In this setting, the higher response rate seen with older regimens was not associated with a survival advantage due in large part to toxicity, and an inadequate definition of complete response (CR was defined as a 75% reduction in the m-protein, a measure that now would be considered a partial response). It was around this time that several groups were beginning to explore the potential benefit of high dose therapy with melphalan and autologous bone marrow transplant as a treatment modality for relapsed myeloma, and then demonstrated that there were patients who appeared to have durable and long term remissions with this therapy. For most of these patients, the durable responses were associated with the achievement of complete responses (Bensinger 2008). The IFM 94 trial established the benefit of HDT, where patients were randomized to receive either HDT or conventional chemotherapy (Attal et al 1996). What was gleaned from those original trials of HDT was the observation that patients who enjoyed the longest duration of remission and overall survival appeared to have achieved the best responses following HDT; ie, patients in CR appeared to gain more benefit from HDT than those who did not (Alvarez et al 2005, Alexanian et al 2001, Wang et al 2008). *However, patients achieving a CR as currently*

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defined are not cured. Thus improved definitions and treatments are needed to better quantify and eradicate the malignant plasma cell clone.

Figure 1-1 Complete Response Rates in Upfront Myeloma

Upfront Therapy in MM
Traditional Therapy Sub-optimal

Study	N	Regimen	CR/ nCR	CR+ PR	Stem Cell Harvest	Reference
Rajkumar	100	Dex	0%	50%	Yes	JCO 2008
Goldschmidt	203	VAD	3%	63%	Yes	ASH 2005
Rifkin	97	DVd	3%	43%	Yes	Cancer 2006
IFM90	100	VMCP	5%	52%	Yes/No	NEJM 1996
Palumbo	126	MP	7%	48%	No	Lancet 2006

Figure: Response rate for conventional agents as induction therapy for myeloma. While the overall response rate has improved with newer therapies, the CR rate remains low and requires high dose therapy as consolidation in order to achieve durable remissions and CRs, which are then associated with improved overall survival.

Randomized Comparison of Conventional vs. High Dose Therapy

		Patients (n)	CR (%)	EFS (median, mo)	OS (median, mo)
Attal *NEJM 1996*	Conv	100	5	18	37
	HDT	100	22	27	52
Barlogie *JCO 2006*	Conv	255	-	14% at 7 yrs	38% at 7yrs
	HDT	261	-	17% at 7 yrs	38% at 7yrs
Fermand *Blood 1998*	Conv	91	-	13	24
	HDT	94	-	39	64.6
Blade *Blood 2001*	Conv	83	11	34.3	66.9
	HDT	81	30	42.5	67.4
Child *NEJM 2003*	Conv	200	8.5	19.6	42.3
	HDT	201	44	31.6	54.1

The next major step in the treatment of transplant eligible patients was the development of thalidomide, which demonstrated significant activity in the setting of relapsed myeloma, and was identified as an active agent when combined with dexamethasone in the induction setting as well. Rajkumar and colleagues in ECOG performed a randomized trial comparing thalidomide and dex (TD) versus dex alone (D) and demonstrated a higher overall response rate, without the need for IV access or hospitalization for these patients (Rajkumar et al 2008, Rajkumar et al 2002, Rajkumar et al 2006). While the data from the ECOG trial demonstrated an improvement in overall response, the CR rate remained low (<10%) and thus patients who received induction therapy with TD still required some HDT in order to enhance the CR rate and improve overall survival (OS) (Rajkumar et al 2008). A paper from a group of patients who did not undergo HDT but received either TD or D alone as induction demonstrated a median overall survival of 3 years for the TD arm, further supporting the observation that achievement of CR results in improved OS, and that the goal of induction therapy should be to enhance CR rates (Rajkumar et al 2008). Most recently, a randomized French trial compared patients who received either VAD or TD as induction therapy, and demonstrated that while the overall response rate was higher for the TD group, there was no difference in post-transplant outcomes (Macro et al 2006). *These data in aggregate suggest that induction regimens that do not induce a high CR rate require HDT in order to achieve a CR, which is then associated with a survival advantage (Blade et al 2005).*

Lenalidomide based induction

Induction therapy utilizing the immunomodulatory derivative of thalidomide, lenalidomide was based upon encouraging data seen in the relapsed/refractory setting using the combination of lenalidomide and dexamethasone (Weber et al 2007, Dimopoulos et al 2007). Rajkumar and colleagues from the Mayo Clinic initially reported in a small pilot study of lenalidomide

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and dexamethasone as induction therapy with an overall response rate of 91% and a VGPR or better rate of 31% (Rajkumar et al 2005). The CR/nCR rate from the initial analysis of this study was 11%, and with longer follow up improved to 18% with 54% of patients achieving a VGPR or better (Lacy et al 2007).

Two large randomized trials were conducted to evaluate the benefit of Len/dex in newly diagnosed myeloma. The ECOG E4A03 trial, which randomized 445 patients to receive either lenalidomide/high dose dexamethasone (LD) or lenalidomide/low dose dexamethasone (Ld) demonstrated that while there was more toxicity within the LD arm, the overall response rate for LD was superior to Ld (82% vs 70%, $p<0.05$) (Table 1-2) (Siegel et al 2010). There was no difference in progression free survival between the 2 arms, and while overall survival continued to favor the Ld arm, for patients younger than age 65, there was real difference in OS with a higher response rate for LD.

Table 1-2 Best Responses with high vs low dose dexamethasone

	ORR (CR+PR)	>VGPR	CR/nCR
ECOG E4A03	**LD vs Ld**	**LD vs Ld**	**LD vs Ld**
Response in 4 cycles	82% vs 70%	44% vs 26%	
Best Response	82% vs 71%	53% vs 42%	
SWOG S0232	**LD vs D**	**LD vs D**	**LD vs D**
Best response	84% vs 53%		22% vs 4%

Table 1-2: Response rates for 2 large phase III trials using lenalidomide as induction therapy demonstrates high overall and CR rate following 4 cycles of induction therapy.

The SWOG group evaluated LD vs high dose dexamethasone alone (LD vs D, SWOG S0232 trial). Similar to the ECOG trial, the overall response rate for LD was 84%, with 22% of patients achieving a CR (Zonder et al 2007). Clearly LD is an active induction regimen with reasonable safety and a high overall response rate. Data from most trials in aggregate suggest that 45-55% of patients achieve a VGPR or better, and around 22% of patients achieve a CR from lenalidomide and dexamethasone, with a lower overall response rate seen with a lower dose of dexamethasone.

Bortezomib based induction

The initial experience with bortezomib as induction therapy for myeloma came from Jagannath and colleagues who evaluated the response rate for bortezomib with or without dexamethasone as induction therapy (Jagannath et al 2005). The overall response rate from this trial was 88% with 25% of patients achieving a CR/nCR. Richardson and colleagues presented data in a trial that we joined them on using single agent bortezomib with an overall response rate of 45% and 10% of patients achieving a CR/nCR (Anderson et al 2006).

Two phase III trials were performed evaluating the effects of bortezomib based inductions. The first was from Harousseau and colleagues in which 482 patients were randomized to receive either VAD or velcade/dex (VD) as induction therapy (Harousseau et al 2007). Patients then went on to receive a single course of high dose therapy and autologous transplant. After the completion of induction therapy, the overall response rate for the VAD

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arm was 62.8% compared with 80% following VD induction (p<0.001, Table 1-3). Following high dose therapy and autologous transplant, the proportion of patients who achieved a VGPR or better rate continued to favor VD over VAD (61.7% vs 41.7%, p<0.001). Importantly, this benefit in depth of response occurred independent of the presence of an elevated β2M or adverse cytogenetic risk groups (Jagannath et al 2007, Sagaster et al 2007).

In another similarly large phase III study from an Italian group, Cavo and colleagues presented a randomized trial comparing VTD (velcade, thalidomide and dexamethasone) vs TD (thalidomide and dexamethasone) as initial therapy (Cavo et al 2007). Following primary therapy, the overall response rate clearly favored the 3 drug combination over the 2 drug combination (Table 1-3), with 36% of patients achieving either a complete response or near complete response (CR/nCR). Again, response to induction was found to be independent of adverse prognostic factors such as the presence of deletion of chromosome 13 or the presence of (4:14).

Both the Italian and French randomized studies are very important as they are the first examples of studies where the choice of induction therapy had a positive effect on post-transplant outcomes (Table 1-3). Clearly more follow up is needed to evaluate the TTP and effects on OS for this approach, but given that OS and TTP have mirrored the CR rate for most transplant based trials, it appears that the addition of newer agents will impact not only the quality of response (higher CR), but may also impact survival. *However, it still appears that the CR rate following induction therapy is suboptimal, suggesting that alternative induction regimens that induce a higher CR rate and take advantage of potential mechanisms of synergy are clearly needed.* **Bortezomib or lenalidomide with dexamethasone are not sufficient**.

Table 1-3 Overall response rate by Induction therapy

	ORR (CR+PR)	**>VGPR**	**CR/nCR**
Harousseau et al	**VAD vs VD**	**VAD vs VD**	**VAD vs VD**
Induction	62.8% vs 80%	18.6% vs 46.7%	8.3% vs 21.3%
Post-Transplant	72.8% vs 89.4%	41.7% vs 61.7%	23.6% vs 35%
Cavo et al	**TD vs VTD**	**TD vs VTD**	**TD vs VTD**
Induction	80% vs 93%	27% vs 60%	9% vs 36%
Post 1st Transplant		54% vs 77%	28% vs 57%
Table 1-3: Response rates for 2 large phase III trials using bortezomib as induction therapy demonstrates high overall and CR rate following 4 cycles of induction therapy.			

The combination of bortezomib with lenalidomide is a strategy supported by preclinical data suggesting that the combination of an immunomodulatory agent with bortezomib is at least additive in killing plasma cells (Mitsiades et al 2002, Richardson et al 2006), and the clinical observation that the combination of lenalidomide and bortezomib is very active in the relapsed disease setting (Richardson et al 2007). Data on the RVD combination in newly diagnosed patients demonstrated an overall response rate of 98%, with 52% of patients achieving a VGPR or better. An update of this data where all 62 patients were evaluable for response demonstrated an overall response rate of 100% in the maximal planned dose cohort,

[redacted]

with 70% of patients achieving a VGPR or better, and 22% achieving a CR at the maximum planned dose (Richardson et al 2008). This makes RVD one of the most active induction regimens that has been tested, and sets a new standard against which future regimens are compared. Furthermore, this trial was a result of preclinical science that predicted the synergistic CR and overall response rate for the combination. Despite the high response rate to RVD therapy, the rate of nCR/CR after 4 cycles of induction therapy with this regimen is low (6% to 7%), as reported in several studies (Richardson et al 2008, Kumar et al 2012). High quality responses are only achieved with prolonged courses of induction therapy (averaging 6 to 8 cycles).

The introduction of drugs with novel mechanisms of action including HDAC inhibitors and others, affords the opportunity to deliver more effective combination therapies in frontline treatment of MM, with the potential to achieve maximal cytoreduction and deep clinical responses with significantly shorter courses of induction than with regimens currently used. This can decrease the risk of adverse events associated with prolonged courses of combination therapy, and potentially minimize the biological emergence of resistant clones owing to decreased time for clonal evolution. Given the mounting clinical evidence supporting the role of achieving early deep responses as a surrogate for improved PFS and OS, there remains a need for novel induction regimens that result in high CR rates early into the course of induction therapy for NDMM.

Maintenance therapy in NDMM

The efficacy and safety of maintenance therapy with both PIs and IMIDs after maximal cytoreduction has been studied in several studies. In general, randomized studies have demonstrated improved PFS (Mccarthy et al 2010, Palumbo et al 2012, Attal et al 2012) and OS (Mccarthy et al 2010) with lenalidomide maintenance. Maintenance therapy with low dose lenalidomide after induction/ASCT has demonstrated improved PFS and OS in patients with newly diagnosed multiple myeloma. In the Cancer and Leukemia Group B (CALGB) 100104 study, 462 multiple myeloma patients were randomized to lenalidomide 10 mg daily or placebo after single autologous HCT. The median time to progression (TTP) was 46 months for the lenalidomide arm and 27 months for the placebo arm ($P < .001$). At a median follow-up of 34 months, the 3-year OS rates were 88% for the lenalidomide arm and 80% for the placebo arm ($P = .028$). A total of 23 out of 231 patients (10%) on lenalidomide arm discontinued maintenance due to adverse events. In the Intergroupe Francophone du Myélome (IFM) 05-02 study, 605 myeloma patients were randomized to lenalidomide 10 mg daily versus placebo until disease progression after single or tandem autologous HCT The median PFS was 41 months for the lenalidomide arm and 23 months for the placebo arm ($P < .001$). The OS was 74% for the lenalidomide arm and 76% for the placebo arm ($P = .7$) at a median follow-up of 45 months. A total of 83 patients (27%) discontinued lenalidomide due to adverse events. Fixed duration of maintenance therapy with lenalidomide was studied in a recent trial conducted by the IFM in newly diagnosed patients who received RVD induction, ASCT, and consolidation followed by one year of lenalidomide maintenance. Three year PFS and OS reported in this study were 77% and 100%, respectively.

Borezomib has also been studied as a maintenance therapy in NDMM patient who underwent ASCT. In a phase 3 study of 827 patients with NDMM randomized to induction with VAD or bortezomib, doxorubicin, dexamethasone (BDD) followed by ASCT, patients were assigned

to maintenance with thalidomide (VAD arm) or bortezomib (BDD) arm (Sonneveld et al). The CR rate overall were 24% and 36% for the VAD and BDD arms respectively. Maintenance therapy with thalidomide and bortezomib improved the responses in 24% and 23% of patients, respectively. Median PFS was 28 months in the VAD vs. 36 months in BDD arm, respectively.

While studies of maintenance therapies have shown that responses can be deepened after induction and ASCT with low dose continuous therapy, and lead to improved PFS and OS, the optimal duration of maintenance therapy is still unclear. Ideally, one should balance the overall PFS and OS benefits of maintenance therapy with the risk of accumulated toxicity associated with continuous exposure to drugs commonly used in maintenance, including PIs and IMIDs. Lenalidomide maintenance was associated with increased toxicity compared to placebo in randomized studies, with higher grade 3/4 hematologic toxicity (48% vs. 17%, $p<0.001$) and secondary malignancies (8% vs. 3%, $p=0.008$) (Mccarthy et al 2012). Nevertheless, the PFS and OS benefits realized with continuous therapy in large phase 3 studies, particularly in high risk disease subgroups, support the practice of continuing maintenance until disease progression (Mccarthy et al 2012).

As rates of MRD negativity with induction and transplant improve with the addition of novel therapies in the newly diagnosed setting, finite duration of maintenance therapy is being explored in ongoing studies. In the phase 2 IFM study by Roussel et al, in which patients discontinue lenalidomide maintenance after 1 year, median PFS and OS are 77% and 100%, respectively (Roussel et al 2014). Longer term follow up is required before meaningful comparisons can be made with studies employing treatment until relapse/progression model. Nevertheless, the strategy of finite maintenance duration is feasible and needs to be further explored, particularly in patients who are in iCR/mCR, to better understand the optimal duration of such therapy in the setting of disease undetectable by such sensitive methods.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Panobinostat

Panobinostat (LBH589) belongs to a structurally novel cinnamic hydroxamic acid class of compounds and is a pan-inhibitor of Class I, II, and IV histone (and non-histone) DACs (HDAC) which are epigenetic modulators and important cancer targets due to the dysregulation of these enzymes in many types of tumors. DAC enzymes also target lysine groups on various non-histone proteins such as p53, α-tubulin, Hsp90, and HIF1-α; thus panobinostat is also referred to as a pan-DAC inhibitor.

Through its effects on histone acetylation and gene expression, as well as on the oncogenic function of non-histone proteins such as Hsp90, panobinostat offers a multifaceted approach for the inhibition of cancer cell proliferation and survival. Panobinostat is highly effective at inhibiting the HDAC activity of the majority of class I, IIa, IIb, and IV isoforms at low nanomolar concentrations, and is the most potent pan-HDAC inhibitor developed to date, including those which already received regulatory approval in indications other than MM in select countries, including the US.

[redacted]

Panobinostat (Farydak®) has received approval from the FDA in Feb 2015 for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

1.2.1.1 Non-clinical experience

In multiple models, panobinostat has been shown to impact several pathways that are critical to the biology of MM. These include the up-regulation of cyclin-dependent kinase inhibitor p21 leading to cell-cycle arrest and apoptosis, the disruption of the signaling pathway between MM cells and bone marrow stromal cells, and the inhibition of the aggresome protein degradation pathway by hyperacetylation of α-tubulin.

