Clinical Development

LBH589 / Panobinostat / Farydak®

Protocol CLBH589D2222

A multicenter, randomized, open-label Phase 2 study evaluating the safety and efficacy of three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents

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List of abbreviations

AE(s)	Adverse Event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASO-PCR	Allele-specific oligonucleotide polymerase chain reaction
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical Class
AUC	Area under the curve
BCR	B-cell receptor
b.i.d.	*bis in diem*/twice a day
BIW	Twice a week
BL	Baseline
BM	Bone marrow
BSA	Body surface area
BTZ	Bortezomib (Velcade®)
C	Cycle of study treatment
CCL	Creatinine clearance
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Confidence limit
Cmax	Maximum observed plasma concentration
CMO&PS	Chief Medical Office & Patient Safety
Cmin	Minimum observed plasma concentration
CR	Complete Response
CRAB	Commonly noted signs and symptoms of MM (Calcium elevation, Renal dysfunction, Anemia, Bone destruction)
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
CT	Computer tomography
CTCAE	Common Terminology Criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day of cycle
D	Captured in database
DACi	Pan-deacetylase inhibitor
DAR	Dose administration record
DBP	Diastolic blood pressure
decr.	Decrease
Dex	Dexamethasone
DFS	Disease-free survival
Dia	Diarrhea

diff	Difference
DILI	Drug induced liver injury
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOT	End-of-treatment
EU	European Union
FACT	Functional assessment of cancer therapy
FAS	Full analysis set
FBSS	Full body skeletal survey
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FT4	Free thyroxine
G-CSF	Granulocyte colony stimulating factor
GCP	Good clinical practice
GI	Gastrointestinal
GOG	Gynecologic Oncology Group
H3/4	Histone 3 or 4
HDAC	Histone deacytelase
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSP90	Heat shock protein 90
IA	Interim analysis
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonization
iCR	Immunophenotypic CR
IEC	Independent Ethics Committee
IF	Immunofixation
IHC	Immunohistochemistry
IMiD(s)	Immunomodulatory agent(s)
IMWG	International Myeloma Working Group
incr.	increase
INR	International standardized ratio
INV	Investigator (assessment)
IRB	Institutional Review Board
IRC	Independent Review Committee

IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ISS	International Staging System
ITT	Intent to treat
IWRS	Interactive web response system
i.v. or iv	Intravenous(ly)
LBBB	Left bundle branch block
Len	lenalidomide
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MDRD	Modification of Diet in Renal Disease (study)
MedDRA	Medical dictionary for regulatory activities
MM	Multiple Myeloma
MR	Minimal response
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NC	No change
NCA	Non-compartmental PK analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nCR	Near complete response
NDA	New Drug Application
NTI	Narrow therapeutic index
Ntx	Neurotoxicity
o.d.	omnia die/once a day
ORR	Overall response rate
OS	Overall survival
OW	Once a week
p.o.	per os/by mouth/orally
PAN	Panobinostat / LBH589 / Farydak®
PAS	Pharmacokinetic analysis set
PBO	Placebo
PC	Plasma cells
PCC	Plasma cell count
PD	Progressive disease
PEP	Protein electrophoresis
PFS	Progression free survival
PHI	Protected Health Information
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PLT	Platelet count
Pop PK	Population PK
POS	Probability of success
PPS	Per-protocol-set

PR	Partial response
PRO	Patient reported outcomes
PS	Performance score
PT	Prothrombin time
PT-FU	Post Treatment Follow-up
QLQ	Quality of life questionnaire
QOL	Quality of Life
QTcF	Corrected QT interval using Fridericia's correction
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RVDP	Revlimid, velcade and dexamethasone and panobinostat
s	In serum, e.g. sPEP, sIF
S	Source data
SAE	Serious Adverse Event
SBP	Systolic blood pressure
s.c. or sc	sub-cutaneous(ly)
SC	Steering Committee
Scr	Serum creatinine
sCR	Stringent CR
SD	Stable disease
S-FU	Survival follow-up
SOP	Standard Operating Procedure
SPD	Sum of the products of the diameters
STP	Soft tissue plasmacytoma
TBIL	Total bilirubin
TCP	Thrombocytopenia
TIW	Three times a week
T½	Half life
Tmax	Maximum plasma concentration time
TNT	Time to next treatment
TP1	Treatment period 1: first four cycles of study treatment, when patients ≤ 75 years receive bortezomib (BTZ) twice a week (BIW), and patients > 75 years receive BTZ once a week (OW)
TP2	Treatment period 2: Cycle 5 until disease progression (Cycle 5+) of study treatment, when all patients independent of their age receive BTZ OW
TTP	Time to progression
TTR	Time to response
u	In urine; e.g. uPEP, uIF
UK	United Kingdom
ULN	Upper limit of normal
UNK	Unknown
US	United States of America
VGPR	Very good partial response
WOCBP	Women of child-bearing potential

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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q21 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
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
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
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points
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

Protocol summary

Title	A multicenter, randomized, open-label Phase 2 study evaluating the safety and efficacy of three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents
Brief title	Study of safety and efficacy of panobinostat in combination with bortezomib and dexamethasone in relapsed or relapsed/refractory multiple myeloma
Sponsor and Clinical Phase	Secura Bio II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Results of pivotal Study D2308 demonstrated superiority of the panobinostat (PAN) + i.v. bortezomib (BTZ) + dexamethasone (Dex) combination compared to placebo (PBO) + iv BTZ + Dex in patients with MM who progressed on at least one line of prior therapy. Despite observing efficacy benefit in D2308, safety concerns were noted as the most frequent AEs included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting), and fatigue/asthenia, which were more frequent in the PAN + i.v. BTZ + Dex arm compared to the PBO + i.v. BTZ + Dex arm. Therefore, further evaluation to improve the safety and tolerability of this combination is needed. At the time of conduct, the D2308 study used the intravenous formulation of BTZ but today, the subcutaneous formulation of BTZ has become standard of care as this formulation has been shown to be associated with less GI toxicity and peripheral neuropathy compared to the i.v. formulation, albeit without compromising efficacy. The purpose of this study is to investigate the safety and efficacy of three different regimens of PAN (20 mg TIW, 20 mg BIW, and 10 mg TIW) in combination with s.c. BTZ and Dex and to provide exposure, safety and efficacy data to identify the optimal regimen of PAN in a randomized, 3-arm parallel design. This study will also assess the impact of administering s.c. BTZ (in combination with PAN and Dex) twice weekly for 4 cycles, and then weekly starting from Cycle 5 until disease progression in patients ≤ 75 years of age. Patients > 75 years of age will receive for the entire treatment period s.c. BTZ weekly (in combination with PAN and Dex) until disease progression.
Primary Objective	To assess overall response rate (ORR) up to 8 cycles (by IRC assessment).
Secondary Objectives	To assess overall response rate (ORR) To assess the individual iCR, sCR, CR, VGPR rates To assess progression-free survival (PFS) To assess overall survival (OS) To evaluate overall safety of the combination of PAN, BTZ and Dex To assess pharmacokinetics To assess exposure-response (efficacy and safety) relationship To assess time to progression (TTP), time to response (TTR), duration of response (DOR) To assess Health-related quality of life (HRQoL)
Exploratory Objectives	To assess the pharmacodynamic effect of PAN To evaluate novel predictive markers of response in bone marrow aspirate and blood

Study design	Global, randomized, open-label, multicenter, three-arm phase II study evaluating three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone to assess safety and efficacy in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents. Up to 240 patients will be randomized in a 1:1:1 ratio into one of the 3 treatment arms, distinguished by different regimens of PAN (20 mg TIW, 20 mg BIW and 10 mg TIW) according to the following strata: 1 - Number of prior lines of anti-myeloma treatment: 1 vs. 2 vs. 3 or 4 2 - Age of patient on 1st day of screening (which is equivalent to the day when the main ICF is signed): ≤ 75 years vs. > 75 years of age Patients will receive study treatment of PAN (20 mg TIW, 20 mg BIW and 10 mg TIW) in combination with s.c. BTZ and Dex in 21-day cycle duration: Treatment Period 1 (TP1) of 4 cycles (Cycle 1 to 4): Patients who are ≤ 75 years of age on 1st day of screening, will receive BTZ twice a week independent from the treatment arm to which they were randomized. Patients who are > 75 years of age will receive BTZ once a week in this treatment period. Treatment Period 2 (TP2) starting from Cycle 5: all patients (independent of age and treatment arm) will receive BTZ once a week until documented disease progression, unless they discontinue earlier due to unacceptable toxicity or for other reasons. Patients who discontinued study treatment for reasons other than documented disease progression, death, lost to follow-up or withdrawal of consent will be entered in the Post Treatment follow-up (PT-FU), to assess efficacy every 6 weeks until documented disease progression, death, lost to follow up or withdrawal of consent. All patients will eventually enter the Survival Follow-up (after completion of study treatment or the PT-FU, whichever occurs last) and be followed for survival every 12 weeks until last patient entering long-term follow up has completed a 3 year survival follow-up or discontinued earlier.
Population	The study will include adult patients with measurable relapsed or relapsed/refractory multiple myeloma who have received 1 to 4 prior lines of therapy and require re-treatment based on IMWG 2011 criteria; patients who have been exposed to an IMiD and whose disease is not bortezomib-refractory.
Inclusion criteria	Patient has a previous diagnosis of multiple myeloma, based on following IMWG 2014 definition: 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 (at initial diagnosis by local assessment), specifically: ● Hypercalcaemia ● Renal insufficiency ● Anaemia ● Bone lesions: one or more osteolytic lesions Any one or more of the following biomarkers of malignancy: ● Clonal bone marrow plasma cell percentage ≥60% ● Involved: uninvolved serum free light chain ratio ≥100 ● >1 focal lesion(s) on MRI studies Patient must have measurable disease defined by at least 1 of the following conditions present at screening by central assessment: ● Serum M-protein by PEP ≥ 0.5 g/dL (≥ 5 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 Patient with 1 to 4 prior lines of therapy who requires re-treatment of myeloma for one of the 2 conditions below as per IMWG 2011: Relapsed myeloma: defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory myeloma” categories Relapsed-and-refractory myeloma: defined as nonresponsive while on salvage therapy (except BTZ), or progresses within 60 days of last therapy in patients having

	achieved minimal response (MR) or better at some point before progressing in their disease course Patients with prior IMiD exposure (e.g. thalidomide, lenalidomide and/or pomalidomide) Patient has an ECOG performance status (PS) ≤ 2 Patient has the following laboratory values (performed at local laboratory) within 4 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 in the week prior to the screening tests for ANC or platelet count) ● Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L ● Platelet count ≥ 75 x 10^9/L ● AST and ALT ≤ ULN ● Serum total bilirubin ≤ ULN ● Creatinine clearance (CCL) assessed by estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73 m^2 (using Modification of Diet in Renal Disease (MDRD) study equation) ● Serum calcium greater or equal to lower normal limits (≥ LLN), and not higher than CTCAE Grade 2 in case of elevated value. Patient age ≥ 18 years at time of signing the informed consent Written informed consent prior to any screening assessments
Exclusion criteria	Patients with primary refractory myeloma defined as disease nonresponsive in patients who have never achieved a minimal response or better with any therapy Patients refractory to BTZ Any concomitant anti-cancer therapy (other than BTZ/Dex) Unresolved diarrhea ≥ CTCAE Grade 2 or presence of medical condition associated with chronic diarrhea (such as irritable bowel syndrome, inflammatory bowel disease) Patient has grade ≥ 2 peripheral neuropathy or Grade 1 peripheral neuropathy with pain on clinical examination at screening Patient received prior treatment with DAC inhibitors including Panobinostat Patient who received: ● prior anti-myeloma chemotherapy or medication including IMiDs and Dex ≤ 2 weeks prior to start of study. Dex as supportive treatment (e.g. for pain relief) is allowed. ● 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 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 Pregnant or nursing (lactating) women 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 3 months after having stopped all study medication Sexually active males unless they use a condom during intercourse while taking drug and for 6 months after having stopped all study medication and should not father a child in this period
Investigational and Study Treatment	“Investigational study drug(s)” or “study drug(s)” will refer to oral panobinostat (also known as LBH589 or Farydak® or PAN) capsules, to subcutaneous bortezomib (also known as BTZ or Velcade®) and to oral dexamethasone (also known as Dex) tablets. “Study treatment” refers to the combination of PAN, BTZ and Dex

Efficacy assessments	Central Serum M-protein by electrophoresis (sPEP) Central Urine M-protein by electrophoresis (uPEP) Central Serum immunofixation (sIF) Central Urine immunofixation (uIF) Central Serum free light chain (FLC) ratio Clinical evaluation of soft tissue plasmacytoma (STP) Central ionized calcium level (in serum) Local bone marrow plasma cell count Local assessment of aberrant cells from bone marrow for component of sCR Lytic bone lesion by skeletal survey (X-ray, CT/MRI by local radiologist review) on suspected region is only to be performed to assess PD (compared to full skeletal survey at baseline), or relapse (for patients in CR). Only required if clinically indicated (e.g. bone pain) Imaging by CT or MRI (by local radiologist review) is only to be performed at baseline (screening or C1D1) if STP is suspected by clinical assessment; and every 6 weeks, thereafter, for STP present at study entry; If STP is not present at screening or C1D1, imaging by CT or MRI (by local radiologist review) is only performed during study if clinically indicated. Additional response assessments (by central lab) to determine residual disease as component of iCR (multiparametric flow cytometry).
Safety assessments	Physical examination ECOG performance status Weight and vital signs 12 lead ECGs Laboratory assessments including hematology, chemistry, electrolytes, thyroid function, coagulation, Troponin I (locally or centrally or Troponin T locally), CCL (assessed by eGFR), pregnancy tests for WOCBP. Adverse events
Other assessments	Central cytogenetics by FISH within 28 days of planned first dose European Organization for Research and Treatment of Cancer's core quality of life questionnaire C30 (EORTC QLQ-C30) Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Diary for diarrhea management Pharmacokinetic: Pharmacokinetic blood samples will be obtained on all patients for the analysis of PAN and BTZ plasma concentrations. Biomarkers: ● Blood samples will be collected prior and post PAN treatment to assess the pharmacodynamic effect of PAN by treatment arm. ● Blood samples for free cell DNA assessment will be collected at Cycle 1 Day 1, at end of treatment and during PT-FU at time of disease progression ● Bone marrow aspirate sample should be collected prior study treatment, at end of treatment and during PT-FU at time of progression to explore predictive markers of response

Data analysis	The primary analysis will be performed when all randomized patients have been treated for up to 8 cycles. An interim analysis (IA) will be performed when approximately 120 randomized patients (40 in each arm) have been treated up to 8 cycles. A final analysis will be performed when all patients have completed a 3-year Survival follow-up or discontinued follow-up prematurely. The primary objective of the study is to assess efficacy of study treatment by treatment arm as measured by overall response rate (ORR: iCR, sCR, CR, VGPR and PR) after all randomized patients have received up to 8 cycles of study treatment, assessed by IRC, according to IMWG criteria. All secondary efficacy assessments (iCR/sCR/CR/VGPR rate, PFS, OS, TTR, DOR, TTP, and ORR) will be analyzed as per IRC assessment. No comparison of the treatment arms is planned in this study. The point estimate of ORR along with corresponding exact 95% two-sided confidence intervals will be presented by treatment arm. Survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The estimations are performed by treatment arm. Median PFS, Median OS time and its two-sided 95% confidence intervals will be reported for each treatment arm. Median TTR, DOR and TTP along with corresponding 95% confidence intervals will be reported for each treatment arm. For efficacy analyses, the full analysis set (FAS) will be used. All listings and summary tables will be presented by treatment arm. All safety data will be analyzed and reported overall and by treatment arm. PK parameters will be summarized by treatment arm using descriptive statistics. Frequency tables for compliance to complete all patient-reported questionnaires will be provided by treatment arm and visit for EORTC-QLQ-C30 and FACT/GOG-Ntx. Overall QOL scores and subscales will be summarized over time using mean, median, standard deviation, and range by treatment arm. QOL scale means and standard errors will be plotted over time by treatment arm. All biomarker analysis will be performed on the full analysis set.
Key words	Multiple myeloma, DACi-Pan-deacetylase inhibitor, PAN-panobinostat, BTZ-bortezomib, Dex-dexamethasone, IMIDs-immunomodulatory agents, ORR-Overall response rate, IRC-Independent review committee, IMWG-International Myeloma Working Group, PK-pharmacokinetics.

Amendment History

Amendment 02 (30-Oct-2019)

Amendment Rationale

The Investigational Medicinal Product (IMP), panobinostat (also referred to as LBH589 or Farydak®), was acquired by Secura Bio Inc. from Novartis. Updates were made in this document in all sections, as applicable, to reflect that Secura Bio is now the Sponsor for this study. This is an administrative change that does not affect the planned study.

In addition, minor language and format corrections were also done throughout the document.

Amendment 01 (17-Nov-2017)

Amendment rationale

The first patient for this study was randomized in May 2016, and as of end of October 2017 one hundred-twenty two patients have been enrolled and approximately 90% of the planned study sites have been initiated.

This amendment is written to facilitate the study conduct and improve the enrollment rate based on feedback from investigators (via direct contact or surveys).

The major changes to the selection criteria are as follows:

- Based on recent availability of new drugs and combinations in the treatment of multiple myeloma in this patient population, there is a very limited number of patients available, who have 1, 2 or 3 prior lines of therapy. Therefore, the protocol is amended to allow patients with up to 4 prior lines of therapy to be included in this protocol with no limitation on how many patients can be treated with 3 or 4 prior lines of therapy.
- As patients with 3 or 4 prior lines of therapy will have lower platelet counts at study entry, and also as it was found in study CLBH589D2308 that platelets return to baseline counts by Day 1 of the subsequent cycle after an initial decrease, it is considered acceptable to change the platelet limit for inclusion to $\geq 75 \times 10^9$/L. Similar expectations apply for absolute neutrophil count (ANC), and the ANC inclusion criterion was changed to $\geq 1.0 \times 10^9$/L. Both, thrombocytopenia and neutropenia were found to be reversible and not cumulative and to be manageable through close monitoring and dose modification.

To facilitate the study conduct, the following major changes to the study procedures were implemented:

- In case a patient has to be re-screened, the protocol required that the bone marrow collection together with all other assessments have to be repeated. As the bone marrow collection is an invasive procedure, and in general results would not change within the anticipated time frame, with implementation of amendment 1, the bone marrow collection does not have to be repeated, unless patients received alternative anti-myeloma therapy between initial screening and re-screening.
- This amendment also removes the mandatory CT/MRI scan at screening if the clinical assessment of soft tissue plasmacytoma (STP) does not suggest the presence of a STP.

This would be in line with the post baseline assessments of STP when a CT/MRI is only mandatory in case STP is suspected by clinical assessment.

- It was determined that the daily collection/completion of the diary for diarrhea management and PAN/Dex dosing is time intensive and complex, leading to incorrect and/or incomplete entries. In addition, some patients were not able to complete the eDiary due to special circumstances (e.g., peripheral neuropathy) and had to be excluded. This amendment simplifies the diary for diarrhea management by removing the anti-diarrheal medication entries and fluid intake entries, and allows the patient's caregiver or a member of the patient's family to make the entries for the patient in case the patient is not able to make the entries her/himself. In addition, the amendment removes the eDiary to document PAN/Dex dose administration and allows for this feature to be replaced by a paper diary as per local requirements.

The following additional minor changes were implemented:

Description of the change	**Rationale**
Screening period changed from 21 days to 28 days	To allow additional time for availability of central results (lab and ECG) and bone marrow and imaging results.
PK objectives – will also include Cmin of PAN (not only Cmin of BTZ)	Oversight of original protocol
PD objectives – revised to include only H3 and H4 acetylation status (alpha tubulin acetylation status removed)	During the assay validation it was found that alpha tubulin could not be measured due to its limitations in assay
Enrollment period extended to 30 months and overall study duration to 6.6 years (12 months added)	Slow recruitment observed in 2016 and expected enrollment of 9-10 patients per month.
Inclusion criterion 1: - clarified that the defined clinico-pathological manifestation of the disease will be required to have occurred from the date of initial diagnosis, not within screening	To verify the diagnosis of myeloma, the occurrence of the disease defined changes is sufficient, given the patient has documented measurable disease by PEP and/or FLC
Exclusion criterion 11a: use of prior anti-myeloma chemotherapy or medication including IMiDs and Dex within 2 weeks (instead of 3 weeks) prior to start of study treatment. Supportive Dex treatment for analgesic purposes at lower doses (up to 10mg/day) allowed within 2 weeks prior to start of study treatment	To allow progressing patients to be treated with anti-myeloma chemotherapy or medication including IMiDs and Dex 1 week sooner (or stay on prior chemotherapy 1 week longer) and to allow supportive treatment with Dex as needed in the screening period.
Exclusion criterion 15 c: added additional examples of history and presence of any cardiac arrhythmias that are not clinically significant and would not meet exclusion criterion	To allow patients with asymptomatic Grade 1 first degree AV block and second degree AV block type 1 to be included in the study.

Description of the change	Rationale
Exclusion criterion 15d and e: unstable atrial fibrillation and resting bradycardia also requires mean value of triplicate ECGs by central review at screening to be below exclusion criterion	Clarification and conformity with procedure for QTcF eligibility check.
Exclusion criterion 23: The requirement to use additionally a barrier method will be added for WOCBP patients using only hormonal contraceptives	Due to risk of PK interaction between PAN/Dex and the hormonal contraceptives as known CYP3A4 inducers
Dosing regimen: In case of a dose delay, an additional efficacy assessment is requested at the time when the new cycle should have started	To ensure close monitoring and detect progression, as early as possible
Assessments: The frequency of mandatory local assessment of beta 2 microglobulin is reduced to screening, and as clinically indicated	Beta 2 microglobulin is already analyzed at screening and on Day 1 of every cycle by the central lab
Re-screening: if STP imaging, lytic bone lesions assessment, bone marrow collection were adequate at time of first screening – these assessments do not have to be repeated in case a patient is rescreened for other reasons (except for bone marrow collection if patient received alternative anti-myeloma therapy between initial screening and re-screening)	To avoid a repetition of a painful bone marrow aspirate or biopsy with limited additional information and/or to avoid repeated exposure to radiation with limited additional information.
Assessments: If inadequate or uninterpretable, a repetition of the bone marrow baseline assessment is requested within 28 days only if the Plasma cell count was inadequate or uninterpretable	FISH and biomarker assessment are not part of the primary endpoint; If these results are missed a repetition of a painful bone marrow aspirate or biopsy does not seem to be warranted.
Assessments: Troponin I; if this cannot be evaluated by local laboratory; Troponin I can be determined by Covance instead, or Troponin T can be determined by local laboratory	Local laboratories have recently changed to only assessing Troponin T and not Troponin I results. Both Troponin I or T are adequately assessing cardiac status.
Steering committee fulfills role of DMC	Steering committee will fulfill DMC role for this study.

In this protocol amendment, additional clarifications will be implemented, and typos will be corrected as observed during the ongoing review and discussion of the protocol with the investigative sites.

Changes to the protocol

Section 2.2: Changed to allow up to 4 prior lines of therapy, and to remove alpha tubulin as one of the biomarkers to be measured.

Section 3: Added Cmin PAN to assess pharmacokinetics and removed alpha tubulin as one of the biomarkers to be measured for assessment of pharmacodynamics effect of PAN.

Section 4.1: Extended screening period duration to 28 days and changed stratification regarding number of prior lines of anti-myeloma treatment to 1 vs. 2 vs 3 or 4 without limitation in number of patients that can be assigned to each stratum.

Section 4.3: Extended enrollment period to 30 months, and total study duration to 6.6 years.

Section 5.1: Changed study population by allowing four prior lines of therapy.

Section 5.2: Clarified Inclusion criterion 1 to refer to events at time of initial diagnosis; Inclusion criterion 3 – allowed up to 4 prior lines of therapy; Inclusion criterion 6 – decreased ANC limit to $\geq 1.0 \times 10^9$/L and platelet count limit to $\geq 75 \times 10^9$/L; Inclusion criterion 8 – aligned with exclusion criterion 11c.

Section 5.3: Clarified exclusion criterion 2; modified exclusion criterion 11a to exclude prior anti-myeloma chemotherapy or medication including IMiDs and Dex within 2 weeks prior to start of study treatment. Clarified that Dex as supportive treatment (e.g., for pain relief) is allowed in the screening period; Exclusion criterion 15c: was updated to clarify which conduction abnormalities would not be considered an exclusion criterion; Exclusion criterion 15 d and e: updated to indicate that mean value of triplicate ECGs by central review at screening also must meet this criterion; Exclusion criterion 21: it was clarified that WOCBP using only hormonal contraceptives should also use a barrier method.

Section 6.1.1: Added clarification that Dex should not be administered if BTZ is held; removed reference to electronic dosing diary; added additional clarifications that a new cycle only can start if PAN and BTZ are administered together; added additional clarifications that BTZ doses should be administered at least 72 hours apart;

Sections 6.1.2 and 6.4.1.2: Removed statement regarding preferred use of granisetron for the group of 5HT3 antagonists and replaced by a general statement that if use of anti-emetic medication with a known risk of QT prolongation cannot be avoided frequent ECG monitoring should be performed.

Section 6.3.1: Added clarification that ideally a new cycle should only start when BTZ, PAN and Dex can be administered or at least BTZ and PAN can be administered together.

Section 6.3.1.2: Added clarification that if BTZ dose/schedule is reduced to once a week, Dex doses should only be administered on Days 1, 2, 8 and 9 of a cycle.

Section 6.3.1.4: Clarified diarrhea management and PAN/BTZ dose modifications – in case of Grade 2 toxicity with improvement to Grade 1 or 0 after > 48 hours or Grade 3 toxicity with improvement to Grade 1 or 0 – both BTZ and PAN should be reduced if PAN dose is > 10 mg; and only BTZ should be reduced if PAN dose is 10 mg.

Section 6.5.2: clarified that the stratification for prior lines of anti-myeloma treatment will be 1 vs. 2 vs. 3 or 4, allowing patients with 4 prior lines of therapy to be enrolled.

Section 6.6.3.1: removed the use of an electronic dosing diary and replaced with potential use of a paper diary, as per local requirements, if applicable.

Section 7.1: Removed eDiary for PAN/Dex dosing; extended screening period from 21 to 28 days; added clarification on baseline definition; clarification on Troponin I assessment, STP imaging assessment at screening; correction of PD biomarkers in blood to be assessed on Day

8 of Cycles 5 to 8; clarification for bone marrow collection and X-ray/CT/MRI for bone lesions or STP at re-screening; added clarification that beta 2 microglobulin assessment by local labs is only performed at screening and unscheduled, as clinically indicated.

Section 7.1.8: clarified when the first PTFU visit will occur and that additional unscheduled PTFU visits could occur as clinically indicated.

Section 7.2.1: clarified that beta 2 microglobulin is also part of the central laboratory assessment on the days when serum for M-protein PEP is collected. Clarified that STP at screening or C1D1 would only be assessed by CT/MRI if STP is suspected by clinical assessment, and that if imaging was performed at screening, imaging does not have to be repeated on C1D1. In addition, if STP is present at screening clarified that the first of the CT/MRI after start of study treatment should take place on C3D1 and every 6 weeks thereafter. Further clarified that if central ionized calcium could not be assessed or collected, the local corrected calcium may be used on days when local albumin and local calcium results are available. Added unscheduled response assessments by investigator or by IRC that can be performed, as clinically indicated.

Section 7.2.2: Reduced mandatory local assessment of beta 2 microglobulin; Allowed option for site to perform Troponin I (performed locally, or by central lab if the local assessment is not possible) or Troponin T performed locally. Additional information on how the results should be entered on the eCRF is provided. For eGFR calculation according to original or IDMS traceable MDRD study equation clarified that the factor of 1.212 should be applied if the patient's race is 'black' and not only if the patient is of African American origin. Also clarified that the serum creatinine result used in both formulas should be provided in mg/dL. Allowed for body temperature to be assessed as per standard practice at the institution (e.g. orally , via ear, as well as using other methods). Added additional guidance that ECG abnormalities at screening should be presented in medical history, and new or worsened clinical findings after informed consent was obtained must be recorded on the AE CRF page.

Section 7.2.3: Widened the allowed window for pre-dose PAN PK collections and provided additional scheduled time point information regarding the last PAN dose prior to the PK collection.

Section 7.2.4: Aligned the pre-dose biomarker sample collections in blood/plasma window with the pre-dose PAN PK sample collection.

Section 7.2.6: Clarified that anti-diarrheal medication and fluid intake will be removed from the ediary for diarrhea management.

Section 8.1.1: Added clarification about how to report worsening and improving of AEs.

Section 8.1.3: Added additional section to define adverse events of special interest

Section 8.2.2: Updated reporting of AEs and introduced new name for what was formerly known as Drug Safety & Epidemiology.

Section 8.6: Added that the Steering Committee will fulfill the role of the Data Monitoring Committee for this study.

Section 9.3: Removed dosing eDiary for PAN/Dex.

Section 10.2: removed presentation of '25th and 75th percentiles' for continuous demographic data.

Section 10.3.1: removed 'Time to first transfusion' as part of the analysis due to limited number of subjects.

Section 10.5.3.3: removed 'urinary' laboratory tests.

Section 10.5.3.4: removed 'shift table baseline to worst on-treatment result for overall assessments' of ECGs and 'shift table baseline to worst on-treatment result' for vital signs.

Section 10.5.4.1: Added Cmin (PAN)

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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 there is still today no evidence of cure. Multiple myeloma 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. 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).

The management of patients with relapsed and refractory disease represents a clinical challenge, as these patients suffer from continuing symptoms, complications of the disease (including renal failure, blood cytopenia or recurrent infections) and decreased quality of life.

By expert consensus (Rajkumar et al 2011), relapsed MM is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet the criteria for either "primary refractory myeloma" or "relapsed-and refractory myeloma", whereas a relapsed and refractory MM refers to a clinical scenario that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.

Relapsed or relapsed/refractory patients typically receive salvage therapy until relapse or toxicity and then go onto the next salvage option (Richardson et al 2014). However, with each treatment failure and subsequent line of treatment, the clinical benefit typically decreases.

In current clinical practice, the established agents, thalidomide, lenalidomide and bortezomib are widely used in treating patients with relapsed or relapsed/refractory MM. However, despite marked improvements in patients' outcomes, the prognosis of patients with relapsed or relapsed/refractory disease is generally still poor.

In patients who had progressive MM after at least one previous treatment – the patient population studied in the Phase III [Study LBH589D2308] (thereafter named Study D2308) –

the median OS is about 30 months for patients who had received lenalidomide+dexamethasone (Len+Dex) (Weber et al 2007) or bortezomib (Richardson et al 2007). In this population the median time to progression (TTP)/ PFS is in the range of 6 to 9 months with iv bortezomib ±

dexamethasone (Richardson et al 2007, Moreau et al 2011), 10.4 months for sc bortezomib ± dexamethasone (Moreau et al 2011) and 11.1 to 11.3 months for Len+Dex (Weber et al 2007, Dimopoulos et al 2007).

Recently, carfilzomib and pomalidomide were approved in the US as third-line treatment. Pomalidomide was also approved in the EU in August 2013 for the third-line treatment of patients with relapsed and refractory MM. However, both these drugs have similar mechanisms of action compared with the established agents thalidomide, lenalidomide and bortezomib acting either as a new generation proteasome inhibitor (carfilzomib, Kuhn et al 2007) or as a new IMiD (pomalidomide, Richardson et al 2002).

In summary, despite the introduction of two new classes of compounds in the past decade, the use of multiple lines of therapy is limited by the overlapping mechanisms of action of the available agents. Based on these considerations, there is a need for new agents with different mechanisms of action for patients with relapsed or relapsed and refractory MM.

Panobinostat (Farydak®) has received approval from the FDA in Feb 2015 and in the EU in Aug 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 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.

Panobinostat (Farydak®) has received approval from the FDA in Feb 2015 and in the EU in Aug 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 and EU 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 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).

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, as well as safety and efficacy data from Phase Ib study [CLBH589B2207].

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 studies 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 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 not yet available, although at the time of second OS interim analysis, median overall survival was 38.24 months (95% CI 34.63-45.37) for the panobinostat group and 35.38 months (95% CI 29.37-39.92) for the placebo group (HR 0.87, 95% CI 0.70 – 1.07; p=0.1783) (Richardson et al Lymphoma & Myeloma Congress 2014).

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 was 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.

The approved indication of PAN in combination with BTZ and Dex is based on MM patients with 2 or more prior lines including BTZ and an IMiD. This is a subpopulation of the Study D2308 population for which results are presented above.

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).

2 Rationale

2.1 Study rationale and purpose

The registration Study D2308 met its primary objective, demonstrating a statistically significant and clinically relevant reduction in the risk of progression or death of 37% with PAN+iv BTZ

+Dex over the standard regimen of PBO+iv BTZ +Dex (hazard ratio [HR] 0.63; 95% Confidence Interval [CI]: 0.52, 0.76; p <0.0001).

This improvement in PFS translated into a prolongation of median PFS of 3.9 months (from a median of 8.1 to 12.0 months) over the standard regimen of intravenous (iv) bortezomib and dexamethasone.

Despite the efficacy benefit observed in D2308, there were some safety concerns. The most frequent AEs included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting), and fatigue/asthenia, which all were more frequent in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. There were more on-treatment deaths in the PAN+BTZ+Dex arm. Dose reductions were more frequent among patients treated with PAN+BTZ+Dex (50.9% with at least one dose reduction) compared to those treated with PBO+BTZ+Dex (22.8%).

In summary, in patients with MM who progressed on at least one line of prior therapy, the results of Study D2308 demonstrate superiority of the PAN+iv BTZ+Dex combination compared to PBO+iv BTZ+Dex, however, further evaluation to improve the safety and tolerability of this combination is needed.

D2308 study used the intravenous formulation of bortezomib as it was the standard of care for the time. Since then, the subcutaneous formulation of BTZ has become standard of care as this formulation has been shown to be associated with less GI toxicity and peripheral neuropathy compared to the i.v. formulation, without compromising efficacy (Moreau et al 2011). A safety analysis of patients enrolled in D2308 comparing treatment phase 1 (in which bortezomib was administered twice weekly) compared to treatment phase 2 (in which bortezomib was administered once weekly) demonstrated a higher incidence of AEs in the initial 8 cycles of therapy for both treatment regimens (PAN+BTZ+Dex and PBO+BTZ+Dex). Of note, for patients in the PAN+BTZ+Dex arm, the rates of Grade 3/4 events for the most common AEs were markedly reduced in treatment phase 2: thrombocytopenia – 56.7% reduced to 6.0%; diarrhea – 24.1% to 7.1%; fatigue – 16.3% to 1.8%. This was also the case in the PBO+BTZ+Dex arm, in which the frequency of Grade 3/4 thrombocytopenia, diarrhea and peripheral neuropathy decreased (Richardson et al ASH 2014). Although these observations should be interpreted with caution due to potential patient selection bias, they are particularly interesting in the context of published Phase III data showing that weekly bortezomib is associated with an improved tolerability profile particularly with regards to thrombocytopenia, gastro-intestinal AE and neuropathy in comparison with twice a week regimen (Bringhen et al 2010). Therefore, once weekly bortezomib is frequently used in the elderly > 75 years of age and frail patients. Elderly patients have generally a higher frequency of AEs including severe AEs, and require closer patient selection and monitoring as recommended in international MM practice guidelines (Palumbo et al 2011 and Palumbo et al 2014a).

This study is investigating the safety and efficacy of three different regimens of panobinostat (20 mg TIW as evaluated in D2308; 20 mg BIW, and 10 mg TIW) in combination with s.c. BTZ and Dex and will provide exposure - safety and exposure - efficacy data to identify the optimal dose of panobinostat. This study will also assess the impact of administering bortezomib (in combination with PAN and Dex) subcutaneously twice weekly for 4 cycles, and then weekly starting from Cycle 5 until disease progression, unless discontinued earlier due to

unacceptable toxicity or for other reasons in patients ≤ 75 years of age. Patients > 75 years of age will receive for the entire treatment period s.c. BTZ weekly (in combination with PAN and Dex) until disease progression, unless discontinued earlier due to unacceptable toxicity or for other reasons.

2.2 Rationale for the study design

This is a multicenter, randomized, open-label, three arm, phase II study to characterize the safety and efficacy of three different regimens of oral panobinostat in combination with s.c. bortezomib and oral dexamethasone in adult patients with measurable relapsed or relapsed/refractory multiple myeloma having received 1 to 4 prior lines of therapy and requiring re-treatment based on IMWG 2011 criteria. Only patients having been previously exposed to an immunomodulatory agent (IMiD) will be enrolled in this study.

As the objective of this study is to characterize the safety and efficacy of three different regimens of panobinostat and to identify the optimal regimen of panobinostat in combination with s.c. bortezomib and dexamethasone, a randomized, three-arm parallel design has been chosen.

This study is randomized to avoid selection bias and is open-label since effective blinding would be difficult as three different regimens of panobinostat will be administered. If blinding occurs, the dose adjustment would be difficult to perform. In addition, the capsules of different strengths are of different color and size.

The following stratification factors have been selected: the number of prior lines 1 vs. 2 vs. 3 or 4 prior lines of myeloma treatment and age ≤ 75 vs. > 75 years of age. With increasing numbers of prior lines of therapy, the disease status is advancing, which makes stratification by prior lines of therapy necessary.

Patients ≤ 75 years of age will receive BTZ s.c. twice a week over 4 cycles and then weekly BTZ s.c. starting from Cycle 5 until disease progression unless they discontinue earlier for unacceptable toxicity or for other reasons in combination with PAN/Dex. Patients > 75 years of age will receive weekly BTZ and a reduced dose of dexamethasone for the entire study treatment until disease progression, unless they discontinue earlier for unacceptable toxicity or for other reasons, in consideration of the higher susceptibility for treatment toxicity in this elderly population (Palumbo et al 2011 and Palumbo et al 2014a).

Patients being enrolled in this study are required to have been exposed to an immunomodulatory agent (IMiD). Study D2308 met its primary endpoint (PAN+BTZ+Dex demonstrated a median PFS benefit of 3.9 months in MM patients with 1-3 prior lines of therapy, over the PBO combination). Of interest, patients having received a prior treatment line containing an IMiD (e.g. thalidomide, pomalidomide and/or lenalidomide), which was a pre-specified subgroup in this study, derived a significant benefit from the addition of panobinostat, showing a median PFS of 12.3 months, vs 7.4 months in the PBO arm (HR 0.55, 95% CI: 0.44, 0.70) with a safety profile similar to the overall patients' population.

Patients will be treated with study treatment until disease progression, unless they discontinue earlier due to unacceptable toxicity, or for other reasons. Recent Phase 3 studies with BTZ in different combinations (Phase 3 of carfilzomib + Dex vs bortezomib + Dex; Phase 3 of pomalidomid + bortezomib + Dex vs bortezomib + Dex) have been conducted using BTZ

treatment until disease progression. The longer administration of BTZ in this study as compared to a maximum 16 cycles used in D2308 is based on the following rationale. The subcutaneous formulation of BTZ has become standard of care as this formulation has been shown to be associated with less GI toxicity and peripheral neuropathy compared to the i.v. formulation, without compromising efficacy (Moreau et al 2011). A safety analysis of patients enrolled in D2308 comparing treatment phase 1 (in which bortezomib was administered twice weekly) compared to treatment phase 2 (in which bortezomib was administered once weekly) demonstrated a higher incidence of AEs in the initial 8 cycles of therapy for both treatment regimens (PAN+BTZ+Dex and PBO+BTZ+Dex). Of note, for patients in the PAN+BTZ+Dex arm, the rates of Grade 3/4 events for the most common AEs were markedly reduced in treatment phase 2: thrombocytopenia – 56.7% reduced to 6.0%; diarrhea – 24.1% to 7.1%; fatigue – 16.3% to 1.8%. This was also the case in the PBO+BTZ+Dex arm, in which the frequency of Grade 3/4 thrombocytopenia, diarrhea and peripheral neuropathy decreased (Richardson et al ASH 2014). Although these observations should be interpreted with caution due to potential patient selection bias, they are particularly interesting in the context of published Phase III data showing that weekly bortezomib is associated with an improved tolerability profile particularly with regards to thrombocytopenia, gastro-intestinal AE and neuropathy in comparison with twice a week regimen (Bringhen et al 2010). Therefore, the use of BTZ s.c. and an early switch from twice a week to weekly BTZ administration in this study is expected to further improve tolerability of PAN+BTZ+Dex combination over a longer treatment duration.

Patients who discontinued study treatment for reasons other than documented disease progression, death, lost to follow-up or withdrawal of consent will be followed every 6 weeks in the Post-Treatment follow-up (PT-FU) for efficacy until documented disease progression, death, lost to follow-up or withdrawal of consent. All patients will be followed for survival every 12 weeks. Randomized patients who have not received any dose of study treatment will also be included in the Post-treatment follow-up for efficacy until documented disease progression, death lost to follow-up or withdrawal of consent and, thereafter, in the Survival follow-up, as applicable.

The study will end when the last patient who entered the long-term follow-up (Post-Treatment follow-up or Survival follow-up, whichever occurs first) will have completed 3 years of Survival follow-up, which is approximately equivalent to the median overall survival observed for the panobinostat group in D2308.

An interim analysis will be performed when approximately 120 patients (40 in each arm) have completed up to 8 cycles of study treatment. The results of this interim analysis will provide information on the optimal regimen of panobinostat used in combination with BTZ s.c. and Dex for an improved benefit/ risk assessment. The interim analysis will also have a futility rule for stopping the PAN 10 mg TIW and 20 mg BIW arms since they have not yet been extensively tested in patients. The primary endpoint (ORR by IRC assessment) will be analyzed at the time when the last randomized patient has completed up to 8 cycles of treatment.

2.2.1 Rationale for biomarker assessment

The search for biomarkers that may identify which patients will benefit the most from panobinostat will be investigated in the context of this panobinostat regimen optimization study through cytogenetic, targeted and molecular profiling:

To enable this strategy, various biological specimens (e.g. blood, bone marrow aspirate) are being collected in this study to conduct targeted and molecular profiling such as:

- Determine if the baseline cytogenetic profile (number of acquired abnormalities well known in MM cells including t(4;14), t(14;16), del(17p) etc.) is associated to the response to treatment
- Determine the acetylation pattern of H3 and H4 in response to treatment as a pharmacodynamic marker and through PK-PD understand the correlation between acetylation of lysine residues of histone 3 and histone 4 and disease progression to explore optimal drug schedule
- Use cell free DNA profile to characterize patients achieving minimal residual disease (MRD). Circulating DNA carries tumour-related genetic and epigenetic alterations that are relevant to cancer development, progression and resistance to therapy. These alterations may include but are not limited to loss of heterozygosity (LOH) and mutations of tumour suppressor genes (such as TP53) and oncogenes (such as KRAS and BRAF).

2.3 Rationale for dose and regimen selection

This study will assess the safety, efficacy and pharmacokinetics of 20 mg TIW, 20 mg BIW and 10 mg TIW of panobinostat administered 2 weeks on / 1 week off in combination with BTZ s.c. and Dexamethasone.

The cumulative doses for those three PAN regimens are 120 mg, 80 mg and 60 mg of PAN per cycle, respectively.

The 20 mg panobinostat TIW was the starting dose in study D2308, which demonstrated clinically relevant PFS advantage over iv BTZ and oral Dex combination. The dose and schedule of panobinostat (20 mg panobinostat, 2 weeks on / 1 week off) used in Study D2308 was selected based on the clinical experience in the Phase I/II program. The Phase Ib dose-finding Study B2207 evaluating the combination of panobinostat with bortezomib in patients with relapsed or relapsed and refractory MM, following at least one prior line of therapy determined a Maximum Tolerated Dose (MTD) of 20 mg panobinostat TIW in combination with 1.3 mg/m^2 bortezomib. The dosing schedule of 2 weeks on/ 1 week off was introduced into the dose expansion phase of Study B2207 to facilitate platelet recovery and thus minimize dose interruptions and dose reductions due to thrombocytopenia (Lin et al 2009) and was subsequently used in the DUS71 and D2308 studies with demonstrated efficacy.

It is also the approved dose and regimen for panobinostat (Farydak®) in combination with bortezomib and dexamethasone in the US and in EU. Therefore, the same dose and schedule (20 mg Panobinostat, 2 weeks on/ 1 week off) has been chosen to be further investigated in this study. It is expected that the safety and tolerability of panobinostat in combination with bortezomib and dexamethasone may be improved by the use of BTZ sc and the early switch to the weekly schedule of BTZ sc.

A simulation based on exposure-platelet model developed with single-agent panobinostat data (Table 2-1) suggested that 20 mg single-agent panobinostat administered twice weekly 2 weeks on 1 week off (BIW) is expected to reduce G3/4 thrombocytopenia rate from 28.6% (20 mg TIW 2 weeks on 1 week off) to 20.6%. Similar reduction is anticipated when panobinostat is combined with bortezomib and dexamethasone.

Table 2-1 Simulated grade-3/4 thrombocytopenia risk over six weeks for single-agent panobinostat by regimen

Regimen	Dose (mg)	Thrombocytopenia Rate (%)
TIW_2Weeks On, 1Week Off	20	28.6
BIW_2Weeks On, 1Week Off	20	20.6
TIW_2Weeks On, 1Week Off	10	15.6

Based on simulation of 500 patients
Source: /vob/CLBH589/pool/pkpd_002/nonmem/Platelets/FDA2015/SimSumm3.R -> SimSumm3.txt

In addition, the BIW schedule had been tested in 2 single-agent panobinostat studies and was found to be well-tolerated (B2111 and B2101). PAN doses of 20/45 mg BIW were tested in the food effect study B2111 (Shapiro 2012). Panobinostat was generally well tolerated in this study. Most common AEs were fatigue, nausea and vomiting. These were as well the most common Grade 3 or 4 AEs.

In study B2101 (A phase IA, multicenter, dose-escalation study of LBH589 administered orally on two dose schedules in adult patients with advanced solid tumors or non-Hodgkin's lymphoma), 22 patients were treated with panobinostat on Monday and Thursday (MTh) every week (BIW) at doses from 30 to 60 mg/day. The most frequently reported AEs (reported in >50% of patients) in patients treated with the BIW regimen were fatigue, nausea, anorexia and thrombocytopenia.