It has been demonstrated that panobinostat is effective as a single agent in multiple *in-vitro* and *ex-vivo* experiments, including in cells known to be resistant to standard of care agents. The combination of bortezomib and panobinostat has been shown to be synergistic in *in-vitro* and *in-vivo* models of MM (Ocio et al 2010). The combination of these two agents results in a synergistic inhibition of the unfolded protein response pathways (aggresome, proteasome) which are particularly relevant to MM.

1.2.1.2 Clinical experience

The FDA approval of panobinostat for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent received in Feb 2015 was primarily based on data from a large, double-blind, placebo-controlled Phase III study [CLBH589D2308] of panobinostat in combination with bortezomib and dexamethasone (PAN arm) compared to placebo in combination with bortezomib and dexamethasone (PBO arm) in 768 relapsed or relapsed and refractory MM patients (excluding bortezomib-refractory patients) with a primary endpoint of progression free survival (PFS) (San Miguel et al 2014).

Additional data included results from a supportive Phase II study [CLBH589DUS71] in 55 relapsed and bortezomib-refractory MM patients who received at least 2 prior lines of therapy including an IMiD (Richardson et al 2013), as well as safety and efficacy data from Phase Ib study [CLBH589B2207] (San Miguel et al 2013).

Studies B2201, B2202, B2203, B2211, B2101 and B2102 evaluated panobinostat as a single agent in patients with other hematological malignancies and solid tumors and provide additional information on the general safety profile at the relevant dose of 20 mg.

The pharmacokinetic profile of panobinostat has been characterized in a total of 14 single-agent clinical trials conducted in patients with various hematologic malignancies and solid tumors.

The registration Study D2308 met its primary objective, demonstrating a statistically significant and clinically important reduction in the risk of progression or death of 37% with PAN+BTZ+Dex over the standard regimen of PBO+BTZ+Dex (hazard ratio [HR] 0.63; 95% Confidence Interval [CI]: 0.52, 0.76; p <0.0001). Median progression free survival was significantly longer in the panobinostat group than in the placebo group (11·99 months [95% CI 10·32–12·94] vs 8·08 months [7·56–9·23]; hazard ratio [HR] 0·63, 95% CI 0·52–0·76; p<0·0001). The proportion of patients achieving an overall response did not differ between

[redacted]

treatment groups (235 [60·7%, 95% CI 55·7–65·6] for panobinostat vs 208 [54·6%, 49·4–59·7] for placebo; p=0·09); however, the proportion of patients with a complete or near complete response was significantly higher in the panobinostat group than in the placebo group (107 [27·6%, 95% CI 23·2–32·4] vs 60 [15·7%, 12·2–19·8]; p=0·00006). Final overall survival data are available and although there was a trend toward the Median overall survival was 40.8 months (95% CI35.0-44.8–) for the panobinostat group and 35.8 months (29.0-40.6) for the placebo group (HR 0.94, 95% CI 0.78–1.14; p=0.5435) (San Miguel et al 2015).

Consistent benefit was also shown in the Phase II study DUS71 in a more advanced and heavily pre-treated patient population with an ORR of 34.5% (1 near-complete response and 18 partial responses). An additional 10 patients achieved minimal response, for a clinical benefit rate of 52.7%. Progression-free survival was 5.4 months (Richardson et al 2013).

In study D2308, patients who received PAN+BTZ+Dex generally experienced more adverse events (AEs) than patients receiving PBO+BTZ+Dex. This increase in AEs was not unexpected given the overlapping safety profiles of panobinostat and bortezomib, including myelosuppression, fatigue and gastrointestinal (GI) toxicity.

The 3 most frequent severe categories of events were blood disorders, GI toxicities, metabolism disorders and infections and infestations.

- The rate of grade 3/4 thrombocytopenia laboratory abnormalities was higher in the PAN arm (67.4% vs. 31.4%). In this context, the rate of grade 3/4 hemorrhage (mostly GI) was low in both arms (4.2% vs. 2.4%). Thrombocytopenia AEs led to discontinuation in 1.6% and 0.5% of patients in the PAN and PBO arms, respectively.
- GI toxicities were more common in the PAN arm than in the PBO arm, mostly due to diarrhea (grade 3/4: 25.5% vs. 8%), nausea (grade 3/4: 5.5% vs. 0.5%), and vomiting (grade 3/4: 7.3% vs. 1.3%). Diarrhea was a reason for treatment discontinuation in 4.5% and 1.6% of patients in the PAN and PBO arms, respectively.
- The rate of grade 3/4 infections was higher in the PAN arm (31.2% vs. 23.9%). These grade 3/4 infections were primarily pneumonia and sepsis. These severe infections were preceded by a severe neutropenia in only 20% of patients. Patients in the PAN arm experienced more severe neutropenia, but few were grade 4 (6.6% vs. 2.4%). Febrile neutropenia were infrequent (1.0% vs. 0.5%).
- Elderly patients (≥ 65 years) generally had a higher level of toxicity compared to younger patients, in particular for severe (grade 3/4) thrombocytopenia (72.5% vs. 56.6%), diarrhea (31.3% vs. 21.3%) and asthenia/fatigue (48.1% vs. 18.1%).

Thirty patients (7.9%) in the PAN arm died on treatment compared to 18 (4.8%) in the PBO arm. The primary causes of death were disease progression (1.0% vs. 1.6%) and AEs (6.8% vs. 3.2%) in the PAN vs. PBO arms. The main causes of these deaths included infections and hemorrhages. The cases were complex and confounded by the natural history of the disease and concurrent comorbidities.

In a more advanced and heavily pretreated population, the safety data from studies DUS71 and B2207 were consistent with the Phase III Study D2308. In study DUS71, 18% patients discontinued therapy because of an AE suspected to be study treatment related, and there was only one (1.8%) on-treatment death due to AE (a multi-organ failure).

[redacted]

2 Rationale

2.1 Study rationale and purpose

In patients with newly diagnosed multiple myeloma, rapid attainment of good quality response (nCr/CR) is critical, as achieving deeper responses earlier in the course of therapy has been shown to correlate with improved PFS and OS. Furthermore, achieving MRD negativity with frontline therapy, as measured by iCR and mCR, is an important predictor of long term progression free survival[9].

Rates of CR with currently used combination regimens including RVD and more recently, Carfilzomib-lenalidomide, dexamethasone (KRD) are less than 13% at the completion of induction therapy with 4 cycles (Richardson et al, Zimmerman et al). High quality responses with these regimens are only achieved with prolonged courses of induction therapy (averaging 6 to 8 cycles) (Richardson et al) or induction therapy followed by ASCT and consolidation (Zimmerman et al 2014). Accordingly, there remains a need for novel induction regimens that result in high CR rates early into the course of induction therapy for NDMM.

The introduction of drugs with novel mechanisms of action including HDAC inhibitors and others, affords the opportunity to deliver more effective combination therapies in frontline treatment of MM, with the potential to achieve maximal cytoreduction and deep clinical responses with significantly shorter courses of induction than with regimens currently used. This can decrease the risk of adverse events associated with prolonged courses of combination therapy, and potentially minimize the biological emergence of resistant clones owing to decreased time for clonal evolution.

The dramatic improvement in nCR/CR rates seen with panobinostat in the relapsed/refractory setting[6] suggest equal or improved rates of nCr/CR in the newly diagnosed setting. The combination of bortezomib/lenalidomide/dexamethasone (RVD) with the addition of Panobinostat in newly diagnosed myeloma patients has been studied in a phase I trial. The RP2d from this study was panobinostat 10mg administered 3 times a week 2 weeks on/1 week off with full dose RVD (bortezomib administered on twice weekly on day 1, 4, 8, 11). The toxicity limiting higher doses of panobinostat was limited to diarrhea (which resolved with supportive care). Importantly, interim results, presented at ASH 2015, showed nCR/CR rate of 46%, compared to historical nCR/CR rate of <10% after 4 cycles of RVD alone.

Given the important role of maintenance therapy in deepening responses post-induction and AST, and prolonging PFS and OS, combination maintenance therapy with novel drugs like panobinostat may further improve these clinical endpoints, particularly in the setting of high risk disease. In a recent phase 2 study, panobinostat was shown to be safe and efficacious when added to full dose lenalidomide-dexamethasone in patients with relapsed/refractory myeloma. Results published at ASH 2015 from 26 patients on this study showed an ORR of 38% and CBR of 73% in a highly refractory group of patients (85% len refractory, 35% pom refractory, 54% bortez refractory, and 23% Carfilzomib refractory). Grade 3/4 toxicities (regardless of drug attribution) were primarily hematologic, with neutropenia, thrombocytopenia, and anemia noted in 40%, 23%, and 4% respectively13. Grade 3/4 nonheme AEs included infections in 5 (1 while neutropenic), 3 diarrhea (transient), 4 fatigue & 1 pulmonary embolus and 1 pt each with: neck pain, QTc prolongation & weight loss 13.

[redacted]

In light of the dramatic improvements in nCR/CR rates after induction with RVD-panobinostat reported in the single arm phase 1 study by Shah et al, we propose to conduct a phase 2 open-label randomized study comparing RVD with RVD+panobinostat induction in patients with newly diagnosed multiple myeloma who are transplant eligible. Based on evidence from phase 1b and 2 studies supporting the safety and clinically meaningful efficacy of lenalidomide+panobinostat in RRMM, patients who complete induction and transplant will proceed to maintenance therapy for three years with lenalidomide or lenalidomide+panobinostat.

2.2 Rationale for the study design

This is a multicenter, open-label, randomized phase II study which will enroll 112 newly diagnosed symptomatic multiple myeloma patients in a 1:1 fashion. Patients will be enrolled at approximately 20 centers in the United States.

In data presented at ASH 2015, the combination of RVD and panobinostat in newly diagnosed MM patients showed an ORR of 94%, with a 46% CR/nCR rate. This marked improvement from historical data reporting CR/nCR rates of approximately 7% warrants further investigation of this combination in this population.

2.3 Rationale for dose and regimen selection

[CLBH589BUS80T] was a single center, dose escalation trial of panobinostat plus RVD. No DLTs were observed during the first dose cohort of 10mg panobinostat three times a week, two weeks on and one week off, 25mg revlimid QD for 14 days, 1.3 mg/m2 of bortezomib on days 1, 4, 8 and 11 and 20mg of dexamethasone the day of and the day after bortezomib administration. The next dose level escalated the dose of panobinostat to 15mg, where two DLTs were observed. One patient experienced a DLT which included grade four thrombocytopenia, grade 3 diarrhea and grade 4 hypocalcemia. A second patient experienced grade 3 diarrhea that resolved immediately with supportive care, however grade 3 diarrhea with/without supportive care was considered a DLT. Therefore, the first dose cohort was considered the maximally tolerated dose and is the dose further studied in the expansion cohort.

2.4 Risks and benefits

The risk to subjects in this trial may be minimized by adherence to the eligibility criteria and study procedures, and close clinical monitoring. There may be unforeseen risks with the study treatment which could be serious.

A phase Ib study [CLBH589BUS80T] investigating panobinostat in combination with RVD in NDMM is ongoing at [redacted]. As of ASH 2015, 42 patients have been treated with this combination. In 48 patients evaluable for response, the Investigator reports an ORR of 94%, noting that this regimen led to a significant depth of response with a CR/nCR rate of 46%. Grade 3/4 hematologic toxicities included anemia (5/50), neutropenia (7/50) and thrombocytopenia (18/50). Grade 3/4 non-hematologic toxicities included ALT elevation (1/50), AST elevation (1/50), constipation (2/50), diarrhea (4/50), dyspnea (2/50) fatigue/muscle weakness (6/50), syncope (3/50), nausea (3/50) peripheral neuropathy (2/50), rash (2/50), DVT/VTE (3/50). Rates of thrombocytopenia are consistent with what was

[redacted]

reported in the phase III PANORAMA-1 trial, and rates of diarrhea appear to be improved, although patient numbers are small.

In data reported in the abstract (n=42), treatment emergent serious adverse events related to therapy observed were grade 3 pneumonia (9), grade 2 fever (5), grade 3-4 venous thromboembolic events (2), grade 3 diarrhea (2), atrial fibrillation (2). Other events included 1 pt each with grade 3 cellulitis, grade 3 myocardial infarction (MI), grade 3 febrile neutropenia, grade 2 diarrhea, grade 2 seizure, grade 3 hypotension and grade 3 sinusitis. 1 pt had a second primary malignancy – a newly diagnosed breast cancer during cycle 9 of therapy.

Patients will be followed closely during the induction phase of the study and through transplant. Adverse events will be monitored as described in Section 7.

3 Objectives and endpoints

Described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
	Primary	Refer to Section 10.4
To evaluate the efficacy of the combination of RVD + panobinostat compared to RVD alone	nCR/CR rate of the combination of panobinostat with bortezomib, lenalidomide and dexamethasone (P-RVD) vs RVD in newly diagnosed multiple myeloma patients after 4 cycles of therapy	
	Key secondary	Refer to Section 10.5.1
To assess MRD negativity (mCR) after 4 cycles of induction by Next Gen Sequencing	MRD negativity by ClonoSEQ™ assay (Adaptive Biotechnologies)	
	Other secondary	Refer to Section 10.5.2
To assess best overall response rate (ORR) and MRD negativity after ASCT and maintenance	ORR (CR + PR) and MRD negativity after ASCT and maintenance	
To assess depth of response by IMWG criteria	Rate of VGPR, CR and sCR	Refer to Section 10.6
To assess the duration of response	Duration of response	
To assess overall survival and progression free survival at three years	Overall survival and progression free survival at three years	
To assess the toxicity and tolerability	Rates of AEs and SAEs	
[redacted]	[redacted]	

[redacted]

4 Study design

4.1 Description of study design

This is a multicenter, open-label, randomized phase II study which will enroll 112 newly diagnosed symptomatic multiple myeloma patients in a 1:1 fashion. Patients will be enrolled at approximately 20 centers in the United States. The dosing information is as follows:

After completing 4 cycles of induction, all patients will undergo stem cell mobilization with G-CSF and plerixafor as per institutional protocol for this mobilization regimen. Study treatment interruption for stem cell collection may not exceed 30 days. All patients will receive one additional cycle of study treatment after stem cell collection and then proceed to autologous transplant using melphalan 200mg/m^2 (140mg/m^2 for patients > 70), as conditioning. All patients must initiate transplant within 28 days of the completion of cycle 5.

After ASCT, patients still on study will initiate maintenance therapy within the 60-120 day period following ASCT, provided they have adequate blood count and clinical recovery. Criteria for starting a patient on maintenance therapy are as follows:

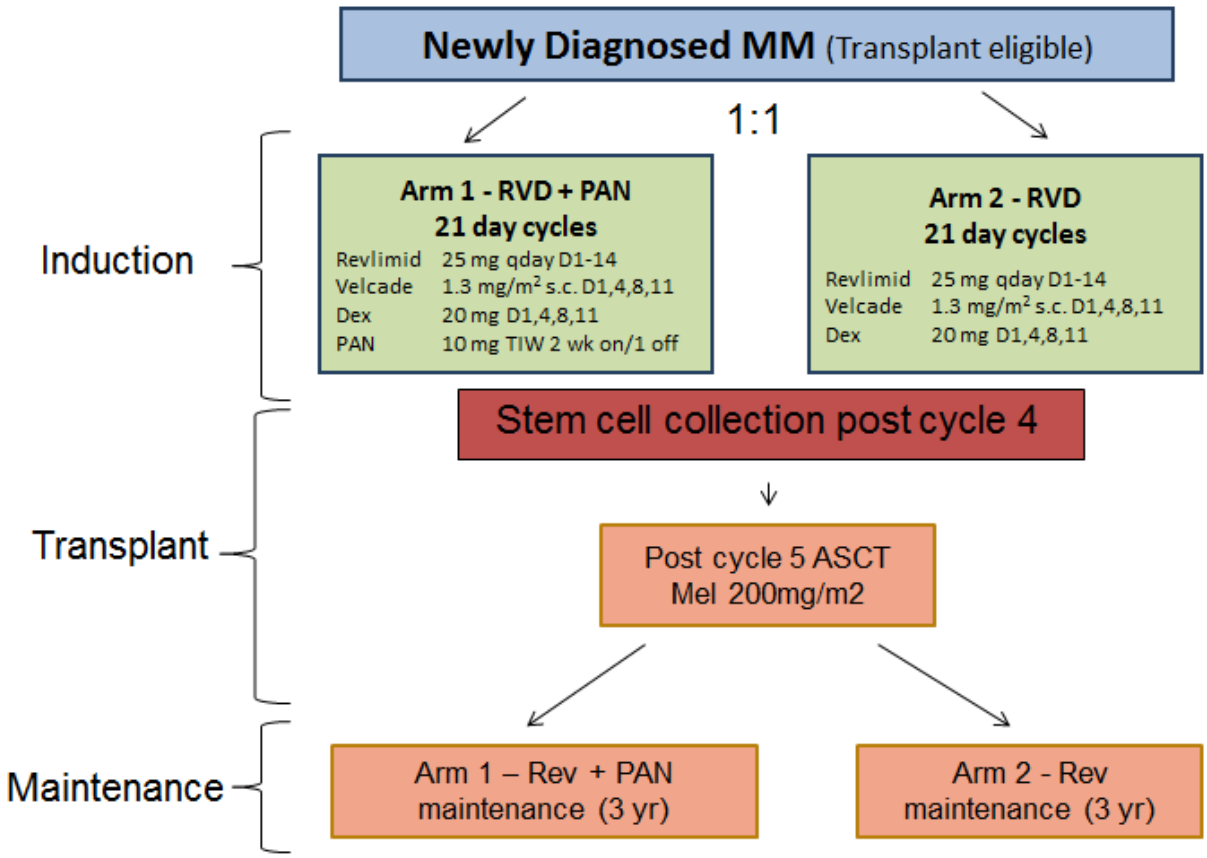
- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ 75,000/μL
- Adequate organ function as detailed in inclusion criteria (Section 5.2)

Patients in the RVD arm will initiate maintenance therapy with lenalidomide alone, and patients in RVD-panobinostat arm will receive lenalidomide + panobinostat maintenance. Lenalidomide will be dosed orally at 10mg/day continuously in both arms. After the first 84 day cycle, the dose of lenalidomide should increase to 15mg/day. Panobinostat will be dosed at 10mg three times a week, every other week. Total planned duration of maintenance therapy will be 3 years.

Patients will remain on study treatment until they complete the maintenance phase, or until they experience disease progression, unacceptable toxicity, or at the discretion of the Investigator.

[redacted]

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

An interim analysis will be performed for the primary endpoint after all patients have completed 4 cycles of induction therapy. A second interim analysis will be performed after all patients complete ASCT.

4.3 Definition of end of the study

The study will end when all enrolled patients have completed or discontinued study treatment AND have at least 3 years of follow up from study entry. (Secondary endpoints include PFS and OS rates at 3 years from study entry.)

Patients who discontinue study treatment for toxicity during the induction phase will be followed every 3 weeks for primary and secondary endpoints until documented disease progression or initiation of a new cancer therapy. All patients will be followed every 12 weeks for overall survival until the completion of the study as defined above.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible to perform an end of treatment visit. Patients in survival follow-up should be contacted for a final survival visit for Study Evaluation

[redacted]

Completion assessments. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Adult female or male patients with measurable newly diagnosed multiple myeloma who are transplant eligible.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who have completed the study may not be enrolled for a second course of treatment.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are randomized into the study. For guidelines on re-screening of patients after they failed the initial screening please refer to Section 7.1.2.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

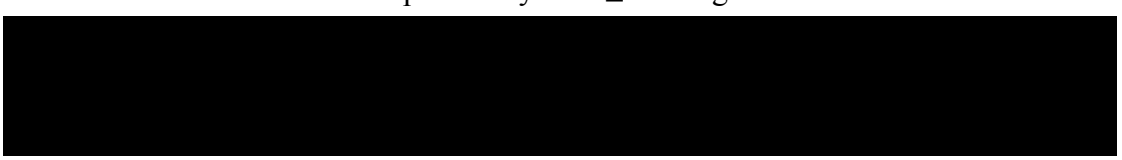
5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

Written informed consent must be obtained prior to any screening procedures

1. Patient must be newly diagnosed with multiple myeloma, based on following IMWG 2014 definition (Rajkumar et al 2014):
   - Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events:
     - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
       a. Hypercalcaemia
       b. Renal insufficiency
       c. Anemia
       d. Bone lesions: one or more osteolytic lesions

2. Patient must have measurable disease defined by at least 1 of the following conditions present at screening:
   - Serum M-protein by PEP ≥ 1.0 g/dL (≥ 10 g/L).
   - Urine M-protein by PEP ≥ 200 mg/24 hours.



- Involved serum free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal.

3. Patient must be eligible for autologous stem cell transplantation based on the investigator's clinical judgement.
4. Patient has an ECOG performance status (PS) ≤ 2
5. Patient has the following laboratory values within 3 weeks before starting study drug (lab tests may be repeated, as clinically indicated, to obtain acceptable values before failure at screening is concluded but supportive therapies are not to be administered within the week prior to screening tests for ANC or platelet count)
   a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 /L
   b. Platelet count ≥ 75 x 10^9 /L (≥ 50 x 10^9 /L for patients in whom > 50% of bone marrow nucleated cells are plasma cells)
   c. AST and ALT ≤ 2.5 x ULN
   d. Serum total bilirubin ≤ 1.5 ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
   e. Calculated creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula)
   f. Ionized calcium greater or equal to lower normal limits (> LLN), and not higher than CTCAE grade 2 in case of elevated value.
6. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of any study medication: Serum sodium, potassium, magnesium, phosphorus.
7. 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. Patient who require concurrent radiotherapy should have entry to the protocol deferred until the radiotherapy is completed and 2 weeks have passed since the last date of therapy
8. Patient's age is ≥ 18 and <75 years at time of signing the informed consent
9. Patient has provided written informed consent prior to any screening procedures
10. Patient is able to swallow capsules
11. Patient must be able to adhere to the study visit schedule and other protocol requirements
12. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Any concomitant anti-cancer therapy (other than bortezomib/lenalidomide/dexamethasone; bisphosphonates are permitted only if commenced prior to the start of screening period)
2. Unresolved diarrhea ≥ CTCAE grade 2 or presence of medical condition associated with chronic diarrhea (such as irritable bowel syndrome, inflammatory bowel disease).

[redacted]

3. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression
4. Patient has shown intolerance to bortezomib or to dexamethasone or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information
5. Patient has grade ≥ 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination at screening
6. Patient received prior treatment with DAC inhibitors including Panobinostat
7. Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment.
8. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period)
9. 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).
10. Patient who received:
    a. prior anti-myeloma chemotherapy or medication including IMiDs and Dex ≤ 3 weeks prior to start of study.
    b. experimental therapy or biologic immunotherapy including monoclonal antibodies ≤ 4 weeks prior to start of study.
    c. prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior start of study.
11. Patient has not recovered from all therapy-related toxicities associated with above listed treatments to < grade 2 CTCAE.
12. Patient has undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy to < grade 2 CTCAE
13. Patients with evidence of mucosal or internal bleeding
14. Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 month prior to screening), such as:
    a. History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
    b. Left Ventricular Ejection Fraction (LVEF) < 45% as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA)
    c. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    d. 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.
    e. Resting bradycardia defined as < 50 beats per minute
    f. Complete left bundle branch block (LBBB), bifascicular block
    g. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

[redacted]

- Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
- Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication.
- Inability to determine the QTcF interval
  a. Any clinically significant ST segment and/or T-wave abnormalities
  b. Corrected QT (QTcF) ≥ 450 ms for males and females using Fridericia's correction on screening ECG (as average of triplicate ECGs)
  c. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
  d. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening.
  e. Other clinically significant heart disease and vascular disease

15. Patient taking medications with relative risk of prolonging the QT interval or inducing Torsade de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug
16. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of panobinostat (e.g. ulcerative disease, uncontrolled nausea, vomiting, malabsorption syndrome, obstruction, or stomach and/or small bowel resection)
17. Patient has any other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause, uncontrolled thyroid dysfunction) that could cause unacceptable safety risks or compromise compliance with the protocol
18. Patient has a known history of HIV seropositivity or history of active/treated hepatitis B or C (a test for screening is not required).
19. Sexually active males unless they use a condom during intercourse while taking the drug during treatment, and for 6 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen
20. Pregnant or nursing (lactating) women.
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months of study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

[redacted]

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

6 Treatment

6.1 Study treatment

The terms "investigational study drug(s)" or "study drug(s)" will refer to oral panobinostat (also known as LBH589 or Farydak® or PAN) capsules, to bortezomib (also known as BTZ or Velcade®), to revlimid (also known as REV or Revlimid®) and to oral dexamethasone (also known as Dex) tablets. "Study treatment" refers to the combination of PAN, BTZ, REV and Dex or BTZ, REV and Dex, depending on treatment assignment.

6.1.1 Dosing regimen

Table 6-1 Induction dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
PAN	Capsule for oral use	10 mg	Days 1,3,5,8,10,12, of a 21 day cycle
BTZ	Sub-cutaneous Injection	1.3 mg/m2	Days 1, 4, 8, 11
REV	Capsule for oral use	25 mg	QD Days 1-14
DEX	Tablet for oral use	20 mg	PO Days 1, 2, 4, 5, 8, 9, 11, 12

Figure 6-1 Induction Dosing Schedule – Arm 1

(3-week cycles)	Week 1 Days 1-7							Week 2 Days 8-14							Week 3 Days 15 - 21
Panobinostat (PAN)	1		3		5			8		10		12			Rest period
Bortezomib (BTZ)	1			4				8			11				Rest period
Dexamethasone (Dex)	1	2		4	5			8	9		11	12			Rest period
Revlimid (REV)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Rest period

[redacted]

Figure 6-2 Induction Dosing Schedule – Arm 2

(3-week cycles)	Week 1 Days 1-7							Week 2 Days 8-14							Week 3 Days 15 - 21
Bortezomib (BTZ)	1			4				8			11				Rest period
Dexamethasone (Dex)	1	2		4	5			8	9		11	12			Rest period
Revlimid (REV)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Rest period

Figure 6-3 Maintenance Dosing Schedule – Arm 1

12-week (84 day) cycles	Week 1, 5 and 9							Week 2, 6 and 10							Week 3, 7 and 11							Week 4, 8 and 12						
Panobinostat (PAN) - Days	1		3		5										1		3		5								
Revlimid (REV) – Days	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7

Figure 6-4 Maintenance Dosing Schedule – Arm 2

12-week (84 day) cycles	Week 1, 5 and 9							Week 2, 6 and 10							Week 3, 7 and 11							Week 4, 8 and 12						
Revlimid (REV)	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7

6.1.2 Dosing administration for induction and maintenance

6.1.2.1 Induction dosing administration

6.1.2.1.1 Panobinostat (PAN)

Patients will self-administer panobinostat as follows:

- The panobinostat dose may be taken with or without food.
- Each dose of panobinostat should be taken with a glass of water (approximately 8 ounces/240mL). Patients should be instructed to swallow the capsules whole and not chew them.
- During all phases of this study, panobinostat should be taken at the same time on each day of administration. Doses should be separated by a minimum of 30 hours within the week of dosing.
- Every effort must be made for the patient to take PAN on the same 3 days of the week consistently throughout the study (e.g. if Cycle 1 day 1, 3, 5 is a Monday, Wednesday, Friday; for subsequent cycles/weeks PAN dosing must again be on Monday, Wednesday, Friday).

[redacted]

- Patients must avoid grapefruits, grapefruit juice, pomegranate, starfruit, starfruit juice, Seville oranges (also in form of bitter orange marmalade) and Seville orange juice during the entire study treatment period.
- If the patient forgets to take a dose of panobinostat, then he/she should take study drug within 12 hours after the missed dose. If more than 12 hours have passed, then that missed dose should be omitted and the patient should continue treatment with the next scheduled dose.
- If vomiting occurs after intake of study drug, then no re-dosing of the patient is allowed before the next scheduled dose.
- During the induction phase, panobinostat should be taken on days 1, 3, 5, 8, 10, and 12 of a 21 day cycle. (Table 6-1)
- During the maintenance phase, panobinostat should be taken on days 1, 3 and 5, every other week of a 12 week (84 day) cycle. (Table 6-3)

6.1.2.1.2 Lenalidomide (REV)

Patients will self-administer revlimid as per the package insert and the site personnel's instructions

- Lenalidomide is an oral drug supplied in 25mg, 10mg or 5mg capsules.
- Administration of Lenalidomide will be at approximately the same time each day. If a dose of lenalidomide is vomited, the patient should continue with the regular schedule of the drug at the next dose. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
- Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.
- Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.
- Research center personnel will review the dosing instructions with subjects. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit.
- During induction phase, patients will take REV orally on days 1 through 14 of a 21 day cycle. (Table 6-1 and Table 6-2)
- During maintenance phase, patients will take REV orally daily, continuously for a 12 week (84 day) cycle. (Table 6-3 and Table 6-4)

6.1.2.1.3 Bortezomib (BTZ) Administration

Site personnel will administer BTZ as per package insert:

- The actual BTZ dose will be defined based on the BSA of the patient which is calculated from the patient's weight determined on Day 1 of every cycle.

  To calculate the BSA the following formula is recommended:
  - Gehan and George Equation: BSA (m^2) = 0.0235 x Height(cm)$^{0.42246}$ x Weight(kg)$^{0.51456}$

[redacted]

- The BSA can be calculated as per standard practice at site. However, the same formula/method should be consistently used for all BSA calculations of a patient.

- During induction phase, patients will receive BTZ by subcutaneous injection on days 1, 4, 8 and 11 of a 21 day cycle. (Table 6-1 and Table 6-2)

6.1.2.1.4 Dexamethasone (Dex) Administration

Patients will self-administer dexamethasone as per the package insert and the site personnel's instructions:

- On the days when BTZ is administered, the patient should bring in their dexamethasone tablets, so that they can take them at the site within 15 – 30 minutes prior to the BTZ injection.
- On the day after the BTZ injection the patient will take dexamethasone at home as instructed.
- During induction phase, patients will take oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21 day cycle. (Table 6-1 and Table 6-2)

6.1.2.2 Dosing Diaries

At the beginning of each cycle, patients will be given a dosing diary to document the self-administered doses of PAN, REV and Dex. The completed dosing diary should be brought back to the site at the beginning of each cycle (starting with Cycle 2) and at EOT and be reviewed by the study personnel for drug accountability records and consideration when entering the dosing information in the respective Dose Administration Record page CRF.

6.1.3 Ancillary treatments

The following ancillary treatments are required while on study treatment:

- Antiviral prophylaxis (e.g. valacyclovir or equivalent)
- Proton pump inhibitors (e.g. lansoprazole) while taking dexamethasone

The following ancillary treatments can be administered while on study treatment at the investigator's discretion:

- Antibiotic prophylaxis (e.g. in first one or two cycles of study treatment)
- Growth factor prophylaxis after Cycle 1 (no growth factors should be given prophylactically in Cycle 1)
- Prophylactic anti-emetics

The preferred 5HT3 antagonist is granisetron. Other 5HT3 antagonists (e.g. ondansetron, dolasetron, etc) should be avoided due to possibility of QT prolongation.

For details please also refer to Section 6.4 for permitted concomitant medication and permitted concomitant medication to be used with caution or concomitant medication that is prohibited during the study.

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.3 Dose Modifications.

[redacted]

6.1.5 Treatment duration

Patients will be treated with RVD +/- panobinostat for four cycles, followed by stem cell collection and one additional cycle of treatment. After stem cell transplant, patients will proceed to maintenance therapy for a period of three years. Patients will remain on treatment until such time as their maintenance period ends, or they experience disease progression, unacceptable toxicity, or at the discretion of the Investigator (Section 7.1.5).

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

Patients unable to tolerate the minimum dose level of Dex may continue treatment with PAN, REV and BTZ alone.

- Patients requiring permanent discontinuation of PAN, BTZ or REV must discontinue all study treatment.
- If a patient requires a PAN, REV and/or BTZ dose delay of more than 28 days from the intended day of the next scheduled dose, the patient should be discontinued from study treatment. If, however, the patient was clearly benefitting from study treatment and the cause of the delay has resolved, the patient may be able to restart study treatment upon agreement of the Investigator and the Sponsor. This option should be used with the highest amount of caution keeping the safety of the patient in mind, and evaluating whether or not the benefit outweighs the risk.

These changes must be recorded on the Dosage Administration Record CRF.

The following table (Table 6-2) provides information on dose modifications of PAN, REV and BTZ for common toxicities.

Adverse events will be graded using the CTCAE criteria version 4.03.

General guidelines for panobinostat dose modifications due to adverse events related to study drug are provided below. If such adverse event(s) are considered possibly related to bortezomib, revlimid or dexamethasone, the relevant dose-modification guidelines for each should be followed.