The above data suggest that this 20 mg BIW regimen in combination with BTZ and dexamethasone may show an improved tolerability and should therefore be further investigated.

The 10 mg panobinostat TIW dose has been selected as plasma exposure of single agent PAN 10 mg does not overlap with 20 mg based on simulation (data on file). Therefore, this lower dose of panobinostat can be considered as an adequate low dose to characterize the dose-response relationship of panobinostat.

Recent literature suggests that thrombocytopenia (TCP) may be an on-target biomarker for histone acetylase inhibition in the bone marrow (Lancu-Rubin et al 2012). Study B2207 data suggest that target inhibition as reflected by G3/4 TCP in the 10 mg TIW cohort was similar to that of 20 mg PAN TIW in combination with 1.3 mg/m^2 BTZ [CLBH589B2207]. Of note, severe AEs including diarrhea were reduced with 10 mg PAN. However, since TCP was one of the overlapping toxicities between PAN and BTZ, single-agent PAN-induced TCP was simulated and compared between 10 and 20 mg TIW. Even though histone acetylase inhibition associated with 10 mg TIW as reflected in the typical longitudinal platelet count-time profile from 10 mg TIW was not as severe as that of 20 mg TIW, individual profiles may overlap due to the variability associated with platelet counts. PAN 10 mg TIW may offer a better balance between efficacy and toxicity associated with HDAC inhibition.

In study D2308, 10 mg panobinostat TIW was the second dose reduction option, and 17% of patients had their dose reduced to 10 mg TIW and stayed on 10 mg TIW. Although no conclusion on exposure data at RDI of 50% of PAN (equivalent to 10 mg dose level) can be made due to very small sample size, a subgroup analysis of 65 patients (17%) who were dose reduced to 10 mg panobinostat dose (median time to reduction of 85 days) and stayed on 10 mg panobinostat dose without any further dose modifications suggests similar efficacy as compared to patients who stayed on 20 mg panobinostat; with similar median PFS (PAN 10 mg: 10.9 vs PAN 20 mg: 10.6 months) and ORR (PAN 10 mg: 61.5% vs PAN 20 mg: 56.8%), and improved tolerability (see Table 2-2, data on file).

Table 2-2 Summary of panobinostat dose reduction to 10 mg TIW in D2308

	Dose reduction to 10 mg TIW*		**Patients staying at 20 mg TIW**
	PAN+BTZ+Dex N=65		PAN+BTZ+Dex N=191
Time to reduction(days), median	85		NA
PFS (Inv), medians	10.91		10.58
ORR %	61.5		56.8
CR/nCR %	36.9		20.3
On treatment deaths, %	7.7		6.8
	Over study period (%)	After reduction to 10 mg (%)	Over study period (%)
Grade 3-4	100	67.7	92.7
Thrombocytopenia	80.0	33.8	60.5
Infections (pneumonia)	13.8	3.1	19.9
Infections (sepsis)	4.6	1.5	7.3
Diarrhea	44.6	18.5	17.3
Fatigue	38.5	13.8	12.0
Hemorrhage	3.1	0.0	3.1

*: without further dose adjustment
Inv: by investigator

In addition, 10 mg panobinostat administered TIW in combination with Revlimid, Velcade and dexamethasone (RVDP) suggested activity (Shah et al 2014).

Finally, it should be emphasized, that in this study CLBH589D2222, 10 mg panobinostat TIW will be added to a full dose of the BTZ s.c. and Dex backbone therapy (in contrast to study D2308 where patients who were dose reduced to 10 mg panobinostat TIW also had a reduction of the BTZ dose).

In summary, these data suggest that the 10 mg panobinostat TIW dose may still be sufficient for histone acetylase inhibition in the bone marrow (based on TCP data from study B2207), and to maintain efficacy when combined with full standard dose of BTZ while improving safety and tolerability as compared to the 20 mg panobinostat TIW dose.

2.4 Rationale for choice of combination drugs

Panobinostat (Farydak®) in combination with bortezomib and dexamethasone 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.

The backbone regimen of intravenous bortezomib with a dose of 1.3 mg/m^2 administered on days 1, 4, 8, 11 of 21-days treatment cycles was the standard approved regimen used in 2009 when the study D2308 was initiated. Since the initiation of this study, BTZ s.c. has been shown to be associated with less GI toxicity and peripheral neuropathy compared to the i.v. formulation, without compromising efficacy (Moreau et al 2011) and has become an approved standard of care for bortezomib containing regimens. A safety analysis of patients enrolled in D2308 comparing treatment phase 1 (in which bortezomib was administered twice weekly) with treatment phase 2 (in which bortezomib was administered once weekly) demonstrated a higher incidence of AEs in the initial 8 cycles of therapy for both treatment regimens (PAN+BTZ+Dex and PBO+BTZ+Dex).

In addition, once weekly BTZ administration has been reported to have similar efficacy and a better safety profile than the twice weekly regimen (Bringhen et al 2010). Therefore, the treatment with BTZ s.c. and the use of weekly BTZ is expected to further improve the safety profile of the combination.

2.5 Rationale for choice of comparators drugs

Not Applicable.

2.6 Risks and benefits

The risk to subjects in this study may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and stopping rules for patients in treatment Arm B and C.

There may be unforeseen risks with the study treatment which could be serious.

In study D2308, the addition of panobinostat to the standard of care regimen of BTZ+Dex to treat patients with relapsed or relapsed and refractory multiple myeloma prolonged the median PFS by 3.9 months over patients treated with standard of care BTZ+Dex (HR=0.63, [95% CI: 0.52, 0.76], p<0.0001) corresponding to a 37% reduction in the risk of progression or death.

At the time of second OS interim analysis, median overall survival was 38.24 months (95% CI 34.63-45.37) for the panobinostat group and 35.38 months (95% CI 29.37-39.92) for the placebo group (HR 0.87, 95% CI 0.70 – 1.07; p=0.1783) (Richardson et al Lymphoma & Myeloma Congress 2014).

The most frequent AEs included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting), and fatigue/asthenia, which all were more frequent in the PAN+BTZ+Dex arm than in the PBO+BTZ+Dex arm. There were more on-treatment deaths in the PAN+BTZ+Dex arm. Dose reductions were more frequent among patients treated with PAN+BTZ+Dex (50.9% with at least one dose reduction) compared to those treated with PBO+BTZ+Dex (22.8%). This study will help to further characterize the safety profile of this combination using different regimens of panobinostat.

Acknowledging the need to further optimize the dose and schedule of the PAN+BTZ+Dex regimen and improve the safety and tolerability of this triple combination, Secura Bio will conduct Study D2222 outlined below:

The study will be a multicenter, randomized, open-label, phase II study to characterize the safety and efficacy of three different regimens of oral PAN in combination with subcutaneous (sc) BTZ and oral Dex in approximately 240 adult patients with measurable relapsed or relapsed/refractory multiple myeloma. Patients previously exposed to an IMiD will be enrolled in this study. In D2308, patients having received a prior treatment line containing an IMiD (thalidomide, pomalidomide and/or lenalidomide), which was a pre-specified subgroup in this study, derived a significant benefit from the addition of PAN, showing a median PFS of 12.3 months, vs 7.4 months in the BTZ+Dex arm (HR 0.56, 95% CI: 0.39, 0.80) with a safety profile similar to the overall patients' population. For patients with relapsed or relapsed/refractory multiple myeloma the clinical benefit typically decreases with each treatment failure and subsequent line of treatment. Therefore there is still an unmet medical need in this patient population.

This study will also assess the impact of sc BTZ in combination with PAN and Dex.

The backbone regimen of intravenous (iv) BTZ with a dose of 1.3 mg/m^2 administered on days 1, 4, 8, 11 of 21-days treatment cycles was the standard approved regimen used in 2009 when the Study D2308 was initiated. Since the initiation of this study, sc BTZ has been shown to be associated with less gastrointestinal (GI) toxicity and peripheral neuropathy compared to the iv formulation, without compromising efficacy (Moreau et al 2011) and has become an approved standard of care for BTZ containing regimens.

In addition, once weekly BTZ administration has been reported to have similar efficacy and a better safety profile than the twice weekly regimen (Bringhen et al 2010). Therefore, once weekly BTZ is frequently used in the elderly > 75 years of age and frail patients. Overall, the treatment with sc BTZ and the use of weekly BTZ is expected to further improve the safety profile of the combination.

In this study s.c. BTZ will be used and patients ≤ 75 years of age will switch BTZ administration from twice a week to weekly BTZ early (after having completed 4 cycles). Patients > 75 years of age will receive BTZ s.c. weekly over the whole study duration.

This study will assess the safety, efficacy and pharmacokinetics of 20 mg TIW, 20 mg BIW and 10 mg TIW of PAN administered 2 weeks on / 1 week off in combination with BTZ s.c. and Dex.

PAN 20 mg TIW, 2 weeks on/ 1 week off is the approved starting dose and regimen for panobinostat (Farydak®) in combination with BTZ and Dex in the US. Data from the PK simulation suggests that the 20 mg PAN BIW regimen is expected to improve safety and tolerability (see Section 2.3). Data on PAN 10 mg TIW suggests that this dose may still be sufficient for histone acetylase inhibition, therefore potentially maintaining efficacy when combined with full standard dose of BTZ while also improving safety and tolerability as compared to the 20 mg PAN TIW regimen.

An interim analysis, including a futility rule for stopping the PAN 10 mg TIW and 20 mg BIW arms in case of insufficient efficacy, will be performed when approximately 120 patients (40 in

each arm) have completed up to 8 cycles of study treatment. The Steering Committee (SC) will review efficacy and safety in the conduct of the interim analysis. The SC's role includes providing recommendations to Secura Bio to continue, modify or stop a treatment arm or the study early. Secura Bio will share the recommendations with the FDA and the final decision will be implemented in agreement with the FDA.

For this study, early monitoring and proactive dose modification and toxicity management guidelines have been implemented, especially for hematologic toxicities such as thrombocytopenia, neutropenia; cardiac toxicity and diarrhea. In addition, for diarrhea a specific diary has been implemented for adequate surveillance.

In conclusion, the modification to s.c. BTZ and an early switch from twice a week to weekly administration, the monitoring and adequate management of the expected toxicities of the PAN+BTZ+Dex combination is expected to further improve tolerability of PAN+BTZ+Dex combination over a longer treatment duration. Therefore, the overall risk benefit profile is considered favorable for initiating this clinical study in a subset of patients with high unmet medical need.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To assess overall response rate (ORR) up to 8 cycles	ORR (according to IMWG criteria by IRC assessment) comprised of immunophenotypic CR (iCR), stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR) and Partial Response (PR) after all randomized patients completed up to 8 cycles of study treatment	
Secondary		Refer to Section 10.5.
To assess overall response rate (ORR)	ORR (according to IMWG criteria by IRC assessment)	Refer to Section 10.5.1.
To assess the individual iCR, sCR, CR, VGPR rates	iCR, sCR, CR, VGPR rates (according to IMWG criteria by IRC assessment)	
To assess progression free survival (PFS)	PFS (according to IMWG criteria by IRC assessment)	
To assess overall survival (OS)	OS	
To evaluate overall safety of the combination of PAN, BTZ and Dex	AEs (graded by CTCAE v4.03), SAEs Abnormalities in vital signs, ECG parameters, and laboratory test values. This will include events up to 30 days after discontinuation of study treatment.	Refer to Section 10.5.3.
To assess pharmacokinetics To assess exposure-response (efficacy and safety) relationship	Cmax (PAN, BTZ), C24h (PAN), Cmin (PAN, BTZ) and AUC0-8h (PAN, BTZ) ORR, Grade 3/4 Thrombocytopenia, Grade 3/4 Diarrhea (relationship with PAN, BTZ PK parameters derived from NCA or Pop PK analysis)	Refer to Section 10.5.4.
To assess Time to Progression (TTP), Time to Response (TTR), Duration of Response (DOR)	TTP, TTR, DOR (according to IMWG criteria by IRC assessment)	Refer to Section 10.5.1.
To assess health-related quality of life (HRQoL)	HRQoL as measured by EORTC QLQ-C30 and FACT/GOG-Ntx	Refer to Section 10.5.6.
Exploratory		Refer to Section 10.5.5.
To assess the pharmacodynamic effect of PAN	H3 and H4 acetylation status	
To evaluate novel predictive markers of response in bone marrow aspirate and in blood	Molecular status of exploratory markers	

4 Study design

4.1 Description of study design

This is a global, randomized, open-label, multicenter, three-arm phase II study evaluating three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone to assess efficacy and safety in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents.

After a screening period of up to 28 days, up to 240 patients will be randomized into one of the 3 treatment arms in a 1:1:1 ratio, distinguished by different regimens (20 mg TIW, 20 mg BIW and 10 mg TIW) of panobinostat (PAN), according to the following strata:

- Number of prior lines of anti-myeloma treatment: 1 vs. 2 vs. 3 or 4
- Age of patient on 1st day of screening (which is equivalent to the day when the main ICF is signed): ≤ 75 years vs. > 75 years of age

Once randomized, patients will be included in the Post-Treatment follow-up (PT-FU) for efficacy until disease progression, death, lost to follow-up or withdrawal of consent, and, thereafter, in the Survival follow-up (S-FU) even if they did not receive a dose of study treatment, as applicable.

After randomization, patients will receive study treatment (the combination of PAN/BTZ s.c./Dex) in 21-day cycles as described below:

- **Treatment Period 1 (TP1) of 4 cycles (Cycle 1 to 4):** Patients who are ≤ 75 years of age at time of first screening, will receive subcutaneous bortezomib (BTZ) twice a week independent from the treatment arm to which they were randomized. Patients who are > 75 years of age will receive BTZ once a week in this treatment period.
- **Treatment Period 2 (TP2) starting from Cycle 5:** all patients (independent of age) will receive BTZ once a week until disease progression, unless they discontinue earlier due to unacceptable toxicity or for other reasons (see Section 7.1.5).

Patients who discontinued study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent will be entered in the **PT-FU**, to assess efficacy every 6 weeks until documented disease progression, death, lost to follow-up or withdrawal of consent.

All patients will eventually enter the **S-FU** (after completion of study treatment or the PT-FU, whichever occurs last) and be followed for survival every 12 weeks until death, lost to follow-up, or patient decision to discontinue S-FU. During this S-FU, data on new anti-neoplastic therapy administered during this follow-up will also be collected. S-FU for all patients will end when the last patient entering the long-term follow-up (PT-FU or S-FU whichever occurs first) has completed a 3-year S-FU or discontinued earlier.

Figure 4-1 Study design

Screening	**Randomization Stratification**	**Treatment arm**	**Study Treatment * PAN/sc BTZ/Dex (21-day cycles, 14d on / 7d off)**		**30d Safety FU**	**Long-term FU (last patient entering will be followed for 3 years)**	
						Post-Treatment FU (PT-FU)	**Survival FU (S-FU)**
within 28 days	1:1:1	n=80/arm	TP-1 C 1 - C4	TP-2 C 5 +	≥30d post trt	every 6 weeks	every 12 weeks
Adult female or male patients with measurable relapsed or relapsed/refractory MM 1-4 prior lines of therapy (PLT) with prior exposure to IMiDs, but not BTZ refractory	**PLT:** 1 vs 2 vs 3 **or 4** **Age:** ≤ 75 vs >75	**A:** PAN 20 mg TIW D 1, 3, 5, 8, 10, 12 **B:** PAN 20 mg BIW D 1, 4, 8, 11 **C:** PAN 10 mg TIW D 1, 3, 5, 8, 10, 12	**≤ 75 years:** BTZ:1.3 mg/m^2 D1, 4, 8 & 11 + Dex: 20 mg D1,2,4,5, 8,9,11 &12 **>75 years:** BTZ:1.3 mg/m^2 D1 & 8 + Dex: 10 mg D1,2,8 & 9	**≤ 75 years**: BTZ: 1.3mg/m^2 D1 & 8 + Dex: 20 mg D1,2, 8 & 9 **>75 years**: BTZ: 1.3 mg/m^2 D1 & 8 + Dex: 10 mg D1,2,8 & 9	All patients 30 days after last dose of study treatment	**Criteria to enter PT-FU**: ☒ randomized but never started study treatment ☒ completed / discontinued study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent	**Criteria to enter S-FU:** ☒ completed / discontinued study treatment and/or PT-FU ☒ had documented disease progression ☒ decided not to be followed for efficacy

*: study treatment will be administered until disease progression, unless study treatment is discontinued earlier due to unacceptable toxicity, or for other reasons (see Section 7.1.5)
C: Cycle; D: Day; TP1: treatment period 1; TP2: treatment period 2; FU: follow-up; PLT: prior lines of therapy; PT-FU: Post treatment follow-up; S-FU: Survival follow-up; MM: multiple myeloma

4.2 Timing of interim analyses and design adaptations

An interim analysis (IA) will be performed using data collected on or before the cut-off date, which corresponds to the time when approximately 120 patients (40 per treatment arm) have completed up to 8 cycles of study treatment or have discontinued earlier.

Patient enrollment will not be stopped during the interim analysis. Results will be used to determine the optimal panobinostat regimen used in combination with BTZ s.c. and Dex for an improved benefit/risk assessment.

Given that the PAN 10 mg TIW arm is the lowest dose level of the dose range, and that PAN 20 mg BIW was never extensively investigated in patients, and in order to avoid exposing patients unnecessarily to an insufficiently efficacious dose, the interim analysis will include a futility rule for stopping the PAN 10 mg TIW and the PAN 20 mg BIW arms in case of insufficient efficacy based on SC recommendations (see Section 10.7).

If the PAN 20 mg BIW and/or 10 mg TIW arm(s) is/are stopped for futility at interim analysis:

- Patients who are on study treatment in the PAN 20 mg BIW and/or 10 mg TIW arms at the time this decision is made, will be given the option to discontinue treatment or to continue their study treatment. The decision to continue treatment will be taken by the investigator on an individual basis dependent on the benefit patient is deriving from study treatment.
- If not all 80 patients are enrolled to the PAN 20 mg BIW and/or 10 mg TIW arms at the time of this decision, further enrollment to the PAN 20 mg BIW and/or 10 mg TIW arm will be stopped.

4.3 Definition of end of the study

The total study enrollment period is expected to be approximately 30 months. Patients will be treated with the study treatment until disease progression unless they discontinue earlier for other reasons. Patients who discontinue the study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, will be followed for efficacy every 6 weeks until disease progression, death, lost-to follow-up or withdrawal of consent. All patients will eventually (after completion of study treatment and/or the PT-FU, whichever ends last) be followed for a maximum of 3 years for survival every 12 weeks until death, lost to follow-up, or patient decision to discontinue S-FU.

The end of the study is reached when the last patient entering the long-term follow-up (PT-FU or S-FU whichever occurs first) has completed a 3-year S-FU or discontinued earlier.

The primary analysis will be conducted 24 weeks (8 cycles of treatment) after the last patient enrolled received the first study treatment. The primary analysis data will be summarized in the primary clinical study report (CSR).

Following the cut-off date for the analysis reported in the primary CSR, patients will continue to be followed according to the visit schedule.

The final analysis will occur at the end of the study. All available data from all patients up to this cut-off date will be analyzed and summarized in a final CSR.

Assuming that the last patient receives study treatment close to the median time to progression of 12.7 months observed in D2308, and enters a long-term follow-up of 3 years, the total study duration including long-term follow-up will be approximately 6.6 years.

4.4 Early study termination

The study can be terminated at any time for any reason by Secura Bio. Should this be necessary, the patients who are on study treatment at the time of termination should be seen as soon as possible for a final End-of-treatment (EOT) visit and the 30-day safety follow-up after the last dose. The patients who are in the PT-FU should be seen for a last PT-FU visit, and the patients in the S-FU at the time of termination – should be contacted by the investigator by phone or in writing (see Table 7-1 for the respective assessments to be done). 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 study.

5 Population

5.1 Patient population

Adult female or male patients with measurable relapsed or relapsed/refractory multiple myeloma who have received 1 to 4 prior lines of therapy and require re-treatment based on IMWG 2011 (Rajkumar et al 2011) criteria; patients who have been exposed to an IMiD and whose disease is not bortezomib-refractory will participate in this study.

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.

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 has a previous diagnosis of 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 at initial diagnosis (by local assessment).

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. Anaemia
  d. Bone lesions: one or more osteolytic lesions
- Any one or more of the following biomarkers of malignancy:
  a. Clonal bone marrow plasma cell percentage ≥60%
  b. Involved: uninvolved serum free light chain ratio ≥100
  c. >1 focal lesion on MRI studies

2. Patient must have measurable disease based on protein assessment defined by **at least 1** of the following conditions present at screening by central assessment:
   a. Serum M-protein by PEP ≥ 0.5 g/dL (≥ 5 g/L).
   b. Urine M-protein by PEP ≥ 200 mg/24 hours.
   c. Involved serum free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided the serum free light chain ratio is abnormal.
3. Patient with 1 to 4 prior lines of therapy who requires re-treatment of myeloma for one of the 2 conditions below as per IMWG 2011:
   a. Relapsed myeloma: defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories.
   b. Relapsed-and-refractory myeloma: defined as nonresponsive while on salvage therapy or progresses within 60 days of last therapy in patients having achieved minimal response (MR) or better at some point previously before then progressing in their disease course. Note: Patients refractory to BTZ are excluded.
4. Patients with prior IMiD exposure (thalidomide, lenalidomide and/or pomalidomide)
5. Patient has an ECOG performance status (PS) ≤ 2
6. Patient has the following laboratory values (performed at local laboratory) within 4 weeks before randomization (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 in 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
   c. AST and ALT ≤ Grade 1
   d. Serum total bilirubin ≤ ULN
   e. Creatinine clearance as assessed by eGFR ≥ 30 mL/min/1.73m^2 (applying MDRD study equation (Section 7.2.2.5.7; Dimopoulos et al 2010)
   f. Serum calcium greater or equal to lower normal limits (> LLN), and not higher than CTCAE Grade 2 in case of elevated value.