6.2.1.1 Dose reductions for BTZ/Dex/REV

Table 6-2 Dose reduction steps for S.C BTZ

Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction	3nd Dose Reduction
BTZ S.C.	1.3 mg/m^2 twice a week (BIW) D 1, 4, 8 & 11	1.0 mg/m^2 D 1, 4, 8 & 11	0.7 mg/m^2 D 1, 4, 8 & 11	Discontinue
Total BTZ dose to be administered is calculated using weight determined on Day 1 of each cycle				

[redacted]

Table 6-3 Dose reduction steps for oral Dex

Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
Dex	20 mg PO the day of and 1 day after BTZ injection	10 mg PO the day of and 1 day after BTZ injection	6 mg PO the day of and 1 day after BTZ injection	Discontinue Dex Continue with PAN/BTZ alone
Dexamethasone tablets should be taken approximately 15-30 minutes prior to BTZ s.c. injection; and approximately at the same time the following day.				

Table 6-4 Dose reduction steps for REV

Induction Phase (21 Day Cycle)			
Starting Dose	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
25 mg QD, Days 1-14	20 mg QD	15 mg QD	Discontinue
Maintenance Phase Beginning at Cycle 6 (84 day cycle)			
Starting Dose (Cycle 6)	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
10 mg QDay Days 1-84	5 mg QDay	Discontinue	----
Starting Dose (Cycle 7+)	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
15 mg QDay Days 1-84	10 mg QDay	5 mg QDay	Discontinue

6.2.1.2 Dose reduction for PAN

Panobinostat dosing may be modified based on Table 6-5 below. An investigator can use his/her discretion when making dose-reduction decisions unless otherwise specified in the guidelines below. Any plan to deviate from these guidelines must be previously discussed with and agreed upon by the Sponsor.

Table 6-5 Dose reduction steps for PAN*

Induction Phase (21 day cycles)		
Starting Dose	**1st Dose Reduction**	**2nd Dose Reduction**
10 mg TIW, two weeks on-one week off	5 mg TIW, two weeks on-one week off	Discontinue
Maintenance Phase (84 day cycle)		
Starting Dose	**1st Dose Reduction**	**2nd Dose Reduction**
10 mg TIW, every other week	5 mg TIW, every other week	Discontinue
*Perform dose reduction of panobinostat only if patient experiences recurrence of toxicity on current dose (i.e patient can be re-treated at same dose level if first occurrence of ≥ grade 3/4 toxicity resolves as defined in Table 6-6).		

[redacted]

6.2.1.3 Dose reduction criteria for specific toxicity

Table 6-6 Criteria for interruption and re-initiation of PAN, REV, and BTZ treatment

	Worst Toxicity CTCAE Grade* unless otherwise specified (Value)			
Hematologic toxicity				
Drug		**PAN dose**	**REV dose**	**BTZ dose**
Platelet count (PLT) decreased	Grade 3 (PLT < 50 x 10^9/L – 25 x 10^9/L) uncomplicated	No change	No change	No change
	Grade 4 (PLT < 25 x 10^9/L) or Grade 3 (PLT < 50 x 10^9/L – 25 x 10^9/L) with bleeding	Interrupt** until resolved to ≤ Grade 2, or baseline: If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level (see Table 6-5).	Interrupt** until resolved to ≤ Grade 2; Restart at a reduced dose by one dose level (see Table 6-4).	Interrupt** until resolved to ≤ Grade 2; if only one dose was omitted prior to correction to these levels, BTZ should be restarted at same dose; if two or more doses were omitted - consecutively, or within the same cycle - then BTZ should be restarted at a reduced dose by one dose level (see Table 6-2).
Neutrophil count (ANC) decreased	Grade 3 uncomplicated ANC < 1.0 - 0.75 x 10^9/L	No change	No change	No change
	Grade 3 ANC < 0.75 - 0.5 x 10^9/L	Single occurrence within cycle, no change in dosing. Two or more occurrences within cycle, hold until return to ≤ Grade 2 (ANC ≥ 1.0 x 10^9/L), and restart at same dose.	Start GCSF daily on day one of next cycle continue GCSF as needed and maintain doses of REV	No change

[redacted]

	Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**			
	Grade 4 (ANC < 0.5 x 10^9/L)	Interrupt** If patient was not receiving GCSF therapy, initiate GCSF therapy. Interrupt PAN until resolved to ≤ Grade 2, or baseline. If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level	Interrupt** If patient was not receiving GCSF therapy, initiate GCSF therapy. Interrupt REV until resolved to ≤ Grade 2, or baseline. Restart at a reduced dose by one dose level	Interrupt** until neutropenia resolved to ≤ Grade 2; if only one dose was omitted prior to correction to these levels, BTZ should be restarted at same dose; if two or more doses were omitted - consecutively, or within the same cycle - then BTZ should be restarted at a reduced dose by one dose level
	Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for > 1 hour)	Interrupt** until fever resolved and ANC ≤ Grade 2 If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level	Interrupt** until fever resolved and ANC ≤ Grade 2, then, restart at reduced dose level of REV.	Interrupt** until neutropenia resolved to ≤ Grade 2; if only one dose was omitted prior to correction to these levels, BTZ should be restarted at same dose; if two or more doses were omitted - consecutively, or within the same cycle - then BTZ should be restarted at a reduced dose by one dose level
	* Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) **: PAN, REV **and** BTZ dosing should be interrupted at occurence of this event			

Non Hematologic toxicity				
Drug		**PAN dose**	**REV dose**	**BTZ dose**
Diarrhea	Grade 1 & 2	See Table 6-11	No change	See Table 6-11
	Grade 3	See Table 6-11	Interrupt until resolved to ≤ grade 2, then re-start at a reduced dose by one dose level	See Table 6-11

[redacted]

	Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**			
	Grade 4	See Table 6-11	Discontinue treatment	See Table 6-11
Nausea/ vomiting	Grade 1& 2 no requiring treatment or controlled using standard anti-emetics	No Change	No change	No change
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Interrupt until resolved to ≤ Grade 1. If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level	Interrupt until resolved to ≤ Grade 1. Restart at a reduced dose by one dose level	Interrupt until resolved to ≤ Grade 1. if only one dose was omitted prior to correction to these levels, BTZ should be restarted at same dose; if two or more doses were omitted - consecutively, or within the same cycle - then BTZ should be restarted at a reduced dose by one dose level
AST/ALT increase	> 5.0-20.0 x ULN	Temporarily interrupt dosing until resolved to ≤ Grade 1, or baseline, then: ● If resolved within 7 days restart at the same dose level ● If resolved in more than 7 days, then, restart at reduced dose by one dose level	Interrupt until resolved to ≤ Grade 1, or baseline, then: If resolved within 7 days restart at the same dose level ● If resolved in more than 7 days, then, restart at reduced dose	Interrupt until resolved to ≤ Grade 1, or baseline, then: If resolved within 7 days restart at the same dose level ● If resolved in more than 7 days, then, restart at reduced dose
	> 20.0 x ULN	Temporarily interrupt dosing until resolved to ≤ Grade 1, or baseline. If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level	Interrupt until resolved to ≤ Grade 1, or baseline, then restart at a reduced dose by one dose level.	Interrupt until resolved to ≤ Grade 1, or baseline, then restart at reduced dose

[redacted]

	Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**			
Total Bilirubin	Grade 3	Temporarily interrupt dosing until resolved to ≤ Grade 2, or baseline: If first occurrence on current dose, restart PAN at the same dose; if second occurrence on current dose, restart with reduced dose of PAN by one dose level	Interrupt until resolved to ≤ Grade 2 and restart at reduced dose	Interrupt until resolved to ≤ Grade 2 and restart at same dose
	Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.			
Fatigue	Grade 3	Temporarily interrupt dosing until resolved to ≤ Grade 2, or baseline, then: ● If resolved within 7 days, then restart at the same dose level ● If resolved in more than 7 days, then, restart at reduced dose level	Interrupt until resolved to ≤ Grade 2 and restart at reduced dose level	Interrupt until resolved to ≤ Grade 2 and restart at same dose
Peripheral neuropathy	Any Grade	No change	No change	See Table 6-8
HSV reactivation	Any grade	No change	No change	See Table 6-7
Renal dysfunction	Calculated GFR 15-30 ml/min	No change	Interrupt until resolved to > 30ml/min and restart at reduced dose level	No change
Cardiac-Prolonged QTcF	Please refer to Section 6.2.1.6.3 (see Table 6-5)			
Other drug related non hematologic toxicity	≥ Grade 3	Determine attribution of toxicity if possible and hold appropriate therapy. Follow at least weekly. If toxicity resolves to ≤ Grade 2 therapy may be resumed, unless the investigator decides otherwise. In case therapy will be resumed, consideration for one level dose reduction of appropriate drug will be given.		
All dose modifications should be based on the worst preceding toxicity. * Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) ** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing *** See also concomitant medication				

[redacted]

Table 6-7 Drug related adverse events dose modification guidelines for BTZ

CTCAE Category	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
HEMATOLOGICAL TOXICITIES	
(ANC, PLT)	See Table 6-6
NON-HEMATOLOGICAL TOXICITIES	
Peripheral Neuropathy	See Table 6-8
Herpes Zoster reactivation any grade	Hold therapy until lesions are dry.
Other BTZ related non-hematologic toxicity ≥ Gr 3	Determine attribution of toxicity and hold therapy. If toxicity resolves to ≤ Gr 2, resume therapy with one level dose reduction (see Table 6-6).

6.2.1.4 Management of patients with BTZ-related neuropathic pain and/or peripheral sensory neuropathy

The neurotoxicity-directed questionnaire (FACT/GOG-Ntx) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

Table 6-8 Recommended dose modification for BTZ-related neuropathic pain and/or peripheral sensory neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Gr 1 (Asymptomatic; loss of deep tendon reflexes or paresthesia)	No action
Gr 1 with pain or Gr 2 (Moderate symptoms; limiting instrumental ADL) a	Reduce by one dose level (see Table 6-6)
Gr 2 with pain or Gr 3 (Severe symptoms; limiting self-care ADL)	Hold BTZ therapy until toxicity resolves to < Gr 2 When toxicity resolves, reinitiate with a reduction by one dose level (see Table 6-6) If no more dose reductions are possible, discontinue BTZ
Gr 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue BTZ
Grading based on NCI Common Terminology Criteria CTCAE v4.03 NCI Common Toxicity Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

[redacted]

Table 6-9 Dex dose modifications

Dexamethasone dose modifications		
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Gr 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, reduce Dex by one dose level (see Table 6-7)
	> Gr 3 (requiring hospitalization or surgery)	Hold Dex until symptoms adequately controlled. Restart and reduce one dose level (see Table 6-7) along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue Dex and do not resume.
	Acute pancreatitis	Discontinue Dex and do not resume.
Cardiovascular	Edema > Gr 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and reduce Dex by one dose level (see Table 6-7); if edema persists despite above measures, reduce another dose level. Discontinue Dex and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Gr 2 (interfering with function +/- interfering with activities of daily living)	Hold Dex until symptoms resolve. Restart with one dose level reduction (see Table 6-7). If symptoms persist despite above measures, discontinue Dex do not resume.
Musculoskeletal	Muscle weakness > Gr 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Reduce Dex by one dose level (see Table 6-7). If weakness persists despite above measures reduce another dose level. Discontinue Dex and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Gr 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, reduce by one dose level (see Table 6-7) until levels are satisfactory.

6.2.1.5 Management of Diarrhea (including PAN and BTZ dose modifications)

Patients should be instructed to contact the physician/other study personnel at the first sign of diarrhea. The patient should also be instructed on the use of loperamide and lomotil at home (see Table 6-11).

At the beginning of every cycle, each patient should be asked if he/she experienced any diarrhea and if any self-care measures were taken for this event. The study personnel should ensure that adverse event(s) of diarrhea and use of concomitant anti-diarrheal medication are documented on the relevant pages of the CRF as needed.

If the regimen described below is inadequate or at the investigator's discretion, additional evaluation and treatment should be pursued including hospitalization as needed. Replacement i.v. fluids and electrolytes may be used as appropriate. Additional treatment should be provided in accordance with institutional standard of care and/or local guidelines.

At the time of the first screening visit:

History and physical are documented and patient is counseled on diet, use of laxatives, as follows:

- Take thorough history of diarrhea and obtain a description of number of stools and stool composition (e.g. watery, blood, mucus in stool)

[redacted]

- Assess the patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out sepsis, clostridium difficile, bowel obstruction, or dehydration)
- Obtain patient's medication profile (i.e., to identify and limit the use of any diarrhea causing agents)
- Obtain dietary profile and counsel patient on dietary modifications:
  - Instruct the patient to stop all lactose-containing products
  - Instruct the patient to stop taking laxatives, bulk fiber (i.e. Metamucil®), and stool softeners (docusate sodium; Colace®)
  - Instruct the patient to drink 8 to 10 large glasses of clear liquids per day (i.e. water, Pedialyte®, Gatorade®, broth)
  - Instruct the patient to eat frequent small meals (bananas, rice, applesauce, Ensure®, toast)
  - Instruct the patient to stop consuming high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)

The patient should be given loperamide and lomotil to take home in order to be able to have anti-diarrheal medications if needed. Additional loperamide and lomotil should be given to the patient during study treatment as needed, based on the amounts taken.

Proposed diarrhea management after 1st screening visit and during study treatment

Table 6-11 and Table 6-12 describe the anti-diarrheal medications and other diarrhea management steps (including dose modifications) proposed after the first screening visit, respectively.

Table 6-10 Proposed anti-diarrheal medications

	Medication	Dose
Step 1	standard dose loperamide (Imodium)	4 mg followed by 2 mg every 4 hours OR after each loose stool (maximum 16 mg/day).
Step 2	high dose loperamide (Imodium)	4 mg followed by 2 mg every 2 hours OR 4 mg every 4 hours (maximum of 16 mg/day)
Step 3	diphenoxylate and atropine (Lomotil)	5 mg every 6 hours

Dose modifications for bortezomib and dexamethasone may be performed based on Table 6-2, Table 6-6 and Table 6-7 below. Further clarification can be obtained in consultation with the Sponsor.

[redacted]

Table 6-11 Diarrhea management and PAN/BTZ dose modifications

Diarrhea CTCAE grade		Diarrhea management	PAN and BTZ dosing
Prior to first planned dose			
Grade 1 Increase of < 4 stools / day over baseline; mild increase in ostomy output compared to baseline		Standard dose loperamide	Give full dose of both PAN and BTZ
On study treatment			
Grade 1 Increase of < 4 stools / day over baseline; mild increase in ostomy output compared to baseline		Standard dose loperamide	Give full dose of PAN and BTZ
Grade 2 increase of 4-6 stools / day over baseline; moderate increase in ostomy output compared to baseline	Grade 2	High dose loperamide	Interrupt both, PAN and BTZ
	when improved to ≤ Grade 1 w/i 24h	Modify antidiarrheal medication as appropriate	Restart both, PAN and BTZ, at current doses
	Grade 2 for > 24h	Start diphenoxylate/atropine, continue high dose loperamide	Interrupt both, PAN **and** BTZ
	when improved to ≤ Grade 1 w/i 48 h	Modify antidiarrheal medication as appropriate	Restart both, PAN and BTZ, at current doses
	Grade 2 for > 48h	Continue diphenoxylate/atropine and high dose loperamide	Interrupt both PAN **and** BTZ
	when improved to ≤ Grade 1 after >48 h	Modify antidiarrheal medication as appropriate	Dose reduce BTZ first by one dose level (Table 6-2). Continue PAN at the same dose on the first occasion. If second occasion, restart PAN at a reduced dose by one dose level (Table 6-5)
Grade 3 increase of ≥7 stools / day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; self-limiting care ADL	Grade 3	High dose loperamide and diphenoxylate/atropine Consider hospitalization for monitoring / volume management	Interrupt both, PAN **and** BTZ
	until diarrhea improves to ≤ Grade 1	Continue high dose loperamide and diphenoxylate/atropine and supportive care until ≤ Grade 1	Interrupt both, PAN **and** BTZ
	when improved to ≤ Grade 1	Modify antidiarrheal medication as appropriate	Dose reduce BTZ first by one dose level (Table 6-2). Continue PAN at the same dose on the first occasion. If second occasion, restart PAN at a reduced dose by one dose level (Table 6-5)
Grade 4 Life threatening consequences; urgent intervention indicated	Grade 4	Hospitalize and provide intensive supportive care and antidiarrheals	Discontinue study treatment

[redacted]

6.2.1.6 Management of other non-hematologic toxicities

6.2.1.6.1 Grade 2 non-hematologic toxicity

Patients experiencing CTCAE grade 2 non-hematologic adverse event(s) not listed in Table 6-4, which the patient believes is/are tolerable and in the Investigator's judgment is/are acceptable, may continue treatment at the current dose and schedule. More frequent patient monitoring may be required, and patients must be informed to call the Investigator immediately if there is any worsening of symptoms.

If a patient experiences new (or treatment emergent) grade 2 non-hematologic adverse event(s) considered at least possibly related to panobinostat, and which the patient finds intolerable or in the Investigator's judgment is/are not acceptable, treatment must be held until the adverse event(s) resolves to ≤ CTCAE grade 1. Panobinostat treatment may then be restarted at the same dose and schedule. If the same intolerable grade 2 adverse event(s) occurs again, panobinostat treatment must again be temporarily interrupted until the toxicity resolves to ≤ CTCAE grade 1 and can be restarted at reduced dose level if current PAN dose was 10mg, and at same dose level if current PAN dose was 5mg (see Table 6-3). At the discretion of the Investigator and in consultation with the Sponsor, patients with grade ≥ 2 adverse events of major organs (e.g. heart, lungs, CNS) may be discontinued from further study therapy without being retreated with a dose reduction.

6.2.1.6.2 Grade 3 or 4 non-hematologic toxicity

Patients experiencing new (or treatment emergent) CTCAE grade 3 or 4 non-hematologic AEs not listed in Table 6-4, must have their treatment temporarily interrupted until the adverse event resolves to ≤ CTCAE grade 1 or baseline unless otherwise specified in Table 6-4. If the AE was considered related to panobinostat, the drug should then be restarted at reduced dose level if current PAN dose was 10mg, and at same dose level if current PAN dose was 5mg (see Table 6-3). If the AE was considered not related to panobinostat then therapy may be restarted (when the AE resolves to ≤ grade 1 or baseline) at the current dose; if a dose reduction is considered it must be agreed upon by the Investigator and the Sponsor prior to the patient being dose reduced.

6.2.1.6.3 Dose modification of panobinostat for prolonged QTcF interval

All cardiac events should be treated as per the local standard of care and referred to a cardiologist if clinically indicated. The local readings of ECGs will use the Fridericia correction for QTc interval assessment: QTcF. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be based on the assessment performed by the Investigator and after discussion between the Investigator and Sponsor. Any plan to deviate from these guidelines must be previously discussed and agreed upon by the Sponsor.

[redacted]

Table 6-12 Criteria for dose interruption of PAN due to QTcF prolongation

Time Point	Average QTcF*	Action
Screening and pre-dose cycle 1 day 1	≥ 450 msec	Correct any electrolyte abnormal values ** and repeat ECG, if the average QTcF ≥ 450 msec, do not commence treatment
Post-dose cycle 1 days 1 and 5	≥ 480 msec or above 60 msec from baseline	Correct any electrolyte abnormal values ** and repeat ECG in triplicate (3 ECGs 5 to 10 minutes apart). Monitor QTcF until prolongation is resolved If unresolved within 7 days, discontinue treatment If resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if recurrent
	Above 500 msec	Patient must discontinue treatment
Pre-dose cycle 1 day 5 Pre-dose day 1 of subsequent cycles	≥ 480 msec or above 60 msec from baseline for any pre-dose ECG after the patient has commenced treatment***	Correct any electrolyte abnormal values ** and repeat ECG in triplicate (3 ECGs 5 to 10 minutes apart), if the average QTcF ≥ 480 msec, do not dose. If the average QTcF is < 480 msec, resume dosing. If unresolved within 7 days, discontinue treatment If resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if recurrent
	Above 500 msec	Permanently discontinue treatment
*QTc F: Heart rate corrected QT interval using the Fredericia formula: QTc=QT/RR0.33 **: serum potassium, magnesium and phosphorus ***If a single pre-dose QTcF is ≥ 480 msec or 60 msec from baseline, subsequent ECGs should be performed in triplicate		

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

Further guidelines and recommendations for the management of specific study drug combination induced toxicities (diarrhea and cardiac toxicities) are provided in Section 6.3.1.3 and Section 6.3.1.4. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

If an adverse event requiring treatment interruption resolves to ≤ grade 1 within the same cycle, resume dosing as scheduled for that cycle. During the induction phase, If an adverse event requiring treatment interruption resolves to ≤ grade 1 after the end of a cycle (D21), resume dosing with a brand new cycle. Otherwise, continue dosing according to current cycle schedule. For adverse events requiring treatment interruption during the maintenance phase, dosing can be resumed within the same cycle, provided that the AE resolves to ≤ grade 1 within 28 days.

[redacted]

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

6.3.1.1 Growth factors

Granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) should not be used prophylactically in the first cycle. G-CSF may be initiated for an individual patient in accordance with American Society of Clinical Oncology's guidelines (Smith et al 2006), if the patient experiences febrile neutropenia and/or grade 4 neutropenia for > 7 days. Growth factors may then be administered prophylactically in all subsequent cycles for that patient.

Patients who were receiving available recombinant erythropoiesis stimulating agents such as epoetin and darbepoietin prior to starting study treatment may continue to receive it throughout the study. Likewise these can be introduced during the study. Investigators should follow available guidelines on criteria for initiation, target and doses provided in ASCO/ASH guidelines (Rizzo et al 2010).

6.3.1.2 Bisphosphonate Therapy

Bisphosphonate therapy is permitted only if commenced prior to the start of screening period. Mouth care is recommended in these patients.

Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion.

Patients taking bisphosphonates prior to entering the study should continue with the same bisphosphonate treatment, given as per local medical practice.

6.3.1.3 Anti-emetic medication

Anti-emetics such as granisetron can be administered at the discretion of the Investigator. Granisetron is the preferred 5HT3 antagonist, due to the possibility of QT prolongation with the other 5HT3 antagonists (e.g. ondansetron, dolasetron, etc). These should be avoided.

6.3.1.4 Anti-diarrheal medication

At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication. Please refer to Section 6.3.1.4 for details on management of diarrhea.

6.3.1.5 Prophylaxis treatment

Please refer to Section 6.1.2 for ancillary treatment.

[redacted]

6.3.2 Permitted concomitant therapy requiring caution and/or action

6.3.2.1 Anti-coagulant therapy/ anti-platelet therapy

Panobinostat therapy, especially in combination with bortezomib, is commonly associated with moderate to severe degree of thrombocytopenia. This may lead to an increase in the risk of bleeding especially if co-administered with long acting anticoagulation, such as sodium warfarin (Coumadin®). It is recommended that patients who require anticoagulation therapy while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible or indicated, patients on vitamin K inhibitors such as sodium warfarin may continue such therapy while on panobinostat but for such patients, a close and frequent monitoring of the coagulation parameters, especially PT/INR should be followed and maintained within a therapeutic range (suggested INR 2-3). Warfarin should be used with caution and the dose of sodium warfarin may be adjusted as needed while on study treatment. It is recommended that if the platelet count falls below 50 x 10^9/L, withholding of thromboprophylaxis be considered to minimize the risk of bleeding. Newer direct FX and thrombin inhibitors should not be used as there is no effective antidote available and fresh frozen plasma is not effective in reversing their effects.

For patients requiring anti-platelet therapy while on panobinostat, Aspirin ≤ 325mg or Plavix ≤ 75mg daily are allowed. It is recommended that anti-platelet therapy be held if platelet counts fall below 50 x 10^9/L.

6.3.2.2 Medications that are known to be strong CYP3A inhibitors

See Section 14.1.

Panobinostat is a substrate of CYP3A with minor involvement of CYP2D6, and CYP2C19 in in vitro evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study [CLBH589B2110].

Multiple ketoconazole doses at 400 mg increased Cmax and AUC of panobinostat by 1.6- and 1.7-fold, respectively, but with no change in Tmax or half-lives in 14 cancers patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition. Patients with impaired liver function (as defined by NCI CTEP criteria, Synold et al 2007) are recommended not to receive panobinostat concomitantly with strong CYP3A inhibitors due to lack of safety data in this population.

6.3.3 Prohibited concomitant therapy

The following medications are prohibited during this study:

- Systemic anticoagulation or drugs that inhibit platelet function, WITH THE EXCEPTION OF (see Section 6.4.2):
  - Aspirin ≤ 325 mg/day
  - Plavix ≤ 75 mg/day
  - Low molecular weight heparin (LMWH).

[redacted]

- Titrated dose warfarin may be used in patients requiring chronic anticoagulation
- Any investigational medication (other than PAN)
- Chemo-, biologic or immunologic therapy is not allowed while the patient is on study treatment. Palliative radiation therapy may be permitted, but the need for radiation therapy is usually indicative of disease progression.
- DAC inhibitors, including valproic acid, for any clinical indication while on PAN treatment.

6.3.3.1 Drugs that are known to prolong the QT interval and/or induce Torsade de Pointes ventricular arrhythmia

Patients who are currently receiving treatment with any of the medications in Section 14.1.1 which have a known risk of prolonging the QT interval or inducing Torsades de pointes and cannot either discontinue this treatment or switch to a different medication prior to study enrollment, will be excluded from the study. Patients may not begin treatment with any of the medications listed in Section 14.1.1 unless this is discussed with the Sponsor and an approval is granted by the Sponsor.

Sponsor may agree to temporarily discontinue panobinostat treatment during administration with these drugs.

Ensure that patient is off panobinostat treatment for at least 72 hours prior to starting treatment with a medication listed in Section 14.1.2.

It is of importance to avoid combining drugs listed in Table 14-1 (QT prolonging drugs) and Table 14-2 (CYP3A inhibitors) in the presence of electrolyte abnormalities notably decreased potassium or magnesium levels commonly associated with diuretic usage.

The current panobinostat guidance (as specified in Section 14.1) includes an updated list of medications which was developed in collaboration with an external cardiologist consultant and is based on the ARIZONA CERT website on drugs that prolong the QT interval and/or induce Torsades de Pointes or ventricular arrhythmia.

6.3.3.2 Medications which are known strong CYP3A inducers are to be avoided

Panobinostat plasma exposure was reduced by 20% or more when combined with bortezomib and dexamethasone (B2207 and D2308). Co-administration of panobinostat with strong CYP3A inducers was not evaluated in a clinical trial however, an approximately 70% decrease in the systemic exposure of panobinostat in the presence of strong inducers of CYP3A was observed in simulations using mechanistic models. Therefore, the concomitant use of strong CYP3A inducers should be avoided.

6.3.3.3 Medications which are known sensitive CYP2D6 substrates or substrates with narrow therapeutic index

Panobinostat was also shown to be a CYP2D6 inhibitor (Ki 0.17 µM) in vitro. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorphan as CYP2D6 substrate was recently conducted in study [CLBH589B2109].

[redacted]

Panobinostat increased the median Cmax and AUC of a sensitive substrate of CYP2D6 by approximately 80% and 60%, respectively; however these increase were highly variable (increased the Cmax and AUC0-∞ of dextromethorphan by 20% to 200% and 20% to 130% (interquartile ranges), respectively).

Avoid co-administrating panobinostat with sensitive CYP2D6 substrates (Table 14-4) or CYP2D6 substrates that have a narrow therapeutic index (i.e., thioridazine, pimozide). If concomitant use of CYP2D6 substrates is unavoidable, monitor patients frequently for adverse reactions.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator.

6.4.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1.

Randomization will be performed using random permuted block scheme.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.4.3 Treatment blinding

Not applicable.

[redacted]

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the PAN, REV and Dex as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. BTZ will be reconstituted and handled as per the manufacturer's instructions by the responsible site personnel and administered as subcutaneous injection at the site.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Table 6-13 Preparation and dispensing

Study treatments	Dispensing	Preparation
PAN	PAN capsules are given to the patient on the 1st day of a cycle by study personnel. Additional capsules including instructions for administration are dispensed by study personnel on an outpatient basis. *Patients will be provided with adequate supply of study treatment for self-administration at home until at least the first day of the subsequent cycle.*	Not applicable
BTZ s.c.	Not applicable	Refer to product information
Dex	Dex tablets are given to the patient on the day of BTZ s.c. injection by study personnel. Additional tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least the first day of the subsequent cycle.	Not applicable
REV	REV capsules are provided to the patient via a prescription. Additional capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least the first day of the subsequent cycle.	Refer to local product information.

6.5.1 Study drug packaging and labeling

Each study site will be supplied by Novartis with PAN (LBH589 5mg and 10mg) capsules. Site personnel will add the patient number on the label.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the PAN should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

[redacted]

Bortezomib, dexamethasone and Revlimid should be stored according to the local product information.

6.5.2.1 Study drug compliance

The total daily doses of study treatment (PAN/BTZ/REV and Dex) taken, the date of dose, information regarding dose change, dose interruption, permanent discontinuation and reason(s), as well as information whether the study drug was dispensed in error, will be recorded on the respective Dose Administration Record of the CRF. For BTZ the dose prescribed in mg/m^2 will also be captured.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Patients will be asked to record self-administered PAN/REV/Dex doses in a dosing diary, and to bring in the diary (together with any unused study medication or empty study medication bottles, as applicable) on Day 1 of every cycle starting with Cycle 2, as well as at the EOT visit. The information in the diary will be reviewed and new diaries will be dispensed by site personnel at the beginning of each cycle and information will be used to support/record information on PAN/REV/Dex dosing on the respective Dose Administration Record CRF page.

6.5.2.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

It's preferred that the study drug supply is destroyed on site, after your CRA has had an opportunity to perform drug accountability. If this is not possible, drug can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

[redacted]

Table 7-1 Visit evaluation schedule

Day of cycle	Category	Protocol Section	Screening	Study Treatment														End of treatment	Long-term FU
				Induction 21 days/cycle									Maintenance 84 day cycles						
				Cycle (C) 1 21 days/cycle				Cycle 2 – 5 21 days/cycle					Cycle 6			Cycle 7+			Survival FU
			Day -21 to 1	1 (BL)	4	8	11	1	4	8	11	21 (only cycle 4)	1	29	57	1		EOT	Every 90 days
Obtain informed consent (IC)	D	11.3	X																
[redacted]																			
Registration / Randomization with IRT/IWRS																			
Registration after signing of IC	S	6.4.2	X																
Randomization if eligible	D	6.4.2		X															
Patient history																			
Demography	D	7.1.1.3	X																
Inclusion/exclusion criteria	D	5.2/5.3	X																
Medical History	D	7.1.1.3	X																
MM Diagnosis/history and extent of cancer	D	7.1.1.3	X																
Local cytogenetics (FISH)	D	7.1.1.3	X																
Prior/concomitant medications and non-drug therapy	D	7.1.1.3	Continuously from 14 days prior to first dose until 30 days after last dose of study treatment																

[redacted]

Day of cycle	Category	Protocol Section	Screening	Study Treatment													End of treatment	Long-term FU
				Induction 21 days/cycle									Maintenance 84 day cycles					Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 5 21 days/cycle					Cycle 6			Cycle 7+		
			Day -21 to 1	1 (BL)	4	8	11	1	4	8	11	21 (only cycle 4)	1	29	57	1	EOT	Every 90 days
Transfusions of blood products	D	7.1.1.3	Continuously from 14 days prior to first dose until 30 days after last dose of study treatment															
Efficacy / Disease Assessment																		
M-Protein by Protein Electrophoresis (PEP)																		
- in serum (sPEP)	D	7.2.1.1	X	X				X					X	X	X	X	X	
- in urine (uPEP)	D	7.2.1.1	X	X				X					X	X	X	X	X	
M-Protein by Immunofixation (IF)																		
- in serum (sIF)	D	7.2.1.1	X	X				X					X	X	X	X	X	
- in urine (uIF)	D	7.2.1.1	X	X				X					X	X	X	X	X	
Free light chain protein assessment (FLC)																		
- in serum (sFLC)	D	7.2.1.2	X	X				X					X	X	X	X	X	
Local plasma cell count in bone marrow (PCC)																		
- Plasma cell count (2-4 color flow)	D	7.2.1.2	X									X	X	During the study as clinically indicated to confirm CR, sCR, and PD for patients with non-measurable disease			X	
Assessment of soft tissue plasmacytoma (STP)																		
- By CT/MRI/PET	D	7.2.1.6	X					During the study as clinically indicated to confirm CR, sCR; and PD for patients										

[redacted]

Day of cycle	Category	Protocol Section	Screening	Study Treatment														End of treatment	Long-term FU
				Induction 21 days/cycle										Maintenance 84 day cycles					
				Cycle (C) 1 21 days/cycle				Cycle 2 – 5 21 days/cycle						Cycle 6			Cycle 7+		Survival FU
			Day -21 to 1	1 (BL)	4	8	11	1	4	8	11	21 (only cycle 4)	1	29	57	1	EOT	Every 90 days
								with non-measurable disease											
Full body skeletal survey (FBSS)																			
- by X-ray and/or CT/MRI	D	7.2.1.7	X					During the study as clinically indicated; In case of newly symptomatic areas with no finding by X-ray a targeted CT/MRI assessment should be performed.											
Response assessment by investigator	D	7.2.1.8						X				X	X	X	X	X	X	X	
MRD assessment in marrow for component of mCR (ClonoSEQ™)	D	7.2.1.5	X									In all patients who are in CR on or after C4D21							
Clinical examination																			
Physical exam (including brief neurological exam)	S	7.2.2.1	X	X				X					X	X	X		X		
Vital signs	D	7.2.2.2	X	X				X					X	X	X	X	X		
Height	D	7.2.2.3	X																
Weight / BSA calculated by site	D	7.2.2.3	X	X				X					X	X	X	X	X		
ECOG Performance status	D	7.2.2.4	X	X				X					X	X	X	X	X		
Local laboratory assessments																			
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X		X		X	X	X	X	X	X		