7. Patient must have the following laboratory values (performed at local laboratory) within normal limits or corrected to within normal limits with supplements before randomization: serum sodium, potassium, magnesium, phosphorus.
8. Patient treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, is eligible. Patients 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. See also exclusion criterion 11c.
9. Patients must avoid consumption of grapefruit, pomegranates, starfruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study treatment, due to potential CYP3A4 interaction with the study treatment. Orange juice is allowed.
10. Patient's age is ≥ 18 years at time of signing the informed consent
11. Patient has provided written informed consent prior to any screening procedures
12. Patient is able to swallow capsules
13. Patient must be able to adhere to the study visit schedule and other protocol requirements
14. 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. Patients with primary refractory myeloma defined as disease nonresponsive in patients who have never achieved a minimal response or better with any therapy.
2. Patients refractory to bortezomib, i.e. patients who progressed while receiving salvage therapy with BTZ, or patients who progressed within 60 days of their most recent BTZ containing treatment.
3. Any concomitant anti-cancer therapy (other than bortezomib/dexamethasone; bisphosphonates are permitted only if commenced prior to the start of screening period)
4. Unresolved diarrhea ≥ CTCAE Grade 2 or presence of medical condition associated with chronic diarrhea (such as irritable bowel syndrome, inflammatory bowel disease).
5. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression
6. 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
7. Patient has grade ≥ 2 peripheral neuropathy or Grade 1 peripheral neuropathy with pain on clinical examination at screening
8. Patient received prior treatment with DAC inhibitors including Panobinostat
9. Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment.
10. Patient has a second 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).
11. Patient who received:

a. prior anti-myeloma chemotherapy or medication including IMiDs and Dex ≤ 2 weeks prior to start of study treatment. Use of Dex as supportive treatment (e.g. for pain relief) is allowed.
b. experimental therapy or biologic immunotherapy including monoclonal antibodies ≤ 4 weeks prior to start of study treatment.
c. prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks priorstart of study treatment.
d. Stem cell transplant ≤ 3 weeks prior to start of study treatment

12. Patient has not recovered from all therapy-related toxicities associated with above listed treatments to < Grade 2 CTCAE.
13. 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
14. Patients with evidence of mucosal or internal bleeding
15. Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months prior to randomization), such as:
    a. History of angina pectoris, symptomatic pericarditis, or myocardial infarction
    b. Left Ventricular Ejection Fraction (LVEF) < 40%, as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA)
    c. History or presence of any cardiac arrhythmias, e.g. ventricular, supraventricular, nodal arrhythmias, or conduction abnormality other than asymptomatic Grade 1 first degree AV block (asymptomatic long PR interval) or asymptomatic second degree AV block type 1 (asymptomatic Mobitz 1)
    d. Presence of unstable atrial fibrillation (ventricular response rate >100 bpm; mean value of triplicate ECGs by central review at screening). 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 (mean value of triplicate ECGs by central review at screening)
    f. Complete left bundle branch block (LBBB), bifascicular block
    g. Congenital long QT syndrome
    h. Any clinically significant ST segment and/or T-wave abnormalities
    i. Corrected QT (QTcF) > 450 ms for males and females using Fridericia's correction on screening ECG (mean value of triplicate ECGs by central review at screening)
    j. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    k. 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.
    l. Other clinically significant heart disease and vascular disease
16. 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

17. 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)
18. 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
19. Patient has a known history of HIV seropositivity or history of active/treated hepatitis B or C (a test for screening is not required).
20. Pregnant or nursing (lactating) women.
21. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and 3 months after stopping all 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
    - 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.

      In women of child-bearing potential using only hormonal contraceptives, a barrier method should be additionally used due to the unknown risk of PK interaction between hormonal contraceptives and panobinostat and dexamethasone (weak/moderate CYP3A4 inducer) that might result in reduced efficacy of hormonal contraceptives.

      Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

22. Sexually active males unless they use a condom during intercourse while taking drug and for 6 months after having stopped all study medication 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 seminal fluid.

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 subcutaneous bortezomib (also known as BTZ or Velcade®) and to oral dexamethasone (also known as Dex) tablets. "Study treatment" refers to the combination of PAN, BTZ and Dex.

6.1.1 Dosing regimen

Table 6-1 Dose and study treatment schedule

Study treatments	Pharmaceutical form and route of administration	Initial dose*	Frequency and/or Regimen
PAN – Arm A	Capsule for oral use	20 mg/d	Three times a week (TIW) 14 days on / 7 days off (21-day cycles); Day 1, 3, 5, & 8, 10, 12 (e.g. Mon, Wed, Fri)
PAN – Arm B		20 mg/d	Two times a week (BIW) 14 days on/7 days off (21-day cycles); Day 1, 4, 8, 11 (e.g. Mon, Thur)
PAN – Arm C		10 mg/d	Three times a week (TIW) 14 days on / 7 days off (21-day cycles); Day 1, 3, 5, & 8, 10, 12 (e.g. Mon, Wed, Fri)
BTZ – all treatment arms	Sub-cutaneous injection	1.3 mg/m^2	**In TP1 (Cycle 1 – 4):** **Patients ≤ 75 yrs of age:** Twice a week (BIW); 14 days on / 7 days off (in 21-day cycles) Day 1, 4, 8, 11 (e.g. Mon, Thur) **Patients > 75 yrs of age:** Once a week (OW); 14 days on / 7 days off (in 21-day cycles) Day 1, 8 (e.g. Mon)
		same as BTZ dose administered at the completion of TP1	**In TP2 (Cycles 5+):** **All patients independent of age:** Once a week (OW); 14 days on / 7 days off (21-day cycles); Day 1, 8 (e.g. Mon)
Dex – all treatment arms	Tablets for oral use	20 mg/day for patients ≤ 75 years of age on 1st day of screening; 10 mg/d for patients > 75 years of age on 1st day of screening	On the day of BTZ treatment (about 15 – 30 minutes prior to BTZ s.c. injection) and the day after BTZ treatment. Dexamethasone should not be administered if BTZ treatment is on hold.
* initial doses only, for dose reductions please see Table 6-3 for PAN, Table 6-5 for BTZ and Table 6-6 for Dex.			

Figure 6-1 Recommended dosing schedule for Arm A and Arm C of PAN/BTZ/Dex for patients less than or equal to 75 years of age (on 1st day of screening) from Cycle 1 to 4 (TP1)

(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

Figure 6-2 Recommended dosing schedule for Arm A and Arm C of PAN/BTZ/Dex for patients greater than 75 years of age (on 1st day of screening) from Cycle 1 to 4 (TP1), and all patients (in Arm A and Arm C) starting from Cycle 5 (TP2)

(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							8							Rest Period
Dexamethasone (Dex)	1	2						8	9						Rest Period

Figure 6-3 Recommended dosing schedule for Arm B of PAN/BTZ/Dex for patients less than or equal to 75 years of age (on 1st day of screening) from Cycle 1 to 4 (TP1)

(3-week cycles)	Week 1 Days 1-7							Week 2 Days 8-14							Week 3 Days 15-21
Panobinostat (PAN)	1			4				8			11				Rest Period
Bortezomib (BTZ)	1			4				8			11				Rest Period
Dexamethasone (Dex)	1	2		4	5			8	9		11	12			Rest Period

Figure 6-4 Recommended dosing schedule for Arm B of PAN/BTZ/Dex for patients greater than 75 years of age (on 1st day of screening) from Cycle 1 to 4 (TP1), and all patients (in Arm B) starting from Cycle 5 (TP2)

(3-week cycles)	Week 1 Days 1-7							Week 2 Days 8-14							Week 3 Days 15-21
Panobinostat (PAN)	1			4				8			11				Rest Period
Bortezomib (BTZ)	1							8							Rest Period
Dexamethasone (Dex)	1	2						8	9						Rest Period

Study treatment in general will be administered in 21-day cycles. It is recommended that a new cycle should only start if when BTZ, PAN and Dex or at a minimum PAN and BTZ can be administered together. A delay of a cycle of up to 3 weeks is allowed (please refer to Section 6.3).

Patients will self-administer panobinostat as follows:

- Every effort must be made for the patient to take PAN at approximately the same time on each day of administration in the morning and consistently on the same days of the week throughout the study
  - For patients randomized to Treatment Arm A or C, e.g. if Cycle 1 day 1, 3, 5 is a Monday, Wednesday, Friday; for subsequent cycles/weeks PAN dosing should again be on Monday, Wednesday, Friday.
  - For patients randomized to Treatment Arm B, e.g. if Cycle 1 day 1 & 4 is a Monday and Thursday; for subsequent cycles/weeks PAN dosing should again be on a Monday and Thursday.
- For patients randomized to Treatment Arm A or C, doses should be separated by a minimum of 30 hours within the week of dosing. For patients enrolled to Treatment Arm B, doses should be separated by a minimum of 60 hours.
- On the days of PK sampling:
  - **For patients randomized to Treatment Arm A or C**:
    - Patients should bring PAN to the clinical site to be administered upon instructions from study personnel on Days 1 and 8 of Cycle 1 and on Day 8 of Cycles 2 to 8. The dose administration time of PAN will be recorded by the study personnel to determine the actual PK collection time.
    - Patients should document the time when panobinostat was taken at home on Days 3, 5 and 10 of Cycle 1 and Day 5 of Cycles 2 to 8 and provide this information to the study personnel the next visit/day when PK samples are collected.
  - **For patients randomized to Treatment Arm B**:
    - Patients should bring PAN to the clinical site to be administered upon instructions from study personnel on Days 1, 4, 8 and 11 of Cycle 1 and on Day 8 of Cycles 2 to 8. The dose administration time of PAN will be recorded by the study personnel to determine the actual PK collection time.
    - Study personnel should also record the time when panobinostat was taken on Day 4 of Cycles 2 to 8 after BTZ administration at the site to determine the actual PK collection time.
- 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 / 240 mL). Patients should be instructed to swallow the capsules whole and not chew or open them.
- Patients must avoid consumption of grapefruits, pomegranates, starfruit, Seville oranges or products containing the juice of each (e.g. also in form of bitter orange marmalade) during the entire study treatment period and preferably 7 days before the first dose of study treatment, due to potential CYP3A4 interaction with the study treatment. Orange juice is allowed.
- Patients should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 12 hours after the approximate time of the

usual daily dosing. 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.

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

- On the days when BTZ s.c. 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 s.c. injection.
- On the day after the BTZ s.c. injection the patient will take dexamethasone at home as instructed, about 24 hours after the Dex dose on the day of the BTZ injection.

At the start of the study, patients, depending on local requirements, will be given a paper diary to document the self-administered doses of PAN/Dex starting on Cycle 1 Day 1. The PAN/Dex dosing data will be reviewed by the study personnel at the beginning of each cycle (starting with Cycle 2) and at EOT for drug accountability and consideration when entering the dosing information in the respective Dose Administration Record page CRF.

Site personnel will administer BTZ s.c. as per package insert:

- BTZ doses must be administered at least 72 hours apart.
- 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 one of the following is recommended:
  - BSA calculated using Gehan and George Equation: BSA (m^2) = 0.0235 x Height(cm)$^{0.42246}$ x Weight(kg)$^{0.51456}$
  - 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.
- On PK sampling days, when BTZ is administered on Cycle 1 Days 1, 4, 8 and Day 11 & on Day 8, Cycle 2 to 8, the site personnel must document the time of BTZ s.c. injection, as well as the time of PAN administration. When BTZ and PAN are given on the same day, the BTZ s.c. injection must be shortly followed by PAN ingestion (within 1-5 minutes of end of BTZ s.c. injection). Please note that the BTZ dose on Day 4 and 11 will only be administered in Cycles 1 to 4 to patients who are ≤ 75 years of age at time of signing the initial main informed consent.

Figure 6-5 Sequence of dosing of PAN/BTZ/Dex on days when PK samples are collected

All Treatment Arms (A, B & C): Cycles 1: Day 1 and 8; Cycles 2 – 8: Day 8 – all patients:

-35 to -16 minutes prior 0h	-5 to -1 minute(s) prior 0h	0h = time when or just prior to when PAN was taken on day 1 or 8
e.g. 08:25 to 08:44	*e.g. 08:55 to 08:59*	*e.g. 09:00*
take Dex tablets	s.c. BTZ injection	take PAN capsule(s)

Treatment Arm A & C: Cycle 1 Day 4 and 11 – for patients ≤ 75 years of age:

-35 to -16 minutes prior 0h	-5 to -1 minute(s) prior 0h	0h = 24h after time when PAN was taken on day 3 or 10
e.g. 08:25 to 08:44	*e.g. 08:55 to 08:59*	*e.g. 09:00*
take Dex tablets	s.c. BTZ injection	no PAN capsule(s)

Treatment Arm A & C: Cycle 1 Day 4 and 11 – for patients > 75 years of age:

-35 to -16 minutes prior 0h	-5 to -1 minute(s) prior 0h	0h = 24h after time when PAN was taken on day 3 or 10
e.g. 08:25 to 08:44	*e.g. 08:55 to 08:59*	*e.g. 09:00*
no Dex tablets	no s.c. BTZ injection	no PAN capsule(s)

Treatment Arm B: Cycle 1 Day 4 and 11 – for patients ≤ 75 years of age:

-35 to -16 minutes prior 0h	-5 to -1 minute(s) prior 0h	0h = 72h after time when PAN was taken on day 1 or 8
e.g. 08:25 to 08:44	*e.g. 08:55 to 08:59*	*e.g. 09:00*
take Dex tablets	s.c. BTZ injection	take PAN capsule(s)

Treatment Arm B: Cycle 1 Day 4 and 11 – for patients > 75 years of age:

-35 to -16 minutes prior 0h	-5 to -1 minute(s) prior 0h	0h = 72h after time when PAN was taken on day 1 or 8
e.g. 08:25 to 08:44	*e.g. 08:55 to 08:59*	*e.g. 09:00*
no Dex tablets	no s.c. BTZ injection	take PAN capsule(s)

6.1.2 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
  In case use of anti-emetic medicinal products with a known risk of QT prolongation such as for example 5HT3 antagonists like granisetron, ondansetron and tropisetron cannot be avoided, more frequent ECG monitoring should be performed.

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.

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.3 Dose Modifications.

6.1.5 Treatment duration

Patients will be treated with the study treatment until disease progression unless they discontinue earlier for other reasons (Section 7.1.5).

6.2 Dose escalation guidelines

Patients receiving a reduced dose level due to toxicity of PAN/BTZ/Dex during treatment period may be considered for dose re-escalation if:

- either the study treatment-related adverse event has reverted in severity to grade ≤ 1 or baseline level, and:
  a. at least 9 scheduled doses of PAN for Treatment Arm A, and at least 6 scheduled doses of PAN for Treatment Arm B.
     Note: Treatment Arm C cannot be re-escalated unless dose was previously increased after futility decision.
  b. at least 3 scheduled doses of BTZ
  c. at least 6 scheduled doses of Dex

  at the reduced level have been administered and tolerated.

  Note: For common toxicities of PAN and BTZ (see Table 6-2) the minimum required number of doses for PAN and BTZ should have been administered and tolerated before escalation of either or both study drugs.

  or
- the adverse event due to which the dose was omitted/reduced is determined to be not related to PAN/BTZ/Dex (whichever drug is considered for re-escalation).

Should this guidance be met, then the patient may be dose escalated back to the previous dose (dose that was given prior to the onset of the event(s) for which the dose was modified). However, dose escalations cannot go beyond the initial PAN/BTZ/Dex dose that was assigned to the patient at time of randomization. And for patients ≤ 75 years of age in case dose escalation is proposed after the first 4 cycles, dose escalations cannot go beyond the doses given on Day 1 of Cycle 5.

Prior to consideration for dose re-escalation, the clinical condition of the patient (based on performance status and laboratory data) must be determined to be such that the re-escalated dose will be tolerated.

6.3 Dose modifications

6.3.1 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 and BTZ alone.
- It is recommended that a new cycle should only start when BTZ, PAN and Dex or at least BTZ and PAN can be administered together
- Patients requiring permanent discontinuation of PAN must discontinue study treatment.
- Patients requiring permanent discontinuation of BTZ must discontinue study treatment.
- If a patient requires a PAN and/or BTZ dose delay of more than 3 weeks 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 based on investigator decision. 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 both, PAN and BTZ, for common toxicities.

Table 6-2 Criteria for PAN/BTZ dose modifications for common toxicities

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)			
HEMATOLOGICAL TOXICITIES		**PAN 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
	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, then, restart at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)	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 6-5).
Neutrophil count (ANC) decreased	Grade 3 uncomplicated ANC < 1.0 - 0.75 x 10^9/L	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.	No change
	Grade 4 (ANC < 0.5 x 10^9/L)	Interrupt** until resolved to ≤ Grade 2, or baseline, then, restart at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)	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 (see Table 6-5).
	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, then, restart at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)	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 (see Table 6-5).
For other hematological toxicities (i.e. anemia) that are not common to PAN/BTZ see Table 6-4			

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**	
For other hematological toxicities (i.e. anemia) that are not common to PAN/BTZ see Table 6-4 and Table 6-7, respectively.	
NON-HEMATOLOGICAL TOXICITIES	
Diarrhea	Please refer to Section 6.3.1.4 (see Table 6-11)
For other non-hematological toxicities that are not common to both PAN/BTZ see Table 6-4 and Table 6-7, respectively	
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) **: Both, PAN **and** BTZ dosing should be interrupted at occurence of this event.	

6.3.1.1 Dose modifications of PAN

Panobinostat dosing may be modified based on Table 6-3 below. An investigator can use his/her discretion when making dose-reduction decisions unless otherwise specified in the guidelines below.

Table 6-3 Dose reductions for PAN

Drug/Arm	Starting dose	1st dose reduction	2nd dose reduction	3rd dose reduction
Pan p.o. /A	20 mg/d TIW D 1, 3, 5 & D 8, 10, 12	15 mg/d TIW D 1, 3, 5 & D 8, 10, 12	10 mg/d TIW D 1, 3, 5 & D 8, 10, 12	Discontinue*
Pan p.o. /B	20 mg/d BIW D 1, 4 & D 8, 11	15 mg/d BIW D 1, 4 & D 8, 11	10 mg/d BIW D 1, 4 & D 8 & 11	Discontinue*
Pan p.o. /C	10 mg/d TIW D 1, 3, 5 & D 8, 10, 12	Discontinue*		
*: PAN 10 mg dosing can be interrupted and restarted at the same dose level after resolution within 22 days of next intended dose (see Table 6-2, Table 6-4, Section 6.3.1.1.3 and Table 6-11)				

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

PAN 20 mg will also need to be dose reduced to 10 mg in case of co-administration with a strong CYP3A inhibitor, see Section 6.4.2.2 and Section 14.1.2 for details.

Table 6-4 Criteria for interruption, modification and re-initiation of PAN due to PAN-related toxicity

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of PAN dosing)**
HEMATOLOGICAL TOXICITIES		**Please also refer to Table 6-2.**
Anemia	Grade 2 (Hgb < 10.0 g/dL – 8.0 g/L)	No change in PAN dosing - Consider supportive measures
	Grade 3 (Hgb < 8.0 g/dL; transfusion indicated) or Grade 4 (life threatening consequences, urgent intervention indicated)	Temporarily interrupt PAN dosing and use supportive measures until resolved to ≤ Grade 1, or baseline, then, restart at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QTcF interval**		Please refer to Section 6.3.1.1.3
GASTROINTESTINAL		
Diarrhea**		Please refer to Section 6.3.1.4 (see Table 6-11)
Vomiting**/Nausea***	Grade 1 & 2	No change in PAN dosing
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily interrupt PAN dosing until resolved to ≤ Grade 1, or baseline, then, restart PAN at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)
FATIGUE		
Fatigue	Grade 3	Temporarily interrupt PAN dosing until resolved to ≤ Grade 2, or baseline, then: ● If resolved within 7 days, then restart PAN at the same dose level ● If resolved in more than 7 days, then, restart PAN at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)
INVESTIGATIONS		
Blood bilirubin Increased	Grade 3 (>3.0 – 10.0 x ULN) or 4 (> 10.0 x ULN)	Temporarily interrupt PAN dosing until resolved to ≤ Grade 2, or baseline, then, restart PAN at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of PAN dosing)**
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 PAN dose level and continuation of treatment is at the discretion of the Investigator.		
Aspartate Aminotransferase (AST) increased Alanine Aminotransferase (ALT) increased	> 5.0-20.0 x ULN	Temporarily interrupt PAN dosing until resolved to ≤ Grade 1, or baseline, then: ● If resolved within 7 days restart PAN at the same dose level ● If resolved in more than 7 days, then, restart PAN at reduced dose level if previous PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)
	> 20.0 x ULN	Temporarily interrupt PAN dosing until resolved to ≤ Grade 1, or baseline, then, restart PAN at reduced dose level if current PAN dose is > 10 mg, and at same dose if current PAN dose is 10 mg (see Table 6-3)
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 PAN dosing *** See also concomitant medication		

6.3.1.1.1 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 PAN, 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. PAN treatment may then be restarted at the same dose and schedule. If the same intolerable Grade 2 adverse event(s) occurs again, PAN 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 > 10 mg, and at same dose level if current PAN dose was 10 mg (see Table 6-3). At the discretion of the Investigator, 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.

6.3.1.1.2 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 PAN 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 PAN, PAN should then be restarted at reduced dose level if current PAN dose was > 10 mg, and at same dose level if current PAN dose was 10 mg (see Table 6-3). If the AE was considered not related to PAN then PAN may be restarted (when the AE resolves to ≤ Grade 1 or baseline) at the current dose.

6.3.1.1.3 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 central and/or local readings of ECGs will use the Fridericia's correction for QTc interval assessment: QTcF. Any final decisions concerning PAN dose modifications or permanently discontinuing the patient from study treatment due to QTcF prolongation will be based on the assessment performed by the Investigator.

In case of average QTcF > 450 ms pre-dose (Dex/BTZ/PAN) on Cycle 1 Day 1:

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Do not initiate study treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before initiating study treatment
- Review concomitant medication use for other causes for QT prolongation (refer to Section 6.4.3.1 and qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g., concomitant use of strong CYP3A4 inhibitors, see Section 6.4.2.2)
- Within 7 days, repeat triplicate pre-dose ECG

- If average QTcF >450 ms, do not initiate study treatment
  - If patient was not yet randomized, consider patient a screen failure and complete end of screening disposition form
  - If patient was randomized, complete end of treatment disposition form, and start patient in long-term follow-up.
- If average QTcF ≤ 450 ms, initiate study treatment

In case of average QTcF >480 ms, (or average QTcF prolongation >60 ms from baseline) any time after 1st dose of PAN until end of PAN treatment:

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Interrupt PAN treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
- Review concomitant medication use for other causes for QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and treatment compliance
- Consider more frequent ECG monitoring (e.g. approximately every 2-3 hours between 2 hours post PAN and 6 hours post PAN) until average QTcF is ≤ 480 ms)

After confirming ECG reading at site (and/or receiving central vendor results in case ECGs are performed between 1st PAN dose and end of Cycle 16), if average QTcF > 480 ms:

- Interrupt PAN treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If average QTcF confirmed > 480 ms:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated (e.g., perform approximately hourly ECGs at between 2 h post PAN and 6 h post PAN on the same day an average QTcF > 480 ms is reported and pre-dose and at 2 h post PAN and the next PAN dosing days) until the average QTcF returns to ≤ 480 ms
- After resolution within 7 days to ≤ 480 ms, consider re-introducing PAN treatment at the same or reduced dose, and increase ECG monitoring (e.g., pre-dose PAN and 2 h post PAN) for the next PAN treatment(s):
  - If average QTcF remains ≤ 480 ms, continue planned ECG monitoring during subsequent PAN treatment
  - If average QTcF recurs > 480 ms after re-introduction PAN treatment or remains > 480 ms for more than 7 days prior to re-introduction, discontinue patient from study treatment.

Please note that for unscheduled ECGs at any time during PAN treatment including all ECGs performed after Cycle 16 (i.e. when ECG will only be performed and assessed locally, as clinically indicated):

If a single QTcF is > 480 ms, two additional ECGs should be performed. The three ECGs should be separated by 5-10 minutes. The average QTcF of those three ECGs should be calculated and used for determination of PAN dose modifications.

6.3.1.2 Dose modifications for BTZ/Dex

Dose modifications for bortezomib and dexamethasone may be performed based on Table 6-5 and Table 6-6 below. For criteria for dose modifications for toxicities that are common to PAN and BTZ, see Table 6-2.