[redacted]

Day of cycle	Category	Protocol Section	Screening	Study Treatment														End of treatment	Long-term FU
				Induction 21 days/cycle										Maintenance 84 day cycles					
				Cycle (C) 1 21 days/cycle				Cycle 2 – 5 21 days/cycle						Cycle 6			Cycle 7+		Survival FU
			Day -21 to 1	1 (BL)	4	8	11	1	4	8	11	21 (only cycle 4)		1	29	57	1	EOT	Every 90 days
Calcium	D		If total calcium is abnormal, collect ionized calcium																
Electrolytes	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Thyroid	D	7.2.2.5.4	X																
Coagulation	D	7.2.2.5.5	X																
Troponin I	D	7.2.2.5.6	X																
Creatinine Clearance – calculated using Cockroft-Gault	D	7.2.2.5.7	X	X	X	X	X	X		X		X		X	X	X	X	X	
Pregnancy tests for women of childbearing potential																			
- In serum (w/i 7 days of 1st planned dose)	D	7.2.2.5.8	X																
- In urine	D	7.2.2.5.8		X				X						X	X	X	X		
Cardiac Assessments																			
Central 12-lead ECG up to C 16 (unscheduled as clinically indicated)	D	7.2.2.6.1	X	X	X			X						X	As clinically indicated			X	
Cardiac Imaging (MUGA/ECHO)	D	7.2.2.6.2	X	As clinically indicated															
Adverse events																			
Adverse events	D	8	Continuously after signed ICF until 30 days after last study treatment																

[redacted]

Day of cycle	Category	Protocol Section	Screening	Study Treatment													End of treatment	Long-term FU
				Induction 21 days/cycle									Maintenance 84 day cycles					
				Cycle (C) 1 21 days/cycle				Cycle 2 – 5 21 days/cycle					Cycle 6			Cycle 7+		Survival FU
			Day -21 to 1	1 (BL)	4	8	11	1	4	8	11	21 (only cycle 4)	1	29	57	1	EOT	Every 90 days
Study treatment administration and new antineoplastic therapies after discontinuation of study treatment																		
Panobinostat (PAN)	S	6.1.2.1.1		Day 1, 3, 5, 8, 10, 12, two weeks on one week off, 21 day cycles (for dose reductions please refer to Section 6.3)									Day, 1, 3, 5, every other week of 28 day cycles					
Revlimid (REV)	S	6.1.2.1.2		Every day, two weeks on one week off									Continuously for 28 day cycles					
Dexamethasone (Dex) p.o.	S	6.1.2.1.4		D1, 2, 4, 5, 8, 9, 11, 12														
Bortezomib (BTZ) s.c.	S	6.1.2.1.3		D1, 4, 8, 11														
Dispensing and/or review of patient paper dosing diary by study personnel	S	6.1.2.2		X				X					X	X	X	X		
Survival Follow-up (until all patients have completed 3 years of follow-up from study entry																		
Follow-up for survival endpoints	D	4.3		Beginning at study entry, all patients will be followed for survival for 3 years.														

[redacted]

7.1.1 Screening

Following signature of the main study Informed Consent (ICF), the majority of screening assessments will be performed within 21 days prior to first dose on Cycle 1 Day 1. There are a few assessments (serum pregnancy test for WOCBP) that will need to be performed within 7 days of first planned dose of study treatment (see Table 7-1 for detailed list of assessments to be performed).

Note: Any screening assessment that is done outside the screening window (Day -21 to Day 1 or Day -7 to Day 1 as applicable) must be repeated prior to randomization.

A patient who has (a) laboratory test result(s) and/or (an) ECG finding(s) that do(es) not satisfy the selection criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 3 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient Subject ID number assigned by the investigator will be used. In the event that the laboratory test(s)/ECG(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or the patient's medical condition has changed significantly during the screening phase so that the inclusion/exclusion criteria are no longer met, the patient is considered a screen failure, and must be discontinued from the study.

If the bone marrow sample collected at screening was inadequate/uninterpretable for assessment of FISH and/or PCC, it should be repeated within 21 days of the original collection date prior to randomization.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed. The same Subject ID number will be used, and all required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may be re-screened twice for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

Informed Consent CRF should be completed as appropriate.

7.1.1.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. If patient meets all eligibility criteria, the site personnel can proceed with the randomization of the patient in the IRT. In addition, the Randomization page in the CRF will be completed.

At the end of the screening phase, the Screening Log will be completed for all patients.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered

[redacted]

on the Screening Log. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

If the patient is randomized but then does not start study treatment, the patient will be part of the full analysis set, and will be followed for efficacy and survival in the long-term follow-up. The IRT must be notified *within 2 days* of the fact, that the randomized patient will not receive study treatment and moved to the long-term follow-up.

7.1.1.3 Patient demographics and other baseline characteristics

During the screening period, the following data must be collected/evaluated and recorded for all randomized patients on the appropriate CRFs:

- After the main study ICF is signed the patient will be registered with IRT.
- Demography (date of birth and initials, sex, information on child-bearing status of female patients, race, ethnicity).
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History CRF should include the toxicity grade.
- Diagnosis of Multiple Myeloma and extent of cancer (including staging at study entry).
- BM aspirate/biopsy for cytogenetics (FISH) to be performed prior to study entry
- All other medications and significant non-drug therapies including ancillary medication taken within 14 days before first dose is administered must be recorded on the Prior and Concomitant Medication CRF and updated on a continual basis if there are any new changes to the medication. Medications include prescription medications, over-the-counter medications, vitamins, and herbal and alternative therapy.
- Transfusions of blood products administered within 14 days prior to first dose must be recorded on the Prior Blood Transfusion CRF.

In addition, the following assessments must be performed and recorded for all randomized patients on the appropriate CRFs:

- Complete physical examination (including brief neurological exam, see Section 7.2.2.1 for details, results will not be recorded on CRF, but as appropriate on medical history or adverse event CRF page)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Height, Weight, BSA (although the Gehan and George equation is recommended (see Section 6.1.1), the BSA can be calculated as per standard practice at the site. However, the same formula/method should be consistently used for the BSA calculation for a patient throughout the study)
- Vital signs (sitting blood pressure, sitting pulse, respiratory rate and body temperature)

[redacted]

- Serum pregnancy test performed in WOCBP (within 7 days of first planned dose)
- Cardiac imaging (MUGA/ECHO)
- Central 12-Lead ECG
- Local laboratory evaluations (hematology, chemistry, electrolytes, thyroid, coagulation, troponin I, creatinine clearance calculated based on serum creatinine based on Cockroft-Gault formula)
- Disease assessments
  - Central laboratory evaluations:
    - In serum: M- protein by PEP and IF,
  - Local laboratory evaluations:
    - In serum: FLC protein assessment
    - In urine: M-protein by PEP and IF
  - Local plasma cell count in bone marrow
  - Bone marrow aspirate for diagnostic sample for MRD assessment by ClonoSEQ™ assay
  - Clinical assessment of soft tissue plasmacytomas (STP)
  - Assessment of STP by CT/MRI
  - Full body skeletal survey by X-ray (and/or CT/MRI)

7.1.2 Treatment period

After randomization using the IRT, approximately 112 patients will receive study treatment in 21-day cycles during the induction phase and in 84-day cycles in the maintenance phase until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason (see Section 7.1.5), as described below.

- Induction Phase (Cycles 1 to 5): Newly diagnosed multiple myeloma patients randomized to the first arm will receive bortezomib (BTZ) twice a week, dexamethasone (Dex) four times a week, revlimid (REV) seven days a week, and panobinostat (PAN) three times a week, two weeks on, one week off, on a 21-day cycle. Patients randomized to the second arm will receive bortezomib (BTZ) twice a week, dexamethasone (Dex) four times a week, and revlimid (REV) seven days a week two weeks on, one week off, on a 21-day cycle.
- Maintenance Phase (Cycles 6+): Patients randomized to the first arm will receive revlimid (REV) seven days a week continuously and panobinostat (PAN) three days a week, every other week on an 84-day cycle. Patients randomized to the second arm will receive revlimid (REV) seven days a week continuously on an 84-day cycle.

See Table 7-1 for details of assessments during the treatment period. The general visit window during induction is +/- 3 days and during maintenance +/- 7 days, unless otherwise specified for specific assessments in Section 7.2.

[redacted]

7.1.3 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events (including lab abnormalities, as applicable):
  - Adverse events that require discontinuation of study treatment as per Table 6-5, Table 6-8 or Table 6-12.
  - Adverse events that require dose reductions beyond the permitted dose reductions of PAN/REV/BTZ outlined in Table 6-3 and Table 6-6, respectively
  - Adverse events that lead to a PAN, REV and/or BTZ dose delay of more than 28 days from the intended day of the next scheduled dose, unless the patient was clearly benefitting from study treatment and the cause of the delay has been resolved.
- Pregnancy
- Dose interruption of PAN, REV and/or BTZ of more than 28 days from the intended day of the next scheduled dose for any reasons, unless the patient was clearly benefitting from study treatment and the cause of the delay has been resolved.
- Start of new anti-neoplastic therapy
- Documented disease progression (by investigator)
- Death
- For use of prohibited treatment refer to Section 6.4.3 and Section 14.1.
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should undergo an end of treatment visit within 7 days of last dose (whichever, study drug (PAN/BTZ/Dex/REV) was given last) and enter the 30 day follow-up period (either post-treatment follow-up for efficacy (see Section 7.1.6) or survival follow-up (see Section 7.1.7) based on the reason for discontinuation). For assessments performed at the end of treatment visit please refer to Table 7-1.

If the decision to discontinue study treatment is made on the day of a regular visit, this visit may become the EOT visit rather than having the patient return for an additional visit.

The reason for discontinuation of study treatment should be recorded on the End of Treatment Disposition CRF page.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

[redacted]

7.1.4 Replacement policy

Patients who do not proceed directly to ASCT after induction phase will be replaced. It is expected that approximately 15% of patients will need to be replaced.

7.1.5 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.6 Follow up for Safety Evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment. Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Serum and urine sample collection for central and local M-protein assessment by PEP, and IF

Blood (serum) and 24-h urine for M-protein assessment will be collected at screening, cycle 1 day 1 and the start of every cycle thereafter. An additional assessment of serum and urine for PEP and IF will be done on cycle 4 day 21 prior to stem cell collection. Serum samples will be sent to a central lab for analysis. Samples will be processed and shipped as per instructions

in the respective laboratory manual. Urine samples will be evaluated locally. During the course of autologous transplant, no labs will be collected.

7.2.1.2 Serum sample collection for local FLC assessment

Blood (serum) for FLC assessment will be collected at screening and at the start of each cycle during induction,on cycle 4 day 21 prior to stem cell collection, every 28 days during cycle 6 and at the start of every cycle thereafter. FLC will be analyzed locally. During the course of autologous transplant, no labs will be collected.

7.2.1.3 Cytogenetics in bone marrow by local assessment

A bone marrow aspirate/biopsy for cytogenetics (by FISH) should be performed during the 21 day screening period. Assessment of cytogenetics by FISH will be evaluated locally.

7.2.1.4 Plasma cell count in bone marrow by central assessment

A bone marrow aspirate/biopsy for plasma cell quantification should be performed at screening, cycle 4 day 21, cycle 6 day 1 (prior to the start of maintenance), and EOT. Additional Bone marrow aspirates/biopsies should be performed throughout the trial, at any point after cycle 4 day 21, to confirm a Complete Response. Assessment of PCC will be evaluated locally.

Either BM aspirate or biopsy can be used for plasma cell quantification. However, the same method should be used throughout the trial, if possible. In case both, BM aspirate and BM biopsy were performed, the diagnostic/response criteria need to be satisfied by both assessments and the highest of both percent values should be used.

7.2.1.5 Minimal Residual disease assessments in bone marrow (MRD)

Additional assessment for depth of response will evaluate for the presence of molecular CR (mCR) and will be performed and analyzed using the commercially available ClonoSEQ assay (Adaptive Biotechnologies) (Faham et al 2014). A bone marrow aspirate should be performed during the screening period and sent for central analysis using the kits provided. A repeat aspirate sample should be sent for analysis if a patient achieves CR. When performing the aspirate for PCC to confirm CR, ensure that you have an additional aspirate in the 10cc EDTA tube for central MRD analysis

For additional response categories in MM according to IMWG criteria see Table 14-6 of Section 14.1.5.1.

7.2.1.6 Assessment of soft tissue plasmacytoma

7.2.1.6.1 Imaging assessment by CT/MRI/PET

Baseline imaging assessment: A CT/MRI/PET to assess presence of soft tissue plasmacytoma will be performed at screening within 21 days of start of study treatment (Day -21 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 21 days prior to start of treatment, including before signing the main study ICF, can be

[redacted]

considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

Post-baseline imaging assessments:

Repeat imaging should be done as clinically indicated or to confirm CR, sCR, and PD for all patients. Imaging assessments should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1).

7.2.1.7 Full body skeletal survey

Any X-ray and/or CT/MRI already completed during the regular work-up of the patient within 21 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline X-ray and/or CT/MRI images for this study. Any X-ray and/or CT/MRI imaging assessments obtained after randomization cannot be considered baseline images.

Post-baseline, a full body skeletal survey will only be completed as clinically indicated, e.g. to document a response of PR or better, or to evaluate disease progression.

7.2.1.8 Response assessment by Investigator

The response assessment by Investigator should be based on all available data (including central data) as per IMWG guidelines (see Table 14-5 and Table 14-6). Response assessments by investigator will be done once per cycle beginning with cycle 2.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, ECOG performance status, height and weight, vital signs, ECG, laboratory assessments including hematology, chemistry, electrolytes, thyroid function, coagulation, troponin I, and calculated creatinine clearance, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination at screening will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1. All subsequent physical exams should be abbreviated.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs include blood pressure and pulse measurements, body temperature and respiratory rate will be monitored as per the visit schedule (see Table 7-1). After the patient has been

[redacted]

sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure and pulse will be measured. Body temperature may be measured orally or via ear.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as per visit schedule (see Table 7-1). Height will only be measured at the screening visit, whereas weight will be measured on Day 1 of every cycle and at the EOT visit. The weight measured on Day 1 of a cycle will be used by the study personnel to calculate the BSA of the patient for a specific cycle. Although the use of the Gehan and George equation (see Section 6.1.1) is recommended, the BSA can be calculated as per standard practice at the site. However, the same formula/method should be used consistently throughout the study. The BSA calculated at the beginning of every cycle will be used to calculate the total BTZ s.c. dose/day to be administered during a specific cycle.

7.2.2.4 Performance status

The performance status for a patient will be assessed according to the ECOG performance status scale (Section 14.2) following the visit evaluation schedule given in Table 7-1.

7.2.2.5 Laboratory evaluations

All lab parameters outlined in Table 7-3, will be evaluated locally as per the visit evaluation schedule (see also Table 7-1). Novartis must be provided with a copy of the lab certification and tabulation of the normal ranges for all lab parameters of all local labs used.

The local lab results will be entered on the respective Local Laboratory CRF pages.

During the study treatment, all lab results should be available prior to administration of PAN/BTZ/REV, in order for the investigator to implement dose modifications based on the lab results as necessary (e.g. interrupt dosing, see Section 6.3, and Table 6-2, Table 6-4, Table 6-5, and Table 6-8 for details).

Abnormal laboratory values or test results constitute an AE only, if they induce clinical signs or symptoms, and are considered clinically significant (i.e. require dose modification and/or interruption of study treatment, lead to clinical symptoms, cause study treatment discontinuation or constitute in and of itself an SAE) or require therapy. These events should be recorded on the AE CRF as well as the appropriate laboratory CRF and/or comments CRF page. If the administration of study treatment is delayed/modified due to unacceptable lab toxicities (see Section 6.3), re-evaluation should at a minimum be performed prior to the next scheduled study treatment.

Additional labs parameters should be evaluated as clinically indicated. These results will be recorded on the Unscheduled Visit CRF.

7.2.2.5.1 Hematology

Hematology tests are performed as indicated in Table 7-3.

[redacted]

7.2.2.5.2 Chemistry

Clinical chemistry tests are performed as indicated in Table 7-3.