Table 6-5 Dose reduction steps for BTZ for all Treatment Arms

Drug	Patient age on 1st day of screening	Starting Dose	1st Dose Reduction	2nd Dose Reduction	3nd Dose Reduction	4th Dose Reduction
BTZ s.c.	≤ 75 years	1.3 mg/m^2 twice a week (BIW) D 1, 4, 8 & 11	1.3 mg/m^2 OW D 1 & 8*	1.0 mg/m^2 OW D 1 & 8*	0.7 mg/m^2 OW D 1 & 8*	Discontinue
	> 75 years	1.3 mg/m^2 once a week (OW) D 1 & 8	1.0 mg/m^2 OW D 1 & 8	0.7 mg/m^2 OW D 1 & 8	Discontinue	
Total BTZ dose to be administered is calculated using weight determined on Day 1 of each cycle * Please note the Dex dose remains unchanged but Dex is administered on D1, 2, 8 and 9 only once BTZ schedule is changed to once a week.						

Table 6-6 Dose reduction steps for Dex for all Treatment Arms

Drug	Patient age on 1st day of screening	Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
Dex p.o.	≤ 75 years	20 mg/d the day of and 1 day after BTZ s.c. injection	10 mg/d the day of and 1 day after BTZ s.c. injection	6 mg/d the day of and 1 day after BTZ s.c. injection	Discontinue Dex Continue with PAN/BTZ alone
	> 75 years	10 mg/d the day of and 1 day after BTZ s.c. injection	6 mg/d the day of and 1 day after BTZ s.c. 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 6-7 Drug related adverse events dose modification guidelines for BTZ

CTCAE Category	Dose Modification Guideline - At any time during a cycle of BTZ (including intended day of dosing)
HEMATOLOGICAL TOXICITIES (ANC, PLT)	See Table 6-2.
NON-HEMATOLOGICAL TOXICITIES	
Peripheral Neuropathy	See Table 6-8.
Herpes Zoster reactivation any grade	Hold BTZ until lesions are dry.
Other BTZ related non-hematologic toxicity ≥ Gr 3	Determine attribution of toxicity and hold BTZ. If toxicity resolves to ≤ Gr 2, resume BTZ with one level dose reduction (see Table 6-5).

6.3.1.3 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 BTZ 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)	Reduce BTZ by one dose level (see Table 6-5)
Gr 2 with pain or Gr 3 (Severe symptoms; limiting self-care ADL)	Hold BTZ until toxicity resolves to < Gr 2 When toxicity resolves, reinitiate BTZ with a reduction by one dose level (see Table 6-5) If no more dose reductions are possible, **discontinue** study treatment
Gr 4 (Life-threatening consequences; urgent intervention indicated)	**Discontinue** study treatment
Grading based on NCI Common Terminology Criteria CTCAE v4.03 NCI Common Toxicity Criteria website - http://ctep.info.nih.gov/reporting/ctc.html.	

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 6-6)
	> Gr 3 (requiring hospitalization or surgery)	Hold Dex until symptoms adequately controlled. Restart and reduce one dose level (see Table 6-6) 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 6-6); 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 6-6). If symptoms persist despite above measures, **discontinue** Dex and 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 6-6). If weakness persists despite above measures reduce by 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 Dex by one dose level (see Table 6-6) until levels are satisfactory.

6.3.1.4 Management of diarrhea (including PAN and BTZ dose modifications)

The electronic diary for diarrhea management will be provided to patients to track the frequency, onset, duration, stool consistency. Patients should be instructed on the daily completion of the electronic diary on a hand-held device between first day of screening and last day of Cycle 8, unless study treatment is discontinued earlier. In addition, the patient should be instructed to contact the physician/other study personnel at the first sign of diarrhea (increase of bowel movements/day from baseline and/or increased stool fluidity). The patient should also be instructed on the use of loperamide or other anti-diarrheal medication as per investigator's discretion at home (see Table 6-10).

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. Additionally, on Day 1 of Cycles 1 through 9, the patients' diary entries should be reviewed by the study personnel (see Section 7.2.6). 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 (Definition as per CTCAE: A disorder characterized by frequent and watery bowel movements)
  - Determine average number of bowel movements/day and record in electronic diary
  - Determine average stool type according to the Bristol Stool Form Scale (see Appendix 5) and record in electronic diary
- 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)

In the screening period, patients will complete a daily diary for diarrhea management from the first day of screening until the first day of study treatment. The diary will be in the form of an electronic device that the patients will take home with them. They will be instructed how to turn it on, complete the diary and submit their results after they complete the diary every day for at least one week. The study personnel should review the patient entries, prior to the start of study treatment on Cycle 1 Day 1 and depending on the outcome of the review the following actions should be taken:

- If the patient has normal stools prior to study entry, no anti-diarrheal treatment is needed.
- If the patient has Grade 1 diarrhea that is NOT attributable to infectious or other conditions where anti-diarrheal therapy may be contraindicated, it is recommended that the patient starts standard dose loperamide (Table 6-10). Study treatment may be started.
- If the patient has ≥ Grade 2 diarrhea prior to dosing, study treatment can be delayed for up to 48 hours until diarrhea is ≤ Grade 1.
- Site personnel to determine the baseline of average bowel movements/day and baseline average stool type according to Bristol Stool Form Scale on Cycle 1 Day 1 prior to first

study treatment, move the patient to the treatment phase and record results in electronic diary.

The patient should take loperamide and/or other anti-diarrheal medication as per investigator's discretion/instructions at home.

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

Table 6-10 and Table 6-11 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 medication

	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	other anti-diarrheal medication as per investigator's discretion	as per investigator's discretion and standard of care/package insert (e.g. diphenoxylate/atropine 5 mg every 6 hours)

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* *as captured on first day of screening		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 anti-diarrheal medication as appropriate	Restart both, PAN and BTZ, at current doses
	Grade 2 for > 24h	Start other anti-diarrheal medication, continue high dose loperamide	Interrupt both, PAN **and** BTZ
	when improved to ≤ Grade 1 w/i 48 h	Modify anti-diarrheal medication as appropriate	Restart both, PAN and BTZ, at current doses
	Grade 2 for > 48h	Continue other anti-diarrheal medication and high dose loperamide	Interrupt both PAN **and** BTZ
	when improved to ≤ Grade 1 after >48 h	Modify anti-diarrheal medication as appropriate	Dose reduction of BTZ and PAN if current PAN dose is > 10 mg. Dose reduction of BTZ and no dose reduction if current PAN dose is 10 mg (see Table 6-3).
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 other anti-diarrheal medication Consider hospitalization for monitoring / volume management	Interrupt both, PAN **and** BTZ
	until diarrhea improves to ≤ Grade 1	Continue high dose loperamide and other anti-diarrheal medication and supportive care unit ≤ Grade 1	Interrupt both, PAN **and** BTZ
	when improved to ≤ Grade 1	Modify anti-diarrheal medication as appropriate	Dose reduction of BTZ and PAN if current PAN dose is > 10 mg. Dose reduction of BTZ and no dose reduction in PAN if current PAN dose is 10 mg (see Table 6-3).

Diarrhea CTCAE grade		**Diarrhea management**	**PAN and BTZ dosing**
	for further episodes of Grade 3	Start/Continue high dose loperamide and diphenoxylate/atropine as necessary until improved to ≤ Grade1	Dose reduction of BTZ and PAN if current PAN dose is > 10 mg. Dose reduction of BZT and no dose reduction if current PAN dose is 10 mg (see Table 6-3).
Grade 4 Life threatening consequences; urgent intervention indicated	Grade 4	Hospitalize and provide intensive supportive care and anti-diarrheals	**Discontinue** study treatment
**: determined on Cycle 1 Day 1 prior to first dose of study treatment Note: Diarrhea definition as per CTCAE: A disorder characterized by frequent and watery bowel movements			

Anti-diarrheal medication and IV fluids given as supportive care, should be documented on the anti-diarrheal medication CRF page.

6.3.2 Follow-up for toxicities

Patients whose study 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.

Table 6-12 outlines the follow-up evaluation recommended for toxicities of specific types and CTCAE grades after study treatment is permanently discontinued. For follow-up for toxicities while study treatment is temporarily interrupted see dose modifications in Table 6-2, Table 6-4, Section 6.3.1.1.3, Table 6-7 and/or Table 6-8, respectively.

Table 6-12 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
Blood and lymphatic system disorders	Continue to test weekly until resolution to baseline or stabilization.
Investigations (hematologic) Neutropenia ≥ CTCAE Grade 3 Thrombocytopenia ≥ CTCAE Grade 3	Continue to test weekly until resolution to baseline or stabilization. Perform physical exam for check on bruising in case of major thrombocytopenia.
Investigations (hepatic) Liver enzymes ≥ CTCAE Grade 3	Continue to test weekly until resolution to ≤ CTCAE Grade 1 or stabilization.
Cardiac disorders QT and ECG ECG changes indicative of ischemic event	Perform twice weekly ECGs until normalization or stabilization of ECG findings. ● Central ECGs, if disorder is observed prior to start of Cycle 17 ● Local ECGs, if disorder is observed after start of Cycle 17

Further guidelines and recommendations for the management of specific study treatment related toxicities (diarrhea and cardiac toxicities) are provided in Section 6.3.1.4 and Section 6.3.1.1.3. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury.

In the absence of cholestasis, these **patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results**. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.

A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

Obtain an additional unscheduled PK sample, as close as possible to last dose of PAN, if PK analysis is performed in the study.

Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

6.3.3 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-treatment induced adverse events, i.e., diarrhea are provided in Section 6.3.1.4 and Section 6.4. Refer to preclinical toxicity and/or clinical data found in the PAN Investigator’s Brochure and BTZ and Dex package insert.

6.4 Concomitant medications

6.4.1 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.

6.4.1.1 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 darbepoetin 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).

6.4.1.2 Anti-emetic medication

Prophylactic anti-emetics: may be considered at the discretion of the physician and in accordance with local medical practice. In case use of anti-emetic medicinal products with a known risk of QT prolongation such as for example 5HT3 antagonists like granisetron, ondansetron and tropisetron cannot be avoided, more frequent ECG monitoring should be performed.

Anti-diarrhea medication: Please refer to Section 6.3.1.4 for details on management of diarrhea.

6.4.1.3 Prophylaxis treatment

Please refer to Section 6.1.2 for ancillary treatment.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 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 50×10^9/L, withholding of thromboprophylaxis be considered to minimize the risk of bleeding. Newer direct Factor Xa 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 ≤325 mg or Plavix ≤75 mg daily are allowed. It is recommended that anti-platelet therapy be held if platelet counts fall below 50×10^9/L.

6.4.2.2 Medications that are known to be strong CYP3A inhibitors

See Section 14.1.2.

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. 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 strong CYP3A inhibitors should be avoided. If this is not avoidable, patients should be monitored closely for toxicity.

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.

6.4.3 Prohibited concomitant therapy

See Section 14.1.

The following medications are prohibited during this study:

- Systemic anticoagulation or drugs that inhibit platelet function, WITH THE EXCEPTION OF (see Section 6.4.2.1):
  - Aspirin ≤ 325 mg/day
  - Plavix ≤ 75 mg/day
  - Low molecular weight heparin (LMWH).

  - 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.

6.4.3.1 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.

Ensure that patient is off panobinostat treatment for at least 72 hours prior to starting treatment with a medication listed in Section 14.1.1.

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 (CredibleMeds.org) website on drugs that prolong the QT interval and/or induce Torsades de Pointes or ventricular arrhythmia.

6.4.3.2 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 study 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.

6.4.3.3 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].

Panobinostat increased the median Cmax and AUC of a sensitive substrate of CYP2D6 by approximately 80% and 60%, respectively; however, these increases 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.

6.4.4 Use of bisphosphonates (or other concomitant medications)

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.

6.4.4.1 Other concomitant medications

Please refer to Section 6.1.2 Ancillary treatments.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 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 study. The Subject No. consists of the Center Number (Center No.) assigned 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 through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

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

Randomization will be stratified by:

- Number of prior lines of anti-myeloma treatment: 1 vs. 2 vs. 3 or 4
- Age of patient on 1st day of screening (which is equivalent to the day when the main ICF is signed): ≤ 75 years vs. > 75 years of age

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. A separate medication randomization list will be produced by or under the responsibility of the Sponsor (previously Novartis, now Secura Bio) Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

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.

6.5.3 Treatment blinding

This is an open-label study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the PAN capsules and Dex tablets 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 individual Dosage Administration Record CRFs

Table 6-13 Preparation and dispensing

Study drugs	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 local 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

6.6.1 Study drug packaging and labeling

Each study site will be supplied by Secura Bio with PAN (LBH589 10 mg, 20 mg and 15 mg [for dose reductions only]) capsules. The study medication packaging has a 2-part label. Responsible site personnel will identify the panobinostat bottles/strength to dispense to the patient by using the IRT and obtaining the medication kit number(s) which correspond(s) to treatment arm and/or dose reduction information. Site personnel will add the patient number on the label. Immediately before dispensing the bottle to the patient, site personnel will detach the outer part of the label from the bottle and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be used, and 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 and the medication kit number but no information about the patient.

Bortezomib and dexamethasone will be supplied locally (by investigational site or Secura Bio), unless not commercially available.

Table 6-14 Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
PAN	Capsules in bottles	Labeled as 'LBH589' For Treatment Arm A or C' dosing will be TIW 14 days on / 7 days off every 21 days & For Treatment Arm B dosing will be BIW 14 days on / 7 days off every 21 days. Study drug packaging has a 2-part label.
BTZ s.c.	Refer to local product information (unless not approved in the country)	Refer to local product information or study treatment label in countries where not approved (please see Table 6.1).
Dex	Refer to local product information (unless not approved in the country)	Refer to local product information or study treatment label in countries where not approved in required strengths and/or formulations

6.6.2 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 panobinostat should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

Bortezomib and dexamethasone should be stored according to the local product information (or label if not approved in a country).

Table 6-15 Supply and storage of study treatments

Study drugs	Supply	Storage
PAN (LBH589)	Centrally supplied by Secura Bio	Refer to medication label
BTZ s.c.	Locally (unless not approved in a country)	Refer to local product information or study treatment label in countries where not approved.
Dex	Locally (unless not approved in a country in an adequate strength)	Refer to local product information or study treatment label in countries where not approved.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

The total daily doses of study treatment (PAN/BTZ 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 (DAR) 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.

On days where blood samples for PK are collected (on Cycle 1 Day 1, 4, 8 & 11, and Day 8 of Cycles 2 to 8), compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee and will be verified by determinations of PAN/BTZ concentrations in plasma. On these days, in addition to dose administered and date of dose, time of PAN/BTZ dose taken/administered, and occurrence of vomiting within 2 hours of PAN dosing will be recorded in the CRF on the respective PK Dosing page(s).

Patients will be asked to record self-administered PAN/Dex doses in a paper diary, as per local requirements, if applicable, and to bring in 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 dosing information will be reviewed by site personnel at the beginning of each cycle and information will be used to support/record information on PAN/Dex dosing on the respective DAR CRF page.

6.6.3.2 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, drug labels, and a copy of the completed drug accountability log to the Secura Bio monitor or to the Secura Bio address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

The following non-investigational treatment has to be monitored specifically:

- loperamide
- other anti-diarrheal medication at the discretion of the investigator
- anti-viral prophylaxis
- use of proton pump inhibitor with Dex treatment

Details are described in the monitoring plan.

Loperamide and other anti-diarrheal medication for diarrhea management will be supplied/purchased locally (by the investigational site or the patient), as needed.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Secura Bio 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. The entry in the ‘Category’ column indicates which data will be captured in the database (D) or which data will be part of the source documentation (S) only.

No CRF will be used as a source document.

The patient entries into the electronic devices for Patient Reported Outcome questionnaires (EORT-QLQ-C30 and FACT/GOG-Ntx) and into the electronic diary for diarrhea management.

Table 7-1 Visit evaluation schedule

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Obtain informed consent (IC)	D	7.1.2	X														
Registration / Randomization with IRT/IWRS																	
Registration after signing of IC	S	7.1.2.1	X														
Randomization if eligible	D	7.1.2.1		X													
Patient history																	
Demography	D	7.1.2.3	X														
Inclusion/exclusion criteria	D	5.2/5.3	X														
Medical History	D	7.1.2.3	X														
MM Diagnosis/history and extent of cancer	D	7.1.2.3	X														
Cytogenetic status at diagnosis	D	7.1.2.3	X														
Central cytogenetics (FISH) at study entry	D	7.1.2.3	X														
Prior anti-neoplastic therapy	D	7.1.2.3	X														
Prior/concomitant medications and non-drug therapy	D	7.1.2.3 & 6.4	Continuously from 14 days prior to first dose until 30 days after last dose of study treatment														

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
- Anti-diarrheal medication	D	7.1.2.3 & 6.4	Continuously from 28 days prior to first dose until 30 days after last dose of study treatment														
Transfusions of blood products	D	7.1.2.3 & 6.4	Continuously from 14 days prior to first dose until 30 days after last dose of study treatment														
Efficacy / Disease Assessment (additional unscheduled M-protein, FLC or ionized calcium assessments required to confirm response or disease progression should be performed as soon as possible after response or disease progression is suspected – see Section 7.2.1 for details)																	
Central M-Protein by Protein Electrophoresis (PEP)																	
- in serum (sPEP)	D	7.2.1.1	X	X				X				X		X		X	
- in urine (uPEP)	D	7.2.1.1.	X	X				X				X		X		X	
Central M-Protein by Immunofixation (IF)																	
- in serum (sIF)	D	7.2.1.1	X	X				X				X		X		X	
- in urine (uIF)	D	7.2.1.1	X	X				X				X		X		X	
Central free light chain protein assessment (FLC)																	
- in serum (sFLC)	D	7.2.1.2	X	X				X				X		X		X	
Local plasma cell count in bone marrow (PCC)																	
- PCC	D	7.2.1.3	X		During the study as clinically indicated to qualify for CR, sCR, and iCR; and PD for patients with non-measurable disease by M protein in serum and urine as well as by FLC												

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Local assessment of soft tissue plasmacytoma (STP)																	
- Clinical assessment	D	7.2.1.4	X	X				X				X		X		X	
-by CT/MRI	D	7.2.1.4	CT/MRI at screening or C1D1 is only performed if STP is suspected by clinical assessment. (If at screening STP is suspected by clinical assessment and CT/MRI is performed, CT/MRI does not have to be repeated on C1D1.) During the study every 6 weeks starting from C3D1 in case of presence at screening or C1D1 until disease progression; and as clinically indicated in case not present at screening or C1D1.														
Local full body skeletal survey (FBSS) to assess lytic bone lesions																	
- by Xray and/or CT/MRI	D	7.2.1.5	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.												
Central ionized calcium	D	7.2.1.6	X	X	X	X	X	X	X	X	X	X	X	X		X	
Assessment of aberrant plasma cells from bone marrow for component of stringent CR: Choose one of the two methods below																	
- Local standard flow cytometry (2-4 colors)	D	7.2.1.7			During the study as clinically indicated for component of stringent CR (sCR) Method chosen should be used consistently throughout the study												
- Local standard Immunohistochemistry	D	7.2.1.7															
Additional response assessments in bone marrow for component of iCR																	
- Central multiparametric flow cytometry	D	7.2.1.8			During the study as clinically indicated for component of immunophenotypic CR (iCR)												

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Response assessment by investigator	D	7.2.1.9						X				X		X		X	
Response assessment by IRC	D	7.2.1.10						X				X		X		X	
Clinical examination																	
Physical exam (including brief neurological exam)	S	7.2.2.1	X	X				X				X		X			
Vital signs	D	7.2.2.2	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			
ECOG Performance status	D	7.2.2.4	X	X				X				X		X			
Local laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1	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			
Electrolytes	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X	X	X	X			
Thyroid	D	7.2.2.5.4	X	X										X			
Coagulation	D	7.2.2.5.5	X														
Troponin I (locally or centrally if it cannot be determined locally, or local Troponin T)	D	7.2.2.5.6	X	X				X				X		X			

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
CCL assessed by eGFR using MDRD study equation	D	7.2.2.5.7	X	X	X	X	X	X		X		X	X	X			
Pregnancy tests for women of childbearing potential																	
- In serum (w/i 7 days prior to 1st planned dose)	D	7.2.2.5.8	X											X			
- In urine	D	7.2.2.5.8		X				X				X					
Follow-up on potential drug induced liver injury (DILI) cases	D	6.3.2	In case of potential DILI, a detailed history; additional lab tests to include creatinine kinase, GGT, and alkaline phosphatase; testing for acute hepatitis infection or other hepatotropic viral infection or autoimmune hepatitis should be considered at screening and in case of DILI as clinically indicated. An additional unscheduled PK sample as close as possible to last dose of PAN, should also be obtained. This will be documented in an unscheduled visit.														
Cardiac Assessments		7.2.2.6															
Central 12-lead ECG up to C 16 (triplicate ECGs, and unscheduled as clinically indicated)	D	7.2.2.6.1	X	X				X				C5 to C16		X			
Local 12-lead ECG from C17+	D	7.2.2.6.1			Single or triplicate as clinically indicated, starting from Cycle 17 (locally performed and read)									X			
Cardiac Imaging (MUGA/ECHO)	D	7.2.2.6.2	X	As clinically indicated										X			

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Pharmacokinetics		7.2.3.															
PK sampling in serum (time of PAN/BTZ dose as applicable) (see Table 7-6 and Table 7-7 for exact visit sampling timepoints)	D	7.2.3		X	X	X	X			X			C5 to C8				
Biomarkers																	
Pharmacodynamic biomarkers in blood	D	7.2.4		pre PAN 4h post 8h post		pre				pre			pre C5 to C8	X		at PD	
Whole blood for cell free DNA (cf DNA)	D	7.2.4		pre PAN										X		at PD	
BMA to explore novel predictive markers	D	7.1.2.3	X											X (PD only)		at PD	
Patient-reported Outcomes		7.2.6															
EORTC-QLQ-C30	D	7.2.6		X				C3D1, C5D1, C7D1 and every 4 cycles (12 weeks) thereafter						X		Every 12 weeks	
FACT/GOG-Ntx	D	7.2.6		X				C3D1, C5D1, C7D1 and every 4 cycles (12 weeks) thereafter						X			

Day of cycle	Category	Protocol Section	Screening	Study Treatment										EOT	30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2				Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Electronic diary for diarrhea management	D	7.2.6	The diary should be completed by the patient (or a family member or caregiver) on a daily basis from the first day of screening until the last day of Cycle 8														
- Instructions on diarrhea management and use of electronic diary by study personnel	S	7.2.6	X														
- Review of diary for diarrhea management by study personnel	S	7.2.6		X				On Day 1 of every cycle from Cycle 2 to 9									
Adverse events																	
Adverse events	D	8.	Continuously after signed ICF until 30 days after last study treatment														
Study treatment administration and new anti-neoplastic therapies after discontinuation of study treatment																	
Panobinostat (PAN) p.o.	D	6.1 & 6.3		Treatment Arm A & C: Day (D) 1, 3, 5, 8, 10, 12 q 21 days Treatment Arm B: Day (D) 1, 4, 8, 11 q 21 days (for dose reductions please refer to Section 6.3)													
Bortezomib (BTZ) s.c.	D	6.1 & 6.3		For patients ≤ 75 yrs: D1, 4, 8, 11 q 21 days For patients > 75 yrs: D1 and 8 q 21 days								All patients: D 1 & 8					
Dexamethasone (Dex) p.o.	D	6.1 & 6.3		For patients ≤ 75 yrs: D1, 2, 4, 5, 8, 9, 11, 12 q 21 days For patients > 75 yrs: D1, 2, 8, 9 q 21 days								All patients: D1, 2 & 8, 9					

Day of cycle	Category	Protocol Section	Screening	Study Treatment											30d Safety FU	Long-term FU	
				Treatment Period 1 (TP1)								TP2		EOT		Post-Treatment Efficacy FU	Survival FU
				Cycle (C) 1 21 days/cycle				Cycle 2 – 4 21 days/cycle				Cycles 5 + 21 days/ cycle					
			Day 28 to Day 1	1	4	8	11	1	4	8	11	1	8	EOT	30 days post dose	Every 6 weeks	Every 12 weeks
Dosing diary, if applicable as per local regulations	S	6.6.3.1		The dosing diary should be completed by the patient for all PAN and Dex doses taken during the study as per local requirements, if applicable. Patients enrolled to treatment arms A or C should at a minimum document the time when panobinostat was taken at home on Days 3, 5 and 10 of Cycle 1 and Day 5 of Cycles 2 to 8 and share this information with the study personnel.													
Instructions on dosing and review of dosing information by study personnel	S	6.1 & 6.6		X				X				X		X			
Anti-neoplastic therapies since discontinuation of study treatment	D	6.4												X	X	X	X
Survival Follow-up (until last patient entering long-term follow-up has completed 3 year Survival follow-up or discontinued follow-up prematurely																	
Survival Follow-up	D	7.1.9															X

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Following signature of the main study Informed Consent (ICF), the majority of screening assessments will be performed within 28 days prior to first dose on Cycle 1 Day 1. The serum pregnancy test for WOCBP that will need to be performed within 7 days prior to 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 -28 to Day 1 or Day -7 to Day 1 as applicable) must be repeated prior to randomization. Please perform central lab and central ECG assessments and start eDiary entries within the first week of screening.

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 4 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 4 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 PCC, it should be repeated within 28 days of the original screening start 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 only be re-screened once for the study. If the PCC assessment and the whole body scan for lytic bone lesions was performed as part of the first screening, results are interpretable and patient has not received any new alternative anti-myeloma therapy between initial screening and re-screening, these results can be used for the re-screening and bone marrow collection and imaging do not have to be repeated.

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.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

If patient meets all eligibility criteria, the site personnel can proceed with the randomization/stratification 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 End of Screening Phase Disposition Page will be completed for both, randomized patients and screening failures.

7.1.2.2 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 on the Screening Phase Disposition Page. 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.

7.1.2.3 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.
- Instruction of patient on use of electronic diary for diarrhea management (on first day of screening after main study ICF is signed); discussion of patient diarrhea history, diet, use of laxatives and anti-diarrheals (see Section 6.3.1.4)
- Demography (date of birth and initials (where permitted), 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 and cytogenetic status at diagnosis).
- BM aspirate/biopsy for central cytogenetics (FISH)

- All prior anti-neoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies and stem cell transplants provided as treatment for Multiple Myeloma prior to the administration of study drug.
- All other medications and significant non-drug therapies including ancillary medication (except for anti-diarrheal medication and transfusions of blood products) 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.
- Anti-diarrheal medication taken within 28 days before first dose is administered, will be recorded on the Prior and Concomitant Anti-diarrheal Medication CRF. Besides what is being recorded on the Prior and Concomitant Medication CRF above, the dose unit, dosing frequency pre interval and route of administration will be captured.
- Transfusions of blood products administered within 14 days prior to first dose must be recorded on the 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)
- Serum pregnancy test performed in WOCBP (within 7 days prior to first planned dose)
- Cardiac imaging (MUGA/ECHO)
- Central 12-Lead ECG (triplicate, 5-10 minutes apart)
    - The screening ECG must be reviewed by the central lab to determine eligibility prior to dosing. Therefore, it is advisable to perform the screening at least 3 days prior to planned first dose.
- Local laboratory evaluations (hematology, chemistry, electrolytes, thyroid, coagulation, Troponin I [if Troponin I cannot be determined locally, it can be determined by the central lab or Troponin T can be determined locally], other hepatic assessments, as necessary, creatinine clearance assessed by eGFR based on serum creatinine, age, race and gender using the MDRD study equation (see Section 7.2.2.5.7).
- Disease assessments
    - Central laboratory evaluations:
        - In serum:
          a. M-protein by PEP and IF

b. FLC protein assessment
c. Ionized calcium
- In urine (24-h urine collection required):
M-protein by PEP and IF;

- Local plasma cell count in bone marrow
- Clinical assessment of soft tissue plasmacytomas (STP)
- Local assessment of STP by CT/MRI, if STP is suspected by clinical assessment
- Local full body skeletal survey by Xray (or CT/MRI) for assessment of lytic bone lesions

- Additional BMA sample will be collected for exploratory novel predictive biomarkers

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

After randomization using the IRT, up to 240 patients will receive study treatment in 21-day cycles 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.

- Treatment Period 1 (TP1) of 4 cycles (Cycle 1 to 4): Patients who are ≤ 75 years of age at time of first screening, will receive subcutaneous bortezomib (BTZ) twice a week independent from the treatment arm to which they were randomized. Patients who are > 75 years of age will receive BTZ once a week in this treatment period.
- Treatment Period 2 (TP2) starting from Cycle 5: all patients (independent of age) will receive BTZ once a week.

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

7.1.5 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 should make a reasonable 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/BTZ outlined in Table 6-3 and Table 6-6, respectively
  - Adverse events that lead to a PAN and/or BTZ dose delay of more than 3 weeks 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
- The following deviations from the prescribed dose regimen for study treatment:
  - Dose interruption of PAN and/or BTZ of more than 3 weeks 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.
  - Dose reduction of BTZ below lowest dose reduction step indicated in Table 6-6.
  - Dose reduction of PAN below lowest dose reduction step indicated in Table 6-3.
- 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) was given last) and enter the long-term follow-up period (either post-treatment follow-up for efficacy (see Section 7.1.8) or survival follow-up (see Section 7.1.9) 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.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 6 weeks until documented disease progression (per investigator), death, lost to follow-up, or withdrawal of consent.

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

7.1.5.1 Replacement policy

All randomized patients are part of the full analysis set. There is no plan to replace patients who have stopped the study prematurely.

7.1.6 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.

Secura Bio 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 should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages.

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.

Withdrawal from ICF should be recorded on the Withdrawal of Informed Consent/Withdrawal of Optional Informed Consent CRF(s).

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

If the patient refuses to return for a 30-day safety follow-up visit, the site should at a minimum contact the patient for the 30-day safety follow-up by telephone, email, or letter.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

7.1.8 Post-treatment follow-up

Patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent must continue to be followed for response assessments every 6 weeks +/- 3 days until documented disease progression (by investigator), death, lost to follow-up, or withdrawn consent to efficacy follow-up occurs. The first PT-FU visit will be approximately 6 weeks +/- 3 days from the EOT visit date. Additional unscheduled PT-FU visits could be completed, as clinically indicated.

At that time, the reason for completion/discontinuation of this PT-FU should be recorded on the End of Post treatment Phase Disposition CRF page.

If a patient starts new anti-neoplastic therapy prior to disease progression, every attempt should be made to perform tumor evaluations until documented disease progression. In addition, all new anti-neoplastic therapy administered starting from the last dose of the study treatment until death, lost to follow-up, or withdrawal of consent to survival follow-up will be recorded in the CRFs.

7.1.9 Survival follow-up

All patients will be followed for survival once they discontinued study treatment and/or completed PT-FU for efficacy until the last patient entering long-term follow-up has completed at least 3-years of Survival follow-up or discontinued follow-up prematurely. All patients will be followed for survival status every 12 weeks +/- 14 days (see Table 7-1) until death, lost to

follow-up, or withdrawal of consent to survival follow-up or planned end of the survival follow-up period. In addition, all anti-neoplastic therapy administered during survival follow-up, until disease progression, death, lost to follow-up, or withdrawal of consent will be recorded in the CRFs. The first Survival follow-up visit will occur approximately 12 weeks +/- 14 days from the EOT visit date or from the last PT-FU visit date, whichever comes last.

Survival follow-up visits will be recorded on the Survival Information CRF page and in case of death of the patient on the Death CRF page.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant CRFs.

7.1.10 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 (if the patient is lost to follow-up during screening, study treatment, or post treatment follow-up) or on the Survival Information CRF page (if patient is lost to follow-up during survival follow-up).

7.2 Assessment types

7.2.1 Efficacy assessments

Overall response rate (comprised of iCR, sCR, CR, VGPR and PR) after all randomized patients have completed up to 8 cycles of this study, assessed by IRC is the primary endpoint for this study. For the response classification in MM and additional response categories in MM according to IMWG criteria please refer to Section 14.2, Table 14-7 and Table 14-8, respectively.

Response will be assessed by the investigator and by the Independent Review Committee (IRC) according to the Guidelines for Response Assessment in Multiple Myeloma that are described in Section 14.2 and are based on the IMWG guidance (Rajkumar et al 2011). The response assessment by the investigator and by the IRC will be based on the same CRF efficacy data.

The IRC will periodically review all efficacy data that were used by investigators to determine response. Details of the central IRC review process will be described in the independent review committee charter. The results of the central IRC review will be used for primary and secondary analyses (including interim analysis) purposes. The investigator’s response assessment will be used for sensitivity analysis and treatment decision making. Confirmation of response or disease progression should occur as soon as possible after the response/disease progression was determined by the investigator (e.g. on the same day or on Day 8 of the same cycle). Investigators are asked to hold off on discontinuation of study treatment due to presumed disease progression until all central laboratory data are available to confirm progression.

The disease assessment collection plan is presented in Table 7-2. The assessments that are required to confirm response or disease progression are presented in Table 7-3.

These additional assessments and any other assessments that may be performed more frequently if clinically indicated at the investigator's discretion should be recorded on the Unscheduled Visit CRF pages.

Blood and urine samples will be analyzed at a designated central laboratory for the following assessments:

- Serum and urine M-protein measurements by PEP and IF.
- Serum free light chain protein assessment
- Ionized serum calcium
- Beta 2 microglobulin (assessed on days when serum M-protein measurements by PEP are performed)

Bone marrow samples for multi-parametric flow cytometry (iCR component) will be also be analyzed at a designated central laboratory.

For central laboratory data (from serum, urine and BM collections) for disease assessment, the site personnel designated by the Investigator will enter the information required by the protocol onto the appropriate Assessment Sample Collection Cover pages, as well as the designated laboratory's requisition forms that will be printed on 2- part paper.

Details on the collection of samples and reporting of results can be found in the respective laboratory manuals.

Imaging data (CT/MRI for STP, and X-ray and/or CT/MRI for full skeletal survey) will be locally assessed.

Table 7-2 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Central M-Protein by Protein Electrophoresis (PEP)		
In serum (sPEP) In urine (uPEP)	Screening and Baseline (C1D1)	Day 1 of every subsequent cycle (Cycles 2+); End of treatment; Post-treatment-Follow-up: every 6 weeks Unscheduled: as needed (e.g. to confirm disease progression)
Central M-Protein by Immunofixation (IF)		
In serum (sIF) In urine (uIF)	Screening and Baseline (C1D1)	Day 1 of every subsequent cycle (Cycles 2+); End of treatment; Post-treatment-Follow-up: every 6 weeks Unscheduled: as needed (e.g. to confirm disease progression)
Central Serum Free Light Chain assessment		
FLC in serum	Screening and Baseline (C1D1)	Day 1 of every subsequent cycle (Cycles 2+); End of treatment; Post-treatment-Follow-up: every 6 weeks Unscheduled: as needed (e.g. to confirm disease progression)
Local plasma cell count in bone marrow		

Procedure	Screening/Baseline	During Treatment/Follow-up
Local plasma cell count in bone marrow	Screening	During the study as clinically indicated to qualify for CR, stringent CR, and immuno-phenotypic CR and PD in case of patients with non-measurable disease by M protein in serum and urine as well as by FLC.
Local assessment of soft tissue plasmacytoma (STP)		
Clinical Assessment of STP	Screening and Baseline (C1D1)	Day 1 of every subsequent cycle (Cycles 2+); End of treatment; Post-treatment-Follow-up: every 6 weeks Unscheduled: as needed
Assessment of STP by CT/MRI	Screening or C1D1 is only performed if STP is suspected by clinical assessment. (If at screening STP is suspected by clinical assessment and CT/MRI is performed, CT/MRI does not have to be repeated on C1D1.)	During the study every 6 weeks starting from C3D1 in case of presence at screening or C1D1 until disease progression and if not present at screening or C1D1, as clinically indicated
Local full body skeletal survey		
Assessment of lytic bone lesions by X-ray film and/or CT/MRI scan	Screening	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.
Central ionized calcium in serum		
Ionized calcium	Screening and Baseline (Cycle 1 Day 1)	Cycle 1 Days 4, 8, 11; Cycles 2-4: Days 1, 4, 8, 11; Cycles 5 +: Day 1 & 8; End of treatment; Post-treatment-Follow-up: every 6 weeks Unscheduled: as needed (e.g. to confirm disease progression)
Note: In case central ionized calcium could not be assessed or was not collected, the corrected calcium result from the local lab assessments may be used on days when local albumin and local calcium results are available.		
Assessment of aberrant plasma cells from bone marrow for component of stringent CR Site can choose one of the two methods below		
Local standard flow cytometry (2-4 colors)	n/a	During the study as clinically indicated for component of sCR; The method chosen should be used consistently throughout the study
Local immunohistochemistry	n/a	
Additional Response Assessments in bone marrow for component of iCR		
Central multiparametric flow cytometry (≥4 colors)	n/a	During the study as clinically indicated for component of iCR
Response assessment by investigator and IRC		
Response assessment by investigator	n/a	Day 1 of every subsequent cycle (Cycles 2+) End of Treatment Post-treatment-Follow-up: every 6 weeks Unscheduled: as clinically indicated
Response assessment by IRC	n/a	Day 1 of every subsequent cycle (Cycles 2+) End of Treatment Post-treatment-Follow-up: every 6 weeks Unscheduled: as clinically indicated

Table 7-3 Additional assessments to confirm disease progression or response

Confirmation of disease progression (PD): If PD* is suspected by:	
● rising serum or urine M protein (PEP):	Requires confirmation: Perform an additional assessment from central lab
● hypercalcaemia attributed to solely plasma cell proliferative disorder and as detected by central ionized calcium	Requires confirmation: Perform an additional assessment from central lab (ionized serum calcium values should be > 6.0 mg/dL) If central lab ionized calcium is not assessable, the local corrected calcium result can be used as long as a local albumin and local calcium results are available.
● rising serum FLC (only in patients with non-measurable disease in serum and urine M protein)	Requires confirmation: Perform an additional assessment from central lab
● definite development of new bone lesions or STP or increase in size of bone lesions or STP(s) as identified by local imaging	No confirmation is required.
For the definition of PD, please refer to Table 14-7. Investigators should discontinue patients due to PD only after confirmatory central lab results are available.	
Confirmation of response: All response categories require confirmation (except for stable disease). There is no minimum time interval but confirmation of increase in M-protein or FLC should be done as soon as possible and PD assessment has to be entered in the CRF. Response and PD assessments have to be entered in the CRF per time point without considering confirmation. Confirmation of response will be derived by statistical analysis. Confirmatory assessments can be performed at any time. With the exception of PD, this is performed along the scheduled assessments as defined in Table 7-1. For CR or better, no repetition of bone marrow assessments is required	

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

Blood (serum) and 24-h urine for M-protein assessment will be collected as indicated in Table 7-2. Samples will be processed and shipped as per instructions in the respective laboratory manual.

The central lab will analyze all samples collected by PEP. Beta 2 microglobulin will be determined for all blood samples received for serum M-protein analysis. Analysis by IF will be done for all patients at screening and baseline, and thereafter only in patients/at time-points in case of disappearance of M-protein by PEP.

IgD and IgE immunoglobulin testing will only be performed for patients who are reported as IgD/IgE positive at time of diagnosis/relapse prior to starting study treatment.

7.2.1.2 Serum sample collection for central FLC assessment

Blood (serum) for FLC assessment will be collected as indicated in Table 7-2. Samples will be processed and shipped as per instructions in the respective laboratory manual.

The central lab will analyze FLC only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met.

7.2.1.3 Plasma cell count in bone marrow by local assessment

A bone marrow aspirate/biopsy for plasma cell quantification will be collected as indicated in Table 7-2. The PCC will be evaluated locally only. Either BM aspirate or biopsy can be used for this assessment. However, the same method (aspirate versus biopsy) should be used throughout the study, if possible. In case both, BM aspirate and BM biopsy were performed, the response criteria need to be satisfied by both assessments and the highest of both percent values should be used for the assessment. In case of inadequate/uninterpretable BM sample, the sampling must be repeated in a timely manner but no later than within 28 days. The screening BM sample needs to be repeated and be evaluable prior to randomization. In case a patient is re-screened and has an evaluable BM sample from the first screening, this assessment does not have to be repeated as long as no new anti-myeloma therapy was received between initial screening and re-screening.

7.2.1.4 Assessment of soft tissue plasmacytoma

7.2.1.4.1 Clinical assessment by investigator

The investigator should perform a clinical exam to assess presence of soft tissue plasmacytoma as per Table 7-2.

In case no STP is present at screening, but during the clinical exam there is a suspicion of STP post baseline, CT or MRI must be performed immediately to confirm or disconfirm this suspicion.

7.2.1.4.2 Local Imaging assessment by CT/MRI

Baseline imaging assessment: A CT/MRI to assess presence of soft tissue plasmacytoma will only be performed at screening within 28 days prior to start of study treatment (Day -28 to Day -1 prior to Cycle 1 Day 1,) CT/MRI at screening or C1D1 is only performed if STP is suspected by clinical assessment. (If at screening STP is suspected by clinical assessment and CT/MRI is performed, CT/MRI does not have to be repeated on C1D1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study as long as they can be made available for central storage and review. Any imaging assessments obtained after randomization cannot be considered baseline images.

Post-baseline imaging assessments:

Imaging assessments as described in Table 7-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1).

- If STP is present at baseline, a CT/MRI should be performed every 6 weeks (+/- 7 days) until disease progression starting with Cycle 3 Day 1.
- If STP is not present at baseline, but there is a suspicion of STP and/or disease progression (based on clinical exam or symptoms) during study treatment or in the PT-FU, a CT/MRI should be promptly performed to confirm/disconfirm this suspicion.

7.2.1.5 Full body skeletal survey

A skeletal survey using X-ray and/or CT/MRI in case of newly symptomatic areas with no finding by X-ray a targeted MRI should be performed at Screening within 28 days prior to first dose of study treatment (Cycle 1 Day 1).

Any X-ray and/or CT/MRI already completed during the regular work-up of the patient within 28 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 as long as they can be made available for central storage and review. 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.

7.2.1.6 Central ionized calcium

Ionized calcium in serum for determination of hypercalcemia as part of the response assessment will be evaluated by a central laboratory as per Table 7-2 and Table 7-3.

7.2.1.7 Local assessment of aberrant plasma cells in bone marrow

A local assessment of aberrant plasma cells in bone marrow for the component of sCR, as clinically indicated, can be performed using one of the two methods described below as described in Table 7-2:

- Standard flow cytometry (2-4 colors)
- Immunohistochemistry (IHC)

The method selected should be consistently used for all patients at a specific site throughout the study conduct.

In case of inadequate/uninterpretable BM sample, the procedure must be repeated in a timely manner but no later than within 28 days.

7.2.1.8 Additional central response assessments in bone marrow

Additional response assessments will be performed in a central laboratory and will include the determination of immunophenotypic CR (iCR). For additional response categories in MM according to IMWG criteria see Table 14-6 of Section 14.2.

Absence of aberrant plasma cells in bone marrow for the component of iCR (minimum of 1 million total BM cells analyzed) will be assessed by multiparametric flow cytometry (>4 colors), as clinically indicated (at CR).

For this assessment, 8 mL of bone marrow aspirate will be collected in a 10 cc EDTA tube.

In case of inadequate/uninterpretable BM sample, the procedure must be repeated in a timely manner but no later than within 28 days.

7.2.1.9 Response assessment by Investigator

The response assessment by Investigator should be based on all efficacy data (including central vendor data) as per IMWG guidelines (see Table 14-7 and Table 14-8), as per Table 7-2.

7.2.1.10 Response assessment by IRC

The response assessment by the IRC will be based on all efficacy data as per IMWG guidelines (including central vendor data; see Table 14-7 and Table 14-8). These data are detailed in Table 7-2 and do not include the investigator's response assessment.

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 (or Troponin T), and calculated creatinine clearance, as well as collection 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 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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History CRF page. 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 sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure and pulse will be measured. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Body temperature may be measured as per standard practice at the institution (e.g. orally, via ear, etc.).

7.2.2.3 Height, weight and calculated BSA

Height in centimeters and body weight (in indoor clothing, but without shoes) will be measured as per visit schedule (see Table 7-1). (Note: CRFs are designed to collect the data in the units they are measured in; e.g., height in cm or in and weight in kg or lb). 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 14.3) following the visit evaluation schedule given in Table 7-1.

7.2.2.5 Laboratory evaluations

All lab parameters outlined in Table 7-4, will be evaluated locally as per the visit evaluation schedule (see also Table 7-1). Secura Bio 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, 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 6-7 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 or the same lab parameters as outlined in Table 7-4 should be additionally evaluated as clinically indicated. These evaluations can be done at the site or at the patient's local doctor's office. These results will be recorded on the Unscheduled Visit CRF.

Table 7-4 Local clinical laboratory parameters collection plan

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

Chemistry	BUN/Urea, creatinine, serum albumin, glucose, total bilirubin, AST/SGOT and ALT/SGPT, Beta 2 microglobulin*, total protein, direct and indirect bilirubin only if total bilirubin is abnormal, 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+: Day 1 & 8; End of treatment Unscheduled: as clinically indicated *To be performed by the local laboratory only at screening, and, thereafter, as clinically indicated. Please note that in addition, beta 2 microglobulin is analyzed by the central laboratory every time serum M-protein by PEP is determined.
Electrolytes	serum calcium, sodium, potassium, phosphorus, magnesium **To be performed at:** Screening Cycles 1-4: Days 1, 4, 8, 11; Cycles 5+: Day 1 & 8; End of treatment Unscheduled: as clinically indicated
Thyroid	Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine). **To be performed at:** Screening Cycle 1 Day 1; End of treatment Unscheduled: as clinically indicated
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
Cardiac Enzyme Troponin I	Troponin I* **To be performed at:** Screening Cycles 1+: Day 1; End of treatment Unscheduled: as clinically indicated (e.g. on days when unscheduled 12-Lead ECGs) *Note if Troponin I cannot be performed by the local lab, it can be analyzed centrally, or Troponin T can be analyzed locally instead. The same test should be performed throughout the study. The central Troponin I results, or local Troponin T results still would be entered on the local cardiac enzyme eCRF page by the site.
CCL assessed by eGFR	CCL is assessed by eGFR which is calculated by the site using the MDRD study equation (Dimopoulos et al 2010) based on serum creatinine results (Scr), age, gender and race of a patient and depending on the analytics used to determine Scr (Isotope dilution mass spectrometry (IDMS) traceable technique or other technique used) (See Section 7.2.2.5.7 for details). **To be calculated at:** Screening Cycle 1: Days 1, 4, 8, 11; Cycles 2 +: Day 1 & 8; End of treatment Unscheduled: as clinically indicated (if serum creatinine was determined)
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:** Cycles 1 +: Day 1

7.2.2.5.1 Hematology

Hematology tests are performed as indicated in Table 7-4.