7.2.2.5.3 Electrolytes

Electrolytes are performed as indicated in Table 7-3.

7.2.2.5.4 Thyroid

Thyroid function tests are performed as indicated in Table 7-3.

7.2.2.5.5 Coagulation

The coagulation tests are performed at screening as indicated in (Table 7-3). The coagulation profile should be repeated as clinically indicated and the results should be recorded on the Unscheduled Visit CRF. If the patient is receiving Coumadin or other anti-coagulant therapy then the coagulation parameters should be monitored more frequently at the discretion of the investigator (please also see Section 6.3.2.1).

7.2.2.5.6 Troponin I

Troponin should be evaluated as indicated in Table 7-3.

7.2.2.5.7 Creatinine Clearance

The creatinine clearance is calculated as indicated in Table 7-3 using the Cockroft-Gault formula.

7.2.2.5.8 Pregnancy and assessments of fertility

Since highly effective contraception is required pregnancy testing should be done as indicated in Table 7-2. In case of a positive test, the investigator must contact Novartis to discuss options for the patient.

Post-menopausal women must have been amenorrheic for ≥ 12 months in order to be considered 'of no-childbearing potential'.

Table 7-2 Local clinical laboratory parameters collection plan

Hematology	Complete blood cell count (RBC and WBC) with absolute differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes, blast cells, other), hemoglobin, platelet count ***To be performed at:*** Screening Cycles 1-5: Days 1, 4, 8, 11 (Cycle 4 only: Day 21); Cycle 6: Days 1, 29 and 57; Day 1 of Cycles 7+ End of treatment Unscheduled: as clinically indicated

[redacted]

Basic Metabolic Panel	ionized serum calcium (if total calcium is abnormal, collect ionized calcium), sodium, potassium, BUN/urea, creatinine, phosphorus, magnesium, glucose ***To be performed at:*** Screening Cycles 2-5: Days 4 and 11 Unscheduled: as clinically indicated
Creatinine Clearance (CCL) calculated	CCL is calculated by the site using Cockroft Gault formula based on serum creatinine results in µmol/L (Cr), age, weight (Wt) in kg and sex of patient. **Cockcroft-Gault CCL = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)** On days where weight is not determined as per protocol the last determined weight closest to the visit date can be used (e.g. weight determined on Day 1 of the same cycle). ***To be calculated at:*** Screening Cycle 1: Days 1, 4, 8, 11; Cycles 2-5: Day 1 & 8 (Cycle 4 only: Day 21); Cycle 6 Days 1, 29 and 57; Cycles 7+ Day 1; End of treatment Unscheduled: as clinically indicated
Complete Metabolic Panel	Basic Metabolic Panel plus: Serum albumin, total protein, total bilirubin, direct and indirect bilirubin (only if total bilirubin is abnormal) AST/SGOT, ALT/SGPT, Beta 2 microglobulin, LDH. Biochemistry tests should be performed after the patient has fasted, if possible. ***To be performed at:*** Screening Cycle 1: Days 1, 4, 8, 11; Cycles 2-5: Day 1 & 8 (Cycle 4 only: Day 21); Cycle 6 Days 1, 29 and 57; Cycles 7+ Day 1 Unscheduled: as clinically indicated End of treatment Unscheduled: as clinically indicated
Thyroid	Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine). ***To be performed at:*** Screening End of treatment
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), activated partial thromboplastin time (APTT) and fibrinogen; ***To be performed at:*** Screening Unscheduled: as clinically indicated
Other lab test Troponin 1	Troponin 1 ***To be performed at:*** Screening
Pregnancy Test for all women (female patients) of childbearing potential (WOCP)	***Pregnancy test in serum*:** Screening (within 7 days prior to the first planned dose of study treatment) End of treatment ***Pregnancy test in urine:*** Day 1 of each cycle

[redacted]

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed according to Table 7-3. On days when ECGs are to be performed, the patient should take their study medication at this site, after the pre-dose ECGs have been performed.

The pre-dose ECGs should be performed prior to the planned dose of PAN and BTZ. The 2h post-dose ECGs should be performed around the 2h post-dose time point. Triplicate ECGs should be used in the event that QTcF prolongation $\geq$ 480 msec is observed. Triplicate ECGs should be continued until average QTcF is < 480 msec for 3 consecutive cycles.

Information on the performance of the ECG will be documented on the ECG CRF page, or on the Unscheduled Visit CRF page, as applicable.

Review of all ECGs at site:

Treatment decisions should be based on the real-time assessment of QTcF values at the site, as determined by the automated machine reading or as measured and calculated by trained personnel at the site. All cardiac events should be treated as per the local standard of care and referred to a specialist, if clinically indicated (see Section 6.3.1 for required dose modifications for prolonged QTcF). Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be made after discussion between the Investigator and Sponsor as needed.

It is advisable to perform the screening at least 3 days prior to planned first dose.

Table 7-3 ECG collection plan

Cycle	Day of cycle	ECG monitoring
Screening	n/a	12 Lead ECG to assess eligibility [a]
Cycle 1	1 and 4	Pre-dose and 2h post PAN dose: 12 lead ECG [b]
Cycle 2 to Cycle 5	1	Pre-dose: 12 lead ECG
Cycles 6+	As clinically indicated	Pre-dose: 12 lead ECG
End of Treatment	n/a	12-Lead ECG

[a] Triplicate ECGs should be used in the event that QTcF prolongation $\geq$ 480 msec is observed. Triplicate ECGs should be continued until average QTcF is < 480 msec for 3 consecutive cycles.

[b] Refer to Table 6-12 for the recommended dose modifications due to QTcF prolongation

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

A MUGA scan or ECHO to assess left ventricular ejection fraction (LVEF) will be performed within the screening period prior to the first administration of study treatment. Additional, unscheduled assessments may be performed at the Investigator's discretion if there are signs or symptoms of cardiotoxicity and will be recorded on the Unscheduled Visit CRF page.

[redacted]

The LVEF result and a general comment on the interpretation of the assessment will be recorded on the Cardiac Imaging CRF page.

7.2.3 Resource utilization

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though the Study Evaluation Completion page.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates) (add or Ongoing at End of Study for NOVDD)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or

[redacted]

Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)

- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown) Delete for NOVDD Trials as outcome is not collected
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.1.1 Adverse Events related to ASCT

Adverse events that occur while the patient is off treatment for transplant and are considered to be solely attributable to the transplant will be captured on a separate Adverse Event page.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (for the purposes of this study, inpatient hospitalization for stem cell collection or autologous transplant will not be considered a serious adverse event)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signatures will be provided to each site.

[redacted]

Follow-up information is submitted in the same way as the original SAE Report.. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment to any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

[redacted]

8.7 Steering Committee

The steering committee will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

[redacted]

assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Central lab data, including MRD assessment and M-protein assessments, will be transferred periodically throughout this study. Data will be transferred via WDCS and will be reconciled with the clinical database.

9.4 Database management and quality control

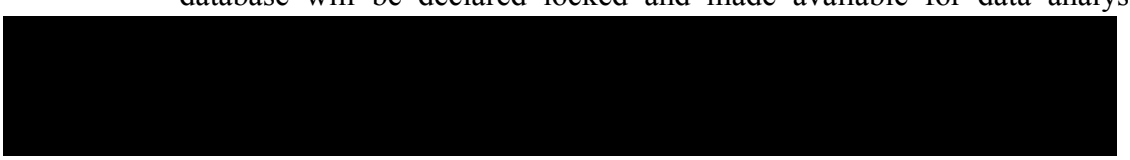
Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, unused drug supplies will be returned to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is



required prior to making any database changes to locked data, by joint written agreement between the Statistician and Medical Director.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by a designated CRO. It is planned that the data from all centers that participate in this study will be used, so that an adequate number of patients will be available for analysis.

Data cut-off date for the clinical study report will be when the last patient completes 4 cycles of induction and has corresponding efficacy assessments, or discontinues study treatment. The analysis performed for the CSR as described above will be considered primary. The CSR will be updated with additional efficacy and safety data from patients continuing in the study including the three year follow-up for survival.

Unless, otherwise specified all statistical tests will be performed at a two-sided significance level of 0.05.

10.1 Analysis sets

Type here

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment (and strata, if applicable) they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment (regimen) they actually received.

A precise definition of "actually received" will be added in the RAP.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of all patients from the FAS population who received at least one dose of the study drug and had no major protocol deviation. Protocol deviations leading to exclusion from the PP population will be justified and specified in the study Validation and Planning (VAP) and Report and Analysis Plan (RAP) documents prior to the data base lock.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data, including disease characteristics, will be summarized descriptively by treatment group and for all patients for the FAS.

[redacted]

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

Data on the study treatment administration will be summarized all study drugs (panobinostat, lenalidomide, bortezomib and dexamethasnae). The duration of treatment and relative dose intensity of each of the components of study treatment will be summarized using descriptive statistics. Dose adjustments and interruptions for panobinostat and bortezomib will also be summarized.

10.3.2 Concomitant medications

Concomitant medications and significant non-drug therapies will be summarized.

10.4 Primary objective

The primary objective for this trial is to evaluate the efficacy of the combination of RVD + panobinostat compared to RVD alone.

10.4.1 Variable

The primary endpoint will be analyzed based on nCR/CR rate of the combination of panobinostat with bortezomib, lenalidomide and dexamethasone (P-RVD) vs RVD in newly diagnosed multiple myeloma patients after 4 cycles of therapy. The analysis will be based on Investigator assessment of response.

10.4.2 Statistical hypothesis, model, and method of analysis

The study is designed to test the following statistical hypothesis:

H_0: nCR/CR rate (RVD combination) - nCR/CR rate (PVD alone=0% versus

H_1: nCR/CR rate (RVD combination) - nCR/CR rate (PVD alone=0% versus >= 18%

This test will be performed using a Z-test at one-sided siginificance level of 0.05.

In addition, point estimate and exact 95% two-sdied confidence interval of of nCR/CR rate in ecah arm and of the difference in rates in the two will be calculated.

The confirmative analysis based on the FAS set will take place after all evaluable patients complete the first four cycles of induction for the primary endpoint. Sensitivity analysis will be performed in the Per-Protocol set.

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed in any manner, except for overall response rate. A patient who discontinues for any reason before the data cut-off date of the CSR without a confirmed assessment of response will be considered a non-responder.

10.4.4 Supportive analyses

Sensitivity analysis of the primary endpoint adjusting for adverse cytogenetic risk and ISS disease stage at baseline will be performed in FAS and the Per-Protocol set.

Details of the sensitivity analysis will be included in the Statistical Analysis Plan before the data base lock.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objective of this study is to assess MRD negativity after 4 cycles of induction by next gen sequencing. Data for this analysis will be provided by a central laboratory. The corresponding endpoint will be MRD negativity by next gen sequencing after 4 cycles of induction therapy.

10.5.2 Other secondary efficacy objectives

There are a number of additional secondary efficacy objectives:

- To assess best overall response rate (ORR) and MRD negativity after ASCT and maintenance. This endpoint will be analyzed by ORR (CR + PR) by Investigator assessment and MRD negativity by next gen sequencing (data provided by a central laboratory) after ASCT and maintenance.
- To assess depth of response by IMWG criteria. This will be measured by the rate of VGPR, CR and sCR by Investigator assessment.
- To assess the duration of response. This will be analyzed by determining the duration of response based on Investigator assessment according to the clinical database.
- To assess overall survival and progression free survival rates three years after study entry. OS and PFS will be analyzed once the last patient to enter the study completes 3 years of therapy..

Progression-free survival (PFS) is defined as the time from the date of first study drug to the date of the first documented disease progression or confirmed relapse or death due to any cause.

Overall survival (OS) is defined as the time from date of first study drug to date of death due to any cause.

Progression-free survival and overall survival will be summarized by using Kaplan-Meier product-limit method and displayed as graphs. If applicable, estimates of the 25^{th} percentile, median and 75^{th} percentile and their respective 95% confidence intervals will be provided.

All analyses will be based on the FAS population.

[redacted]

The point estimate and 95% confidence interval of best overall response and MRD negativity rate and depth of response will be provided in the FAS set.

The duration of overall response (DOR) is defined as the time from the date of first documented occurrence of confirmed response (CR or nCR or PR) to the date of the first documented confirmed disease progression or confirmed relapse or death due to multiple myeloma. Patients who do not have a confirmed response by the data cut-off date of the CSR will be excluded from the analysis of DOR.

For CSR primary analysis of the time to events (DOR and PFS), a patient who didn't have the event at the date the analysis data cut-off would be censored at the time of the cut-off or at the last adequate assessment in case of a discontinued patient. An adequate response assessment is considered any disease assessment indicating disease status apart from "unknown" or "not done".

For OS, if a patient is not known to have died, survival will be censored at the date of the last contact.

All analyses of the secondary endpoints except OS and PFS will occur after all evaluable patients complete transplant and begin maintenance.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to *x* days after last dose of study medication
3. post-treatment period: starting at day *x*+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

[redacted]

Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The study's bio-statistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In cases the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

[redacted]

10.5.3.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results have to part of the CDP, MAP, CSP and RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

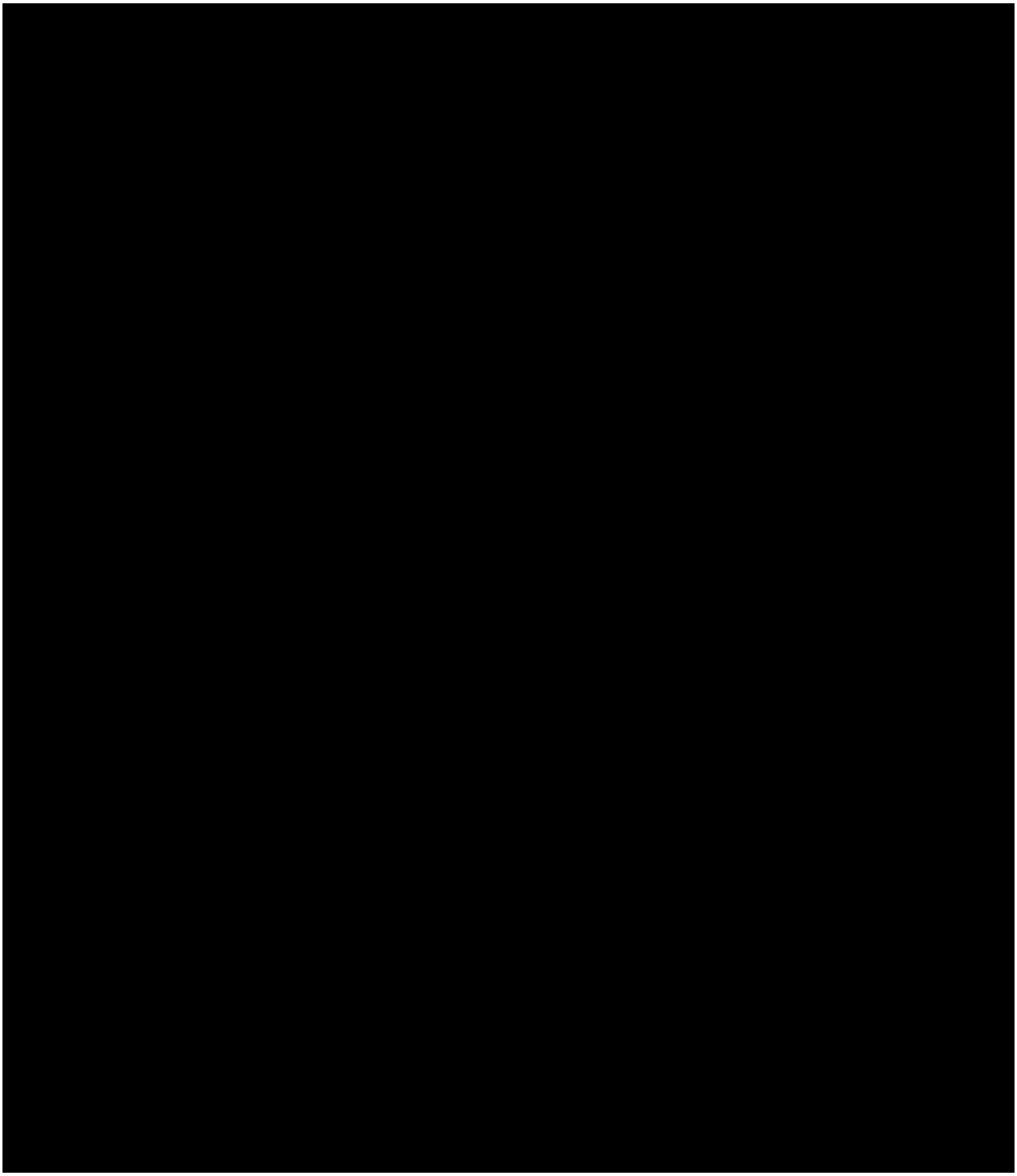
[redacted]

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Not applicable.