7.2.2.5.2 Chemistry

Clinical chemistry tests are performed as indicated in Table 7-4.

7.2.2.5.3 Electrolytes

Electrolytes are performed as indicated in Table 7-4.

7.2.2.5.4 Thyroid

Thyroid function tests are performed as indicated in Table 7-4.

7.2.2.5.5 Coagulation

The coagulation tests are performed at screening (Table 7-4). 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 6.4.2.1).

7.2.2.5.6 Cardiac Enzyme: Troponin I

Troponin I should be evaluated on all visits when ECGs (scheduled or unscheduled) are performed (see Table 7-4). On days when an unscheduled ECG is performed, the Troponin I result is also recorded on the Unscheduled Visit CRF. If Troponin I cannot be performed by the local laboratory, it can be determined by the central laboratory, or Troponin T can be performed locally. The same parameter test should be used consistently for a patient throughout the study. The central Troponin I results or local Troponin T results would also be entered on the local cardiac enzyme eCRF page with the central lab ID.

7.2.2.5.7 Creatinine Clearance (assessed by eGFR)

CCL is assessed by eGFR which is calculated as indicated in Table 7-4 using the MDRD study equation based on serum creatinine in mg/dL (Scr), age, gender and race. Dependent on the method used to determine serum creatinine (IDMS or not), the original or IDMS traceable MDRD study equation should be used:

Original MDRD study equation:

eGFR (ml/min/1.73m^2) = 186 x (Scr) $^{-1.154}$ x age $^{-0.203}$ x (0.742 if female) x 1.212 (if patient's race is black)

IDMS traceable MDRD study equation:

eGFR (ml/min/1.73m^2) = 175 x (Scr) $^{-1.154}$ x age $^{-0.203}$ x (0.742 if female) x 1.212 (if patient's race is black)

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 7-4. In case of a positive test, the patient will need to discontinue the study treatment unless the test result is proven to be false positive.

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

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed according to Table 7-5 on ECG units provided by the CRO from Cycle 1 through 16 or on local ECG units starting from Cycle 17. All scheduled 12-lead ECGs will be done in triplicates to obtain the mean and should be separated by 5 to 10 minutes each. 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 last of the pre-dose triplicate ECGs should be performed prior to the planned dose of PAN and BTZ. The first of the 2h post-dose triplicate ECGs should be performed around the 2 h post-dose time point, the last of triplicates should be within 30 minutes of the 2 h post-dose time point.

Central 12-Lead ECGs performed up to Cycle 16:

All ECGs (scheduled or unscheduled) performed up to Cycle 16, and end of treatment ECGs if last dose was before start of Cycle 17, will be submitted by the site for central review. Central ECG results are uploaded to the portal and will be available for review by the investigator within approximately 1-2 working days. The centralized reading of ECGs will use the Fridericia's correction: QTcF will be the formal data entered into the clinical study database. Local ECG and central review results will not be reconciled.

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

Local 12-Lead ECGs performed starting from Cycle 17:

From Cycle 17 onwards, local single or triplicate ECGs will only be performed as clinically indicated during study treatment and results will be reviewed locally at the site.

If study treatment discontinues after start of Cycle 17, three local triplicate ECGs will be performed and locally reviewed at the EOT visit.

Results will be entered on the Unscheduled Local CRF Page and on the Local Analysis ECG CRF page for triplicates performed at the EOT, as applicable.

Review of all ECGs at site:

The mean QTcF of the 3 ECGs obtained pre-dose on Cycle 1 Day 1 by central review will be used as the baseline value to compare to other QTcF results throughout the study. If a prolonged QTcF interval is noted at any time, additional days of QT monitoring may be required (see Table 6-5).

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 based on the assessment performed by central review in Cycles 1 through 16 and based on the local assessment performed at the site starting from Cycle 17.

The screening ECGs must be reviewed by the central lab to determine eligibility prior to dosing. **Therefore, it is advisable to perform and transmit the screening ECGs in the first week of screening and at least 10 days prior to planned first dose.**

Clinically significant ECG abnormalities present at screening should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

Table 7-5 Central and local ECG collection plan

Cycle	Day of cycle	ECG monitoring[a]
Central 12-Lead ECGs performed on units provided by central vendor and centrally reviewed up to Cycle 16		
Screening [b]	n/a	Triplicate 12 Lead ECG to assess eligibility
Cycle 1	1	Pre-dose and 2h post PAN dose: Triplicate 12 lead ECG
Cycle 2 to Cycle 4	1	Pre-dose: Triplicate 12 lead ECG
Cycles 5 to Cycle 16	1	Pre-dose: Triplicate 12 lead ECG
End of Treatment if last dose was administered within first 16 cycles	n/a	Triplicate 12-Lead ECG
Cycle 1 to 16 Unscheduled	Unscheduled	Any time single or triplicate 12 lead ECG, as clinically indicated
Local 12-Lead ECGs performed on local units starting from Cycle 17		
Cycle 17+ Unscheduled	Unscheduled	Any time single or triplicate 12-lead ECG, as clinically indicated
End of Treatment if last dose was administered after 16 cycles (in Cycles 17+)	n/a	Triplicate 12-Lead ECG

[a] Refer to Table 6-5 for the recommended dose modifications due to QTcF prolongation
[b] Central vendor (for eligibility mean of central triplicate QTcF results will be used)
Note: Triplicate ECGs should be performed approximately 5-10 minutes apart

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 (see exclusion criterion 16b) prior to the first administration of study treatment and at the EOT visit within 7 days of last dose 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.

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 Pharmacokinetics

Serial PK blood samples for both BTZ and PAN will be collected from all patients at the same time points (6 mL of whole blood at collection time points as specified in Table 7-6 for Treatment Arms A & C, and Table 7-7 for treatment Arm B). Non-compartmental PK parameters will be estimated from each individual plasma concentration-time profile using appropriate methods and software. Refer to Section 10.5.4 for a table of PK parameters that will be estimated.

The sequence of administration of study treatment on days where all three study drugs are administered (i.e. Day 1 and Day 8 of Cycle 1 and Day 8 of Cycles 2 through 8): should be as follows:

Dex taken within 15 to 30 minutes prior to BTZ, BTZ s.c. injection within 1-5 minutes prior to PAN. The time when PAN was taken or just prior to when PAN was taken will be considered 0h. On days were PAN is not taken (i.e. Day 4 and Day 11 for Treatment Arms A & C), the sample should be taken approximately 24 hours after the last PAN dose. See Figure 6-5 for details.

Date/time of blood samples must be recorded relative to the PAN dose, actual time of dosing for PAN and for BTZ, as applicable and actual times of blood collection have to be recorded on the corresponding PK blood collection CRF pages.

Table 7-6 Pharmacokinetic blood collection log for panobinostat (PAN) TIW Treatment Arm A & C and bortezomib (BTZ)

Cycle	Day	Scheduled Time Point	Allowed window	PAN		BTZ			Sample Volume In mL
				Dose Reference ID	PK Sample No	Dose Reference ID		PK Sample No	
						Patients ≤ 75 years of age*	Patients > 75 years of age*		
1	1	Pre-dose PAN / 0h	-60 min	101	101	201	201	201	6
1	1	0.5h post PAN	+/- 5 min	101	102	201	201	202	6
1	1	1h post PAN	+/- 10 min	101	103	201	201	203	6
1	1	2h post PAN	+/- 20 min	101	104	201	201	204	6
1	1	4h post PAN	+/- 40 min	101	105	201	201	205	6
1	1	8h post PAN	+/- 60 min	101	106	201	201	206	6
1	4	24h post PAN dose on D3**	+/- 60 min	102	107	201	201	207	6
1	4	26h post PAN dose on D3	+/- 20 min	102	108	202	201	208	6
1	4	28 – 32h post PAN dose on D3	n/a	102	109	202	201	209	6
1	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	103	110	202	201	210	6
1	11	24h post PAN on D10**	+/- 60 min	104	111	203	202	211	6
2	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	105	112	204	204	212	6
2	8	2h post PAN	+/- 20 min	106	113	205	205	213	6
3	8	Pre-dose PAN/0h 72h post PAN on D5	-60min	107	114	206	206	214	6
3	8	2h post PAN	+/- 20 min	108	115	207	207	215	6
4	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	109	116	208	208	216	6
4	8	2h post PAN	+/- 20 min	110	117	209	209	217	6
5	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	111	118	210	210	218	6
5	8	2h post PAN	+/- 20 min	112	119	211	211	219	6

Cycle	Day	Scheduled Time Point	Allowed window	PAN		BTZ			Sample Volume In mL
				Dose Reference ID	PK Sample No	Dose Reference ID		PK Sample No	
						Patients ≤ 75 years of age*	Patients > 75 years of age*		
6	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	113	120	212	212	220	6
6	8	2h post PAN	+/- 20 min	114	121	213	213	221	6
7	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	115	122	214	214	222	6
7	8	2h post PAN	+/- 20 min	116	123	215	215	223	6
8	8	Pre-dose PAN/0h 72h post PAN on D5	-60 min	117	124	216	216	224	6
8	8	2h post PAN	+/- 20 min	118	125	217	217	225	6
Total									**150**

Pre-dose PAN/0h: samples should be drawn pre-dose PAN and BTZ
*: age on first day of screening (date of signing of initial informed consent);
**: sample should be drawn prior to BTZ dosing on this day for patients who are ≤ 75 years of age on first day of screening

Table 7-7 Pharmacokinetic blood collection log for panobinostat (PAN) BIW Treatment Arm B and bortezomib (BTZ)

Cycle	Day	Scheduled Time Point	Allowed window	PAN		BTZ			Sample Volume in mL
				Dose Reference ID	PK Sample No	Dose Reference ID		PK Sample No	
						Patients ≤ 75 years of age*	Patients > 75 years of age*		
1	1	Pre-dose PAN / 0h	-60 min	101	301	201	201	401	6
1	1	0.5h post PAN	+/- 5 min	101	302	201	201	402	6
1	1	1h post PAN	+/- 10 min	101	303	201	201	403	6
1	1	2h post PAN	+/- 20 min	101	304	201	201	404	6
1	1	4h post PAN	+/- 40 min	101	305	201	201	405	6
1	1	8h post PAN	+/- 60 min	101	306	201	201	406	6

Cycle	Day	Scheduled Time Point	Allowed window	PAN		BTZ			Sample Volume in mL
				Dose Reference ID	PK Sample No	Dose Reference ID		PK Sample No	
						Patients ≤ 75 years of age*	Patients > 75 years of age*		
1	4	Pre-dose PAN/0h 72h post PAN on D1	- 60 min	101	307	201	201	407	6
1	4	2h post PAN dose on D4	+/- 20 min	102	308	202	201	408	6
1	4	4-8h post PAN dose on D4	n/a	102	309	202	201	409	6
1	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	102	310	202	201	410	6
1	11	Pre-dose PAN/0h 72h post PAN dose on D8	- 60 min	103	311	203	202	411	6
2	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	104	312	204	204	412	6
2	8	2h post PAN	+/- 20 min	105	313	205	205	413	6
3	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	106	314	206	206	414	6
3	8	2h post PAN	+/- 20 min	107	315	207	207	415	6
4	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	108	316	208	208	416	6
4	8	2h post PAN	+/- 20 min	109	317	209	209	417	6
5	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	110	318	210	210	418	6
5	8	2h post PAN	+/- 20 min	111	319	211	211	419	6
6	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	112	320	212	212	420	6
6	8	2h post PAN	+/- 20 min	113	321	213	213	421	6
7	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	114	322	214	214	422	6
7	8	2h post PAN	+/- 20 min	115	323	215	215	423	6

Cycle	Day	Scheduled Time Point	Allowed window	PAN		BTZ			Sample Volume in mL
				Dose Reference ID	PK Sample No	Dose Reference ID		PK Sample No	
						Patients ≤ 75 years of age*	Patients > 75 years of age*		
8	8	Pre-dose PAN/0h 96h post PAN dose on D4	-60 min	116	324	216	216	424	6
8	8	2h post PAN	+/- 20 min	117	325	217	217	425	6
Total									150
Pre-dose PAN/0h: samples should be drawn pre-dose PAN and BTZ (on days on which BTZ is administered) *: age on first day of screening (date of signing of initial informed consent)									

7.2.3.1 Pharmacokinetic blood collection and handling

At specified time points (Table 7-6 for Treatment Arms A & C and Table 7-7 for Treatment Arm B), blood will be collected in tubes containing sodium heparin. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. If indwelling catheters are used and flushed with saline or heparin, at least 2 mL of blood should be discarded before collecting the blood samples.

Immediately after collection of blood samples for PAN (2 mL) and BTZ (4 mL), the tube should be inverted several times to prevent clotting. Blood samples for PAN and BTZ should be kept in an ice water bath at approximately 4ºC until centrifugation. The tubes should be centrifuged as soon as possible but within no more than 60 minutes after collection at approximately 800 x g at 4ºC for 15 minutes to separate plasma.

PAN plasma (~ 1 mL) will be transferred to a 2-mL polypropylene screw-cap tube (no skirt), the tube capped, and the sample mixed briefly and then immediately placed in a freezer set at ≤ -60ºC until shipment with sufficient dry ice to the central laboratory.

For BTZ, the harvested plasma samples (~2 mL) will be mixed with 20 µL of 20% formic acid (v/v) into a 3-mL polypropylene screw-cap tube (no skirt) with a final formic acid concentration of ~0.2% (v/v). This was followed by capping and thorough mixing prior to being stored at ≤ -60ºC until shipment with sufficient dry ice to the central laboratory.

Refer to the [LBH589D2222 PK Laboratory Manual] for detailed instructions for the collection, handling, and shipping of samples.

Residual plasma used for PK analysis may also be used for exploratory PK analysis. This could include using leftover plasma for protein binding analysis, metabolite profiling, or exploratory biomarker analysis, if there is sufficient sample remaining.

7.2.3.2 Analytical method

7.2.3.2.1 Panobinostat

The plasma samples from all patients who received panobinostat will be assayed for panobinostat concentrations using a validated liquid chromatography-tandem mass spectrometry assay (LC-MS/MS). Values below the lower limit of quantification (LLOQ) of approximately 0.1 ng/mL will be reported as zero. Missing values will be labeled accordingly.

7.2.3.2.2 Bortezomib

The plasma samples from all patients will be assayed for bortezomib. This assay will be validated with a LLOQ of 0.1 ng/mL or lower. Values below LLOQ will be reported as zero. Missing values will be labeled accordingly.

7.2.4 Biomarkers

Biomarker assessments will be performed in blood to measure the molecular pharmacodynamic effects of panobinostat treatment when used in combination with bortezomib and dexamethasone.

Since panobinostat is a pan-HDAC inhibitor, two different assays will be used to measure the acetylation status of histone proteins. These assessments will be performed on peripheral blood samples which are collected at multiple time-points. The data from these studies will be compared with the dose level and pharmacokinetic data to determine whether there is an association of these parameters, and any further association with clinical outcome. These analyses are exploratory.

In addition, blood samples will be collected to assess the molecular status of cell free DNA (cfDNA) at baseline, at the end of treatment visit and for patients who entered the PT-FU at time of disease progression. If the reason for end of treatment is disease progression only the end of treatment sample needs to be collected.

Lastly, biomarker assessments will be performed in bone marrow aspirate (BMA) samples at screening, at the end of treatment and for patients who entered the PT-FU at time of disease progression. The end of treatment sample is only collected if the reason for end of treatment is disease progression, or if the patient who discontinued study treatment for reasons other than disease progression does not wish to continue to the PT-FU.

These samples will be used to explore whether the status of molecular markers might correlate with clinical outcome parameters. The analyses in cfDNA and BMA are for purposes of discovery.

7.2.4.1 Biomarker sample collection

Table 7-8 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point	Allowed window
Blood for pharmacodynamic analysis	8 mL	Cycle 1 Day 1 (C1D1)	Pre-dose/0h	-60 min
	8 mL	Cycle 1 Day 1	4h post PAN	+/- 40 min
	8 mL	Cycle 1 Day 1	8h post PAN	+/- 60 min
	8 mL	Cycle 1 Day 8	Pre-dose/0h	-60 min
	8 mL x 7 = 56mL	Cycle 2-8 Day 8	Pre-dose/0h	-60 min
	8mL	End of treatment	n/a	n/a
	8mL	During PT-FU: At time of disease progression	n/a	n/a
Blood plasma for cfDNA analysis	6mL	Cycle 1 Day 1	Pre-dose/0h	-60min
	6mL	End of treatment	n/a	n/a
	6mL	During PT-FU: At time of disease progression	n/a	n/a
Total	122 mL	Note: If the reason for end of treatment is disease progression only the end of treatment sample needs to be collected.		
BMA to explore novel predictive markers	2mL	Screening	n/a	n/a
	2mL	End of treatment*	n/a	n/a
	2mL	During PT-FU: at time of disease progression	n/a	n/a
*at end of treatment if reason for EOT is a PD or if a patient who discontinued study treatment for other reasons than PD does not wish to continue in PT-FU; i.e. bone marrow is only collected at 2 time points for each patient at screening and at EOT/PD				

Detailed instructions for the collection, handling, and shipping of samples are outlined in the [CLBH589D2222 Laboratory Manual]. Sample collection dates/information will be entered on the appropriate CRF page(s) and/or central laboratory paper requisition forms.

7.2.4.2 Optional additional exploratory biomarker assessments using remaining biomarker samples

If the patient agrees, the remaining biomarker samples (bone marrow, blood) may be stored for up to 15 years and further analyzed to address scientific questions related to the study treatment or cancer. A decision to perform such additional exploratory biomarker research studies beyond what is described in Section 7.2.4 would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

Other assessments

No additional tests will be performed on patients entered into this study.

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Quality of life (QOL) will be assessed by the European Organization for Research and Treatment (EORTC) core 30-item questionnaire (EORTC-QLQ-C30) and by the Functional Assessment of Cancer Therapy / Gynecology Oncology Group Neurotoxicity scale (FACT/GOG-Ntx).

The EORTC-QLQ-C30 will be used to provide patient-reported outcome measures of health-related quality of life. The EORTC-QLQ-C30 is frequently employed in clinical studies of patients with multiple myeloma and is recognized as reliable and valid measures (Aaronson et al 1993; Osoba et al 1994, Benboubker et al 2015, Stewart et al 2014). The EORTC-QLQ-C30 measures functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact) and a global health and quality-of-life scale (Aaronson et al 1993). Higher score values for a functional/QoL scale indicate higher functioning and health-related quality of life. Higher score values for symptom scales indicate greater symptomatology or problems.

The FACT/GOG-Ntx, Version 4 is a 38-item questionnaire designed to assess general quality of life and the severity and impact of neurotoxicity from systemic chemotherapy. The FACT/GOG-Ntx has been used in previous bortezomib clinical studies of patients with MM and is recognized as reliable and valid measure to assess symptoms associated with neurotoxicity (Sonneveld et al 2013; Calhoun et al 2003). The FACT/GOG-Ntx was developed from the Functional Assessment of Chronic Illness Therapy Measurement System and focuses on four general quality of life domains for physical well-being, functional well-being, social/family well-being, and emotional well-being, and includes additional items to characterize treatment-related neurotoxicity. Higher subscales/total scores represent higher QOL. In the case of the neurotoxicity subscale, lower scores correspond to higher neurotoxicity.

Patient questionnaires should be completed before any study drug administrations at the visits as indicated in Table 7-9. The measures will be administered sequentially at the beginning of the study visit prior to any interaction with the study physician or other study personnel including any tests, treatments or receipt of results from any tests to avoid biasing the patient. The questionnaires will be completed by the patient in the patient's local language on an electronic device at the site. In case the patient has difficulties completing these questionnaires by her-/himself, a family member or a caregiver can assist with the completion. Completed questionnaires should be reviewed by the investigator/study personnel before the clinical examination for responses which may indicate potential AEs or SAEs. If an AE or SAE is confirmed, then the physician should record the event as instructed in Section 8 of this protocol. Investigators/study personnel should not encourage the patients to change responses reported in the questionnaires or diary.

In addition, to the above-mentioned PRO measures, a daily diary will be used to measure concepts related to diarrhea to help patients manage their diarrhea symptoms, anti-diarrheal medications and fluid intake. The diary will include a diarrhea event log that records every bowel movement in the last 24 hours, along with stool consistency (as per Bristol Stool Form Scale) and time of day when bowel movement occurred. The diary will be in the form of an electronic hand-held device, which the patient will be provided to fill out daily from the first day of screening until the end of Cycle 8. Log in and usage instructions will be provided by the study personnel at the beginning of the study. Alarms will be set up in the electronic hand-held device to remind the patient to fill out their diaries.

Table 7-9 Patient reported outcomes collection plan

Patient Questionnaires	Treatment Period	Visit / Cycle	Time
EORTC QLQ-C30	Baseline	Cycle 1 Day 1	The EORTC QLQ-C30 will be administered at the beginning of the study visit prior to any interaction with the study physician including any tests, treatments or receipt of results from any tests to avoid biasing the patient. On Day 1 of a cycle the measures should be administered prior to the patient taking any study treatment for this day.
	Study Treatment (in cycles of 21 days)	Cycle 3 Day 1 Cycle 5 Day 1 Cycle 7 Day 1 and every 4 cycles (12 wks), thereafter	
		End of treatment	
	Post Treatment FU	Every 12 weeks	
FACT/GOG-Ntx	Baseline	Cycle 1 Day 1	The FACT/GOG-Ntx will be administered after the EORTC-QLQ-C30 at the beginning of the study visit prior to any interaction with the study physician including any tests, treatments or receipt of results from any tests to avoid biasing the patient. On Day 1 of a cycle, the measures should be administered prior to the patient taking any study treatment for this day.
	Study Treatment (in cycles of 21 days)	Cycle 3 Day 1 Cycle 5 Day 1 Cycle 7 Day 1 and every 4 cycles (12 wks), thereafter	
		End of treatment	

Patient Questionnaires	Treatment Period	Visit / Cycle	Time
Diary for diarrhea management	Screening	Screening (1st day of screening until pre-dose Cycle 1 Day 1)	The diary should be completed by the patient (or a family member or caregiver, if patient is unable to complete it her-/himself) on a daily basis from the first day of screening until the last day of Cycle 8. The study personnel should review the diary entries with the patient on Day 1 of Cycles 1 through 9.
	Study Treatment	Cycle 1 Day 1 to Cycle 8 Day 21 (last day of Cycle 8)	

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 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) is not used in this study; but is collected as a seriousness criteria in the Adverse Event CRF and also in other CRFs (e.g. Study Completion, Death etc.).

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 toxicity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)

- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- 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 sequelae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.

If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For Grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per IMWG Guidelines for response assessment in MM, see Section 14.2), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the study treatment.