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10.7 Interim analysis

There will be two planned interim analyses for this trial. The first will take place after all evaluable patients complete the first four cycles of induction for the primary endpoint. At this time the confirmative analysis of the primary endpoint and descriptive summary of all other efficacy data will be performed. The second interim analysis will occur after all evaluable patients complete transplant and begin maintenance. At the second interim, analysis of all secondary efficacy endpoints except OS and PFS will take place. At each interim analysis, all safety data will be summarized.

No adjustment of the significance level for the tests (s) of the efficacy endpoints will be necessary as result of these interim analyses.

10.8 Sample size calculation

The sample size of the study is based on the assumption that in the RVD alone arm the nCR/CR rate will be 7% and adding Pano to RVD will improve the nCR/CR rate to 25%. For one sided alpha=0.05, fifty patients in each arm will have 81% power to detect this improvement. To get 50 evaluable patients in each arm an additional 6 patients will be randomized in each arm for a total of 112 patients.

PASS 2008 was used to calculate the sample sizes.

10.9 Power for analysis of key secondary variables

The power analysis for the key secondary variable of molecular CR (mCR) is based on the assumption that the mCR rate at 4 cycles will be 4% with RVD alone and will increase to 15% if panobinostat is added to RVD. For a one sided alpha=0.05, fifty patients in each arm will have 81% power to detect this improvement.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this

[redacted]

protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

[redacted]

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

[redacted]

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Appendix 1: Co-medications which are known to prolong the QT interval and/or induce Torsades de Pointes, are strong CYP3A4/5 inhibitors/inducers or sensitive CYP2D6 substrates

14.1.1 Medications which are known to prolong the QT interval and/or induce Torsades de Pointes ventricular arrhythmia should be avoided

Patients who are currently receiving treatment with any of the medications in Table 14-1, and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a panobinostat clinical study, will be excluded from the study. Patients enrolled in a panobinostat clinical study may not begin treatment with any of the medications listed in Table 14-1 unless discussed with the Sponsor and approval is granted by the Sponsor. The Sponsor may agree to temporarily discontinue panobinostat treatment (e.g., for 72 hours) during administration with these drugs or withhold medications in Table 14-1 for at least 72 hours when panobinostat is to be administered.

NOTE: It is of great importance to avoid combining drugs listed below in Table 14-1 and Table 14-2 (CYP3A inhibitors) in combination with panobinostat especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

In general, medications listed in Table 14-1, Table 14-3 and Table 14-4 should be avoided. Medications listed in Table 14-2 and Table 14-3 are to be used with caution when co-administered with panobinostat. The use of any of the drugs in Table 14-1, Table 14-2, and Table 14-3, and Table 14-4 in combination with panobinostat must be discussed with the Sponsor.

Table 14-1 Medications which are known to prolong the QT interval and/or induce Torsades de pointes to be avoided

Antiarrhythmics
amiodarone
disopyramide
dofetilide
flecainide
ibutilide
procainamide
quinidine
sotalol
Anticancer
arsenic trioxide
vavdetanib

[redacted]

Antihistamines
astemizole
terfenadine
Antibiotics
azithromycin
clarithromycin
erythromycin
moxifloxacin
sparfloxacin
Antianginal
bepridil
Antimalarial
chloroquine
halofantrine
Antipsychotics
chlorpromazine
haloperidol
mesoridazine
pimozide
thioridazine
Antinausea
domperidone
droperidol
dolasetron (intravenous and oral)^
Anti-infective
pentamidine
Antilipemic
probucol
Antidpressants
citalopram
Opiate agonists
levomethadyl
methadone
GI stimulant
cisapride
^Intravenous dolasetron is contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Based on this finding, both intravenous and oral dolasetron are prohibited to be taken with panobinostat.

This is not a comprehensive list of medications which may prolong the QT interval and/or induce Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.

The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

Medications listed on the website which do not appear in Table 14-1 above may be used with caution at the discretion of the investigators.

Ondansetron (a known CYP2D6 substrate, Table 14-3 has been associated with Torsades de pointes and QT prolongation but has not been shown to cause Torsades de pointes. Therefore, ondansetron is not per se prohibited to be combined with panobinostat but caution is to be exercised and close monitoring for signs and symptoms of QT prolongation is recommended.

14.1.2 Dose reduce panobinostat when combined with medications which are known strong CYP3A inhibitors

Panobinostat is a substrate of CYP3A4/5 with minor involvement of CYP2D6, and CYP2C19 in in vitro evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study [CLBH589B2110].

Multiple ketoconazole doses at 400 mg increased Cmax and AUC of panobinostat by 1.6- and 1.7-fold, respectively, but with no change in Tmax or half-lives in 14 cancers patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition. However, panobinostat dose should be reduced from 20 mg to 10 mg when combined with medications which are known strong CYP3A inhibitors. If patients are already at reduced doses of panobinostat 15 mg or 10 mg, combination with a strong CYP3A inhibitors should be avoided. If this is not avoidable, patients should be monitored closely for toxicity.

Table 14-2 Medications which are known strong CYP3A inhibitors

Antibiotics
telithromycin
troleandomycin
Protease inhibitors
Indinavir
lopinavir
nelfinavir
ritonavir
saquinavir
tipranavir
Antifungals
itraconazole
ketoconazole
posaconazole
voriconazole
Antivirals
boceprevir
telaprevir
Others
cobicistat
conivaptan
elvitegravir
mibefradil
nefazodone
Miscellaneous drugs or products
Star fruit and pomegranate product and juice
* azithromycin and regular orange juice are allowed.
Although clarithromycin is a known strong CYP3A inhibitor, it is also known to prolong QT intervals which is listed in Table 14-1 and is prohibited to be taken with panobinostat. This drug is thus not listed again in Table 14-3.

This is not a comprehensive list of medications which may inhibit CYP3A4/5. The above list was compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at http//medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp and "drug interaction database" from University of Washington.

Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp.

[redacted]

14.1.3 Medications which are known strong CYP3A inducers are to be avoided

Panobinostat plasma exposure was reduced by 20% or more when combined with bortezomib and dexamethasone (B2207 and D2308). Co-administration of panobinostat with strong CYP3A inducers was not evaluated in vitro or in a clinical trial however, a reduction in panobinostat exposure is likely. An approximately 70% decrease in the systemic exposure of panobinostat in the presence of strong inducers of CYP3A was observed in simulations using mechanistic models. Therefore, the concomitant use of strong CYP3A inducers should be avoided.

Table 14-3 Medications which are known strong CYP3A inducers are to be avoided

Strong Inducers (AUC decreased by ≥ 80%)
avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)

14.1.4 Medications which are known sensitive CYP2D6 substrates or substrates with narrow therapeutic index are to be avoided

Panobinostat was also shown to be a CYP2D6 inhibitor (Ki 0.17 μM) in vitro. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorphan as CYP2D6 substrate was conducted in study [CLBH589B2109].

Panobinostat increased the median Cmax and AUC of a sensitive substrate of CYP2D6 by approximately 80% and 60%, respectively; however these increase were highly variable (increased the Cmax and AUC0-∞ of dextromethorphan by 20% to 200% and 20% to 130% (interquartile ranges), respectively).

Avoid co-administrating panobinostat with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index (i.e., thioridazine, pimozide). If concomitant use of CYP2D6 substrates is unavoidable, patients should be frequently monitored for adverse reactions.

[redacted]

Table 14-4 Medications which are known sensitive CYP2D6 substrates or substrates with a narrow therapeutic index are to be avoided

Antipsychotics	**Tricyclics/tetracyclics**
perphenazine	desipramine
thioridazine[1]	
pimozide[1]	
	Others
Beta blockers	atomoxetine
Metoprolol	dextromethorphan
Nebivolol	tolterodine
Antidepressants	**Antiemetics**
Venlafaxine	ondansetron^
[1] substrate with narrow therapeutic index (NTI): drug whose exposure-response indicates that increases in its exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns. ^ Intravenous dolasetron is a CYP2D6 substrate and contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Please see Table 14-1.	

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website http://medicine.iupui.edu/clinpharm/DDIs/ClinTable.asp.

14.1.5 References (available upon request)

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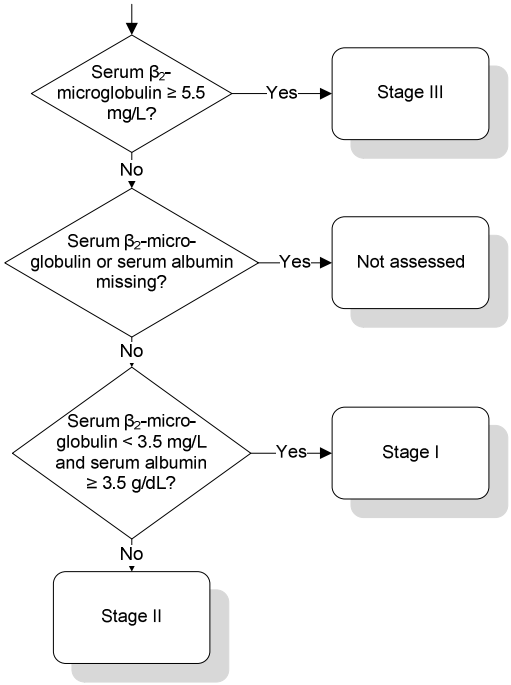
[redacted]

Figure 14-1 International Staging System



14.1.5.1 Response assessment per IMWG criteria

Response assessment according to IMWG criteria is described in Table 14-5 and Table 14-6. For assessing response, criteria for PD should be assessed first. When PD can be ruled out, criteria for positive response should be checked.

For patients with non-measurable disease at baseline or missing baseline assessments of M-protein in urine and serum and FLC, only PD criteria will be checked. In case PD is not met, "unknown" should be assigned.

The response categories sCR, CR, VGPR, PR and PD need to be confirmed. The criteria are defined in Section 14.1.5.1.1 and Section 14.1.5.1.2.

For patients with measurable disease at baseline by one component only (serum M-protein or urine M-protein), the measurable component will be used to derive MR or PR. However, VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Irrespective of the measurability (M-protein measurable by PEP in serum, urine, or both), M-protein should be investigated regularly in both serum and urine and needs to be considered for response assessment.

Assessments to determine PD are dependent on change from nadir.

[redacted]

Table 14-5 Response classification in MM according to IMWG criteria

Response category	Definition*
Stringent complete response (sCR)	• CR criteria as defined below AND • normal FLC ratio AND • Absence of clonal PCs in bone marrow analyzed by immunohistochemistry or 2- to 4-color flow cytometry[#].
Complete response (CR)	• Negative immunofixation of serum and urine AND • In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytoma(s), AND • < 5% plasma cells in bone marrow. • In case the only measurable disease at baseline is the serum FLC assessment, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR.
Very good partial response (VGPR)	• Serum and/or urine M-protein detectable by immunofixation but not on PEP OR ((≥ 90% reduction from baseline in serum) AND (urine M-protein < 100 mg/24h)) AND • In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in the SDP by ≥ 50% from baseline is required In case the only measurable disease in a patient at baseline is the serum FLC level (i.e. no measurable disease in serum and urine PEP), a decrease of > 90% in the difference between involved and uninvolved FLC levels from baseline is required.
Partial response (PR)	• (≥ 50% reduction from baseline in serum M-protein) AND (≥ 90% reduction from baseline in 24h urine M-protein OR urine M-protein < 200 mg/24h) If the serum and urine M-protein are not measurable at baseline a ≥ 50% reduction from baseline in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC assay is also not measurable, ≥ 50% reduction from baseline in percent plasma cells in bone marrow is required instead of M-protein measurement, provided baseline percentage in plasma cells in bone marrow was ≥ 30%. AND • In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in the SPD by ≥ 50% from baseline is required.
Stable disease (SD)	• Not meeting the criteria for mCR, sCR, CR, VGPR, PR, PD

[redacted]

Response category	Definition*

Progressive disease (PD)[&]	• Increase of at least 25% from the nadir in at least one of the following criteria:
	  • serum M-protein (absolute increase must be ≥ 0.5 g/dL)
	  • urine M-protein (absolute increase must be ≥ 200 mg/24h)
	  • only in patients with non-measurable serum and urine M-protein levels: difference in involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
	  • Only in patients with non-measurable disease in serum and urine M protein and by FLC: Bone marrow plasma cell percentage (absolute % must be ≥ 10%)
	OR
	• definite development of new lytic bone lesions or definite increase from baseline in size of lytic bone lesion(s)
	OR
	• definite development of new soft tissue plasmacytoma(s) or definite increase from nadir in existing soft tissue plasmacytomas
	OR
	• development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or ionized calcium > 6 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will be assessed in case the corrected serum calcium level was ≤ 11.5 mg/dL (ionized serum calcium ≤ 6 mg/dL) at an earlier assessment (including baseline/post-baseline) and increased beyond 11.5 mg/dL (> 6 mg/dL).
	"25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

* If not defined otherwise, all of the criteria apply. # Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is a k/l ratio of > 4:1 or < 1:2 & Biological relapse or significant paraprotein release does not constitute PD unless ≥ 1 criterion for PD is met	

In case response assessment is incomplete, e.g. one or more mandatory assessments are missing, at a time point then the category "unknown" will be assigned to the response assessment of that time point unless a criterion for PD is met.

In addition to the criteria above, further response categories are endorsed by the IMWG as defined in Table 14-6.

[redacted]

Table 14-6 Additional response categories in MM according to IMWG criteria

Response category	Definition*
Molecular complete response (mCR)	• All criteria of a CR AND • negative by ASO-PCR (minimal sensitivity 10^{-5}) or equivalent methods such as BCR sequencing
Immunophenotypic CR (iCR)	• All criteria of sCR AND • Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analyzed by multiparametric flow cytometry (>4 colors)
Minimal response (MR)	• (Reduction from baseline in serum M-protein by ≥25%) and (reduction from baseline in 24h urine M-protein by ≥50%) AND • In case of soft tissue plasmacytomas at baseline, a reduction in the size of ≥25% is required AND • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response) **Minimal response should only be assessed in patients with relapsed or refractory myeloma.**

For VGPR, PR and MR: In case disease is measurable in serum or urine only, criteria for serum and urine M-protein are to be checked for the measurable samples only (i.e. serum or urine).

14.1.5.1.1 Confirmation of response

According to IMWG criteria, confirmation of response is required for all response categories other than SD. The intention of this confirmation is to rule out laboratory or other errors (Durie et al 2006). For response confirmation, a consecutive assessment at any time is sufficient; no time window is specified by IMWG. Therefore, confirmation assessment can be performed on the same day of the initial assessment. It is recommended to do the confirmation assessment as soon as possible. This confirmation should be obtained in all instances by M-protein assessments (tests may include part or all of tests PEP/sFLC depending on measurability and response level). Details need to be specified in the study protocol.

Response assessments should be captured in the CRF per time point without considering confirmation. This applies to response assessments by investigator as well as by IRC.

For confirmation of response, the following rules apply which will be implemented for statistical analyses:

- It is not required to repeat assessments on bone marrow. However, at least one bone marrow assessment is required to qualify for CR or better (sCR, iCR or mCR).
- In case imaging studies were done, it is necessary that they exclude evidence of PD with regard to new lytic bone lesions for mCR, iCR, sCR, CR, VGPR, PR, MR and SD.

[redacted]

Imaging is indicated in case of clinical suspicion of new or worsened lytic bone lesions e.g. bone pain.

- In case the confirmation assessment revealed a better category compared to the previous assessment (e.g. VGPR after PR), the response category of the previous assessment will be considered as confirmed (PR).
- In case the confirmation assessment revealed a worse category compared to the previous assessment (e.g. VGPR after CR), the response category of the subsequent assessment will be considered as confirmed (VGPR).
- In case of repeated measurements of a variable at a given response assessment resulting in more values than required for an assessment and confirmation, the worst assessment has to be considered for response assessment by applying the rules given above.

14.1.5.1.2 Confirmation of PD

Declaration of PD requires confirmation in case the PD was determined based on M-protein measurement. There is no minimum time interval but confirmation of increase in M-protein or FLC should be done as soon as possible.

PD has to be assessed and entered in the CRF per time point without considering confirmation. Confirmed PD will be determined by statistical analyses.

This applies to PD assessments by investigator as well as by IRC.

[redacted]

14.2 Appendix 2: ECOG performance status scale

This scale is used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

Table 14-7 ECOG performance status scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit to: the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Post-Authorization Safety Study (PASS)

Is this a PASS study - If yes, follow instructions below	☐ Yes ☒ No

[redacted]