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.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

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 (e.g. hospitalization to receive blood transfusions)
    - 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
- Protocol exempt SAEs:
    a. Progression of disease (including fatal outcomes), if documented by use of appropriate method, should not be reported as serious adverse event.
    b. Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements. Despite the clinical description of "life-threatening or disabling" provided as general guidance for severity of Grade 4 events in the introduction to CTCAE v. 4.03, this does not automatically indicate that all Grade 4

adverse events or lab abnormalities are SAEs unless they meet the definition of serious as indicated above and as per investigator discretion.

8.2.2 Reporting

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

Any additional information for the SAE including, complications, or progression of the initial SAE, and recurrent episodes 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.

Any SAEs experienced after this 30-day period should only be reported to Secura Bio if the investigator suspects a causal relationship to the study treatment.

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 Secura Bio. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

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 Secura Bio study treatment, a Secura Bio representative may urgently require further information from the investigator for Health Authority reporting. Secura Bio 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 Secura Bio 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 Secura Bio representative or Secura bio designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should 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

The Steering Committee (SC) will be fulfilling the role of the Data Monitoring Committee. The details of the role of the Steering Committee will be defined in a SC Charter.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the study, i.e. not being members of the IRC and Secura Bio representatives from the Study 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. The SC will also review safety data approximately every 6 months (after first randomized patient started study treatment). A consultant cardiologist may assist the SC in this safety review, as necessary. The SC should also review the results of the interim, the primary and the final analyses. At time of the interim analysis, the SC will provide recommendations to Secura Bio to continue, modify or stop the study early. These recommendations will be shared with FDA and will only be implemented once FDA concurrence has been obtained. Together with the clinical study 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 SC charter.

8.8 Independent Review Committee

An Independent Review Committee (IRC) will also be established prior to the randomization of the first patient. IRC will perform an independent review of disease response data at all analysis time points for all patients randomized in the study and provide response assessments based on the IMWG criteria, as well as dates of response assessments in a blinded manner. For

PD, the IRC will document the reason for progression. Response and PD assessments will be entered in the CRF per time point without considering confirmation. Confirmation of response will be derived by statistical analysis.

The results of the IRC review will be part of the clinical database.

Responses assessed by the IRC will be used for the primary endpoint of ORR (when all randomized patients have been treated for up to 8 cycles) and all other efficacy related endpoints (for the interim and primary analysis and at time of final data cut-off). It is expected that the IRC will at a minimum consist of three hematologists. There will be a kick-off meeting with the IRC describing their roles and responsibilities, to agree on potential format for data listings and process logistics prior to the finalization of the IRC charter and the IRC statistical analysis plan.

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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Sponsor personnel (or designated CRO) reviewed 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 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. Secura Bio 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 (CRF). The CRFs 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 CRFs 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 CRF is complete, accurate, and that entry and updates are performed in a timely manner.

The following third party vendor data will be acquired for this study and will be transferred directly from the respective CRO to the Secura Bio database:

- **Central ECG data** will be transmitted by the sites to the designated CRO to undergo quality checks and central review.
- **PRO questionnaires (EORTC-QLQ-C30 and FACT/GOG-Ntx)** will be recorded by patients on an electronic device at the site and transmitted by the sites to a designated CRO.
- **The diary for diarrhea management** will be recorded by patients on an electronic hand-held device and transmitted by patient to a designated CRO**.**
- **PK (blood) samples for PAN and BTZ** drawn during the course of the study will be collected from the Investigator sites and analyzed by a Secura Bio assigned laboratory or contracted central laboratory.

- **Biomarker (blood and BMA) samples** drawn during the course of the study will be collected from the Investigator sites and analyzed by a Secura Bio assigned laboratory or contracted central laboratories.
- **An additional bone marrow aspirate sample for cytogenetics (FISH)** assessment will be collected during screening and will be sent to a central laboratory for assessment.
- **Bone marrow samples** for additional response assessments to determine immunophenotypic CR by multi-parametric flow cytometry, will be sent to a central lab for analysis, as needed.
- **Serum for disease assessment** by PEP, IF and FLC; and ionized serum calcium will be collected by the site and sent to a central lab for analysis.
- **Urine samples for disease assessment** by PEP and IF will be collected by the site and sent to a central lab for analysis.

Details regarding all CRO procedures including collection and shipment of data will be described in the manual provided by the respective CRO.

Enrollment will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Secura Bio personnel (or designated CRO).

9.4 Database management and quality control

For studies using electronic CRFs, Secura Bio 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 Secura Bio (or a designated CRO).

Electronic PRO questionnaires will be entered into an electronic device by the patient at the site. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Secura Bio personnel (or designated CRO).

Diary for diarrhea management data will be entered into an electronic hand-held device by the patient from screening until end of Cycle 8. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Secura Bio personnel (or 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 Secura Bio personnel (or designated CRO).

At the conclusion of the study, after return of all unused drug supplies to Secura Bio 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. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM for archiving at the investigational site.

10 Statistical methods and data analysis

The primary analysis will be performed when all randomized patients have been treated for up to 8 cycles.

Interim analysis (IA) will be performed when approximately 120 randomized patients (40 in each arm) have been treated up to 8 cycles.

The final analysis will be performed when all patients have completed a 3-year Survival follow-up or discontinued follow-up prematurely.

10.1 Analysis sets

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 they have been assigned to during the randomization procedure.

The randomized treatment information is taken from the IWRS patient randomization listing.

10.1.2 Safety Set

The safety set consists of all patients who received at least one dose of any component of the study treatment.

Patients who have been randomized but did not take at least one dose of any component of study treatment will not be included in the safety set. 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 a subset of patients in the FAS who received at least one dose of the randomized study drug and had no major protocol deviation.

Protocol deviations leading to exclusion from the PPS are:

- If it is in direct conflict with the population definition given in the title of the study (i.e., patient diagnosis, stage of disease, measurability of disease, or use of prior treatment does not correspond to the intended patient population to be studied).
- Study treatment received different from treatment assigned by randomization
- If the protocol deviation is very likely to confound the scientific analysis of the primary efficacy endpoint(s) or if it precludes any meaningful efficacy assessment.
- Primary refractory multiple myeloma or Bortezomib refractory.
- If the ECOG performance status (PS) is worse than 2

10.1.4 Dose-determining analysis set

Not applicable

10.1.5 Pharmacokinetic analysis sets

The pharmacokinetic analysis set (PAS) for PAN consists of all patients with at least one evaluable PK concentration of PAN after dosing on Day 1. A PK concentration is considered evaluable in a respective cycle if:

- The patient took the full scheduled dose as randomized in a respective cycle
- The patient did not vomit within 4 hours after dosing in a respective cycle

The pharmacokinetic analysis set (PAS) for BTZ consists of all patients with at least one evaluable PK concentration of BTZ after dosing on Day 1. A PK concentration is considered evaluable in a respective cycle if:

- The patient took the full scheduled dose in a respective cycle

Individual samples or PK parameters may additionally be flagged by CP expert for exclusion from analysis. This does not exclude the patient from the analysis set unless they also meet the criteria listed above.

10.1.6 Other analysis sets

Not applicable.

10.1.6.1 Efficacy/evaluable set

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment arm for the FAS.

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

Duration of study treatment, cumulative dose, average daily dose, actual dose intensity and relative dose intensity of each of the components of study treatment will be summarized by treatment arm and by every 21-day cycle. The number of patients with dose changes/interruptions will be presented by treatment arm, along with reasons for the dose change/interruptions. Safety set will be used for the analyses.

10.3.2 Concomitant therapies

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by Anatomical Therapeutic Chemical (ATC) Class, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment (defined as cycle 1 day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

For the analyses of transfusions, only transfusions received after start of study treatment and up to 30 days after last dose will be considered. Number of patients with transfusions, Number of transfusions per patient, Number of transfusion days normalized to study treatment duration will be analyzed by treatment arm.

Safety set will be used for all above mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective of the study is to assess efficacy of study treatment by treatment arm as measured by overall response rate (ORR: iCR, CR, sCR, VGPR and PR) after all randomized patients have been treated for up to 8 cycles of study treatment, assessed by IRC, according to IMWG criteria in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents.

10.4.1 Variable

The primary endpoint, overall response rate (ORR), is defined as the proportion of patients with a confirmed partial response (PR) or better as their best overall response. Best overall response is the best post baseline confirmed overall response observed in a given patient, among the confirmed response categories, excluding “unknown” and “not assessed”. Best overall response is determined based on overall responses observed at all post-baseline response assessments, recorded from the randomization until PD, death, start of new therapy, withdrawal of consent or end of study, whatever comes first. For the primary endpoint of ORR, all the data collected up to end of cycle 8 + 3 days for patients still being on treatment and collected up to 168 + 3 days from randomization for patients who discontinued study treatment earlier will be included. The ORR will be reported as per IRC according to IMWG criteria (see Section 14.2) in patients

with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents.

10.4.2 Statistical hypothesis, model, and method of analysis

The assessment of efficacy of study treatment will be based on ORR per IMWG criteria in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents as determined by IRC. FAS will be used as the primary analysis; PPS will be used as a supportive analysis.

No comparison of the treatment arms is planned in this study.

The point estimate of ORR along with corresponding exact 95% two-sided confidence intervals according to Clopper-Pearson will be presented by treatment arm.

The assessment of efficacy will be based on the IA data and based on the calculated Bayesian predictive probabilities of occurrence of ORR>=55% (i.e. 44 out of 80 patients per treatment arm) and lower bound of 95% exact CI ≥ 35% at the primary analysis. In addition, the PAN 10 mg TIW and PAN 20 mg BIW arms will have an option to be stopped for futility at interim analysis. For the details of interim analysis refer to Section 10.7.

The primary analysis will be performed when all randomized patients have been treated for up to 8 cycles. For the primary endpoint (ORR), the cut-off for the primary analysis will be determined when all randomized patients have been treated for up to 8 cycles.

The final analysis of study data will be when the last patient entering the long-term follow-up (post treatment follow-up or survival follow-up whichever occurs first) has completed a 3-year Survival follow-up or discontinued earlier.

A sensitivity analysis will be performed using investigator assessment at interim, primary and final analysis.

10.4.3 Handling of missing values/censoring/discontinuations

For the purposes of the interim, primary and final analyses, patients with a best overall response of 'Unknown' (UNK) will be treated as non-responders in estimating the ORR in the FAS (per the ITT principle). PFS for patients who are free of disease progression or are lost-to-follow-up will be right-censored at their last adequate response assessment date.

OS time for patients who are alive at the end of the study or are lost to follow-up will be right-censored at the date of last contact.

10.4.4 Supportive analyses

Subgroup analyses based on number of prior lines of anti-MM therapy (1 vs. 2 vs. 3 or 4), age (≤75 vs. >75 years), gender, race, etc. will be performed as appropriate.

10.5 Secondary objectives

All secondary efficacy assessments (iCR/sCR/CR/VGPR rate, PFS, OS, TTR, DOR, TTP, and ORR) will be analyzed as per IRC assessment. All secondary analyses will be performed based on the FAS, unless otherwise specified.

10.5.1 Secondary objective(s)

The individual iCR, sCR, CR, VGPR rates will be assessed based on IMWG criteria (see Section 14.2) as per IRC assessment.

The ORR will be assessed based on the IMWG criteria as per IRC assessment.

Progression-free survival (PFS) will be assessed based on IMWG criteria (see Section 14.2) as per IRC assessment, and is defined as the time from date of randomization to date of first documented disease progression or death (regardless of cause of death).

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

Time to response (TTR) is the time between date of randomization to the date of first onset of PR or better response (iCR or sCR or CR or VGPR or PR) and will be based on IMWG criteria as per IRC assessment.

Duration of response (DOR) is defined as the duration from the first documented onset of PR or better response (iCR or sCR or CR or VGPR or PR) to the date of first documented disease progression or death due to multiple myeloma and will be based on IMWG criteria (see Section 14.2) as per IRC assessment.

Time to progression (TTP) is defined as the time from the date of randomization to the date of the first documented disease progression or death due to multiple myeloma and will be based on IMWG criteria (see Section 14.2) as per IRC assessment.

Survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. The estimations are performed by treatment arm. Median PFS, Median OS time and its two-sided 95% confidence intervals will be reported for three treatment arms.

Median TTR, DOR and TTP along with corresponding 95% confidence intervals will be reported for three treatment arms.

A sensitivity analysis will be performed using investigator assessment at, primary and final analysis for the secondary endpoints (PFS, TTP, TTR, DoR, ORR).

10.5.2 Other secondary efficacy objectives

Not applicable.

10.5.3 Safety objectives

All safety data will be by analyzed and reported overall and by treatment arm.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. 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 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication

The safety summary tables will include only assessments collected within 30 days after study treatment discontinuation and assessments prior to the data cut-off date for ongoing patients, unless otherwise specified.

All data, regardless of observation period, will be listed and assessments collected in the pre-treatment and post-treatment period will be flagged in all the listings.

10.5.3.2 Adverse events (AEs)

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4.03). AEs are coded using the MedDRA terminology version 17.1 or later.

The following summaries will be provided by treatment arm.

- Incidence of treatment-emergent adverse events (new or worsening from baseline) during on-treatment period
- Non-fatal serious adverse events during on-treatment period
- All deaths (on-treatment and post-treatment) will be tabulated.

However, all AEs, deaths and non-fatal serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Adverse Events of Special Interest (AESI) will be analysed. 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 investigational treatment(s).

Adverse events of special interest are defined at the project level and are regularly updated based on emergent data. For each specified AESI, number and percentage of patients with at least one event part of the AESI will be reported.

10.5.3.3 Laboratory abnormalities

Categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or according to normal ranges for those parameters without available CTCAE grading. The calculation of CTCAE grades will be purely based on the observed lab values, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (low and high) classifications based on laboratory normal ranges.

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

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.

- 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.

Listings of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will also be generated.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the RAP.

10.5.3.4 Other safety data

ECGs, Vital signs and ECOG PS will be summarized by treatment arm.

ECG

- listing of ECG evaluations for all patients with at least one abnormality.
- Change from baseline QTcF (mean QtcF value of triplicate ECGs performed pre-dose on C1D1)

Vital signs

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

ECOG PS

- shift tables comparing the baseline PS with the worst result during post-baseline will be summarized for each treatment arm.

10.5.3.5 Supportive analyses for secondary objectives

Subgroup analyses will be provided for specific secondary variables based on number of prior lines of anti-MM therapy (1 vs. 2 vs. 3 or 4), age (≤75 vs. >75 years), gender, race, etc. will be performed as appropriate, more details will be provided in the SAP.

10.5.3.6 Tolerability

Not applicable

10.5.4 Pharmacokinetics and dose response

10.5.4.1 Pharmacokinetics

PK parameters listed in Table 10-1 will be calculated from concentration-time data for panobinostat and bortezomib on Cycle 1 Day 1 using WinNonLin (Pharsight, Mountain View, CA).

Table 10-1 Noncompartmental pharmacokinetic parameters

AUC0-8h (PAN, BTZ)	The AUC from time zero to 8 hours (tlast) (ng*h/mL)
Cmax (PAN, BTZ)	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single and multiple dose administration (ng/mL)
Tmax (PAN, BTZ)	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single and multiple dose administration (h)
Cmin (PAN, BTZ)	The minimum (trough) observed plasma, blood, serum, or other body fluid drug concentration after single and multiple dose administration (ng/mL)
C24h (PAN)	The observed plasma, blood, serum, or other body fluid drug concentration 24 hours after single and multiple dose administration (ng/mL)

PAS will be used in all pharmacokinetic data analysis except where otherwise stated and PK summary statistics. The full analysis set will be used for pharmacokinetic data listings.

Descriptive statistics by dose and, where applicable, scheduled time-point of AUC0-8h, Cmax, C24h and Cmin will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum for panobinostat and bortezomib where applicable. Similar descriptive statistics will be provided by dose and time for concentrations observed after Day 1. Zero concentrations will not be included in the geometric mean calculation. For Tmax median, minimum and maximum will be provided.

The PK data may be analyzed using a population approach with linear or nonlinear mixed-effects models. If so, such analyses will be reported separately.

10.5.4.2 Exposure response

Overall response, incidence of Grade 3/4 thrombocytopenia (based on group term), Grade 3/4 diarrhea and other key adverse events as appropriate will be modeled by separate binary logistic regression models including Cycle 1 Day 1 AUC0-8 (or cumulative AUC up to onsets of AEs), average Cmax and other plasma concentration summaries as appropriate. Bortezomib exposure as well as other baseline covariates may be included in the model if appropriate. In addition cox regression models will be fitted to time to first Grade 3/4 thrombocytopenia, Grade 3/4 diarrhea, other key adverse events and PFS with similar covariate considerations as for the logistic regression models. Analyses of adverse events will be based on patients in the safety set who also have PK data whereas analysis of overall response and PFS will be based on patients in the full analysis set who also have PK data. Full details of the analysis will be provided in the statistical analysis plan.

PK/PD relationships may also be explored using a population approach with linear or nonlinear mixed-effects models. Any such population-model-based analyses will be reported separately.

10.5.4.3 Data handling principles

Plasma concentrations will be expressed in ng/mL All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings and will be treated as zero in calculations of noncompartmental pharmacokinetic parameters.

10.5.5 Biomarkers

This clinical study was not designed to address specific biomarkers-related hypotheses, and the analysis of this data should be viewed as exploratory and hypotheses generating. Additional data from subsequent clinical studies will be required to further investigate and confirm any preliminary findings.

Additional exploratory analyses may be performed after the completion of the end-of-study CSR and all such analyses will be outlined in stand-alone biomarker analysis plans and results will be documented in separate biomarker reports.

10.5.5.1 Outline of the data analysis

The proposed data analysis will be aligned with the exploratory biomarker objectives of the protocol. For biomarker collected only at baseline, the distribution of baseline level will be presented (summary and frequency tables as appropriate). For biomarker collected over the course of the study, eg. Pharmacodynamic biomarker, the changes from baseline will be summarized.

The relationship between Pharmacodynamic biomarkers and dose/PK parameters may be explored via suitable graphical aids. Associations between biomarkers of molecular status and selected efficacy endpoints may also be explored.

In situations where the numbers of samples are inadequate to perform any analysis, the available biomarker data will only be listed.

10.5.5.2 Data handling principles

Relevant aspects of data handling will be addressed in the RAP.

10.5.5.3 Data analysis principles

10.5.5.3.1 Analysis sets

All biomarker analysis will be performed on the full analysis set unless otherwise specified. This includes patients from the FAS with valid biomarker assessments. If associations between biomarkers and safety endpoints are being explored then the safety/per-protocol set will be used.

10.5.5.3.2 Basic tables, figures and listings

Levels and changes from baseline will be summarized at each visit for each continuous biomarker. Both absolute change and relative change will be tabulated. Summary statistics such a number of samples, mean, median etc. will be presented. In addition, a longitudinal plot of the mean/median change over time may be produced for each biomarker, by dose group if sufficient data are available.

Frequency tables for categorical biomarker may also be produced to summarize the number and percentage in each category/group.

Associations between biomarkers at efficacy endpoints of interest may be explored via suitable figures.

All biomarker data will be listed.

10.5.5.3.3 Advanced analysis methods

Advanced analysis methods may be used for exploration and hypothesis generation. These could be to perform meta-analysis or exploration of the relationship between biomarker endpoints and efficacy and safety endpoints and such methods will be described in a stand-alone analysis plan document.

10.5.6 Patient-reported outcomes

10.5.6.1 EORTC-QLQ-C30, FACT/GOG-Ntx

The EORTC QLQ30 will be scored according to the guidelines provided by the EORTC administration and scoring manual (EORTC Scoring Manual 2001). For each domain and item, a linear transformation is applied to standardize the score between 0 and 100. Higher values indicate higher functioning and health-related quality of life.

The FACT GOG/Ntx will be scored in accordance with their specific scoring guidelines (Cella et al 1997). For these scores, lower values denote higher fatigue and neurotoxicity. FACT/GOG-NTX scores range from 0 - 44.

EORTC QLQ-C30 and FACT GOG/Ntx scores will be evaluated among patients who had a valid baseline HRQoL assessment and at least one post-baseline assessment.

Frequency tables for compliance to completing all patient-reported questionnaires will be provided by treatment arm and visit for EORTC-QLQ-C30 and FACT/GOG-Ntx.

Cycle 1, Day 1 QOL measures will be used as baseline. Overall QOL scores and subscales will be summarized over time using mean, median, standard deviation, and range by treatment arm. QOL scale means and standard errors will be plotted over time by treatment arm. Additional exploratory analysis will be pre-specified in the RAP as appropriate.

10.5.6.2 Diary for diarrhea management

The electronic diary for diarrhea management will be provided to patients and will be completed on a daily basis from the first day of screening until the last day of Cycle 8, unless study treatment was discontinued earlier.

The frequency and intensity of bowel movements will be summarized descriptively by cycle, type of bowel movement and by treatment arm. Additional exploratory analysis will be specified in the RAP as appropriate.

10.6 Exploratory objectives

Please refer to Section 10.5.5 - Biomarkers.

10.7 Interim analysis

The preliminary determination of the optimal panobinostat dose in combination with BTZ s.c. and Dex with an improved benefit/risk assessment, will be based on probability of success (POS) and overall safety data at interim analysis. None of the treatment arms will be stopped at

the interim analysis due to efficacy. Only the PAN 10 mg TIW arm and the PAN 20 mg BIW arm will have an option to be stopped for futility as a result of the interim analysis.

10.7.1 Interim efficacy analysis

One interim analysis (IA) is planned and will be based on the data collected on or before the cut-off date, which corresponds to the time after approximately 120 randomized patients (40 in each arm) have completed up to 8 cycles of study treatment. Patient enrollment will not be suspended for the interim analysis (IA). Assuming an accrual rate of 7 patients every month it is expected that approximately 17 months will be needed to accrue approximately 120 patients for IA, and the IA will occur at approximately 26 months from randomization of the first patient.

The Steering Committee (SC) will monitor safety on a regular basis, The SC will also review interim results and provide recommendation(s) to Secura Bio to stop/continue the "PAN 10 mg TIW and 20 mg BIW" treatment arms based on futility criteria and safety data (see Section 8.7). The recommendation to terminate or continue enrollment to any treatment arm will be shared with the FDA and a decision will be made in agreement with the FDA.

The assessment of efficacy at the interim analysis will be based on ORR according to IMWG criteria as determined by IRC assessment. The decision to stop/continue enrollment for futility in the "PAN 10 mg TIW and 20 mg BIW" treatment arms will be based on probability of success:

Based on the predictive probability (PP) that the observed ORR at the primary analysis reaches the target of 55% or more and the lower bound of 95% exact CI ≥ 35% (i.e., the probability of a positive conclusion of the study), given at the interim observed data (x) among patients. Thus,

POS = Prob [Observed ORR at primary analysis >=55% and lower bound of 95% exact CI ≥ 35% | x,n]

= Prob [Observed number of responders>= 44 out of 80 patients and lower bound of 95% exact CI ≥ 35% | x,n]

The efficacy outcome (overall response rate) is binary, namely, response (iCR, sCR, CR, VGPR or PR) vs. non-response (MR, SD, PD or UNK), and the number of responders on each arm is assumed to follow a binomial distribution. Suppose the prior belief regarding the probability of response (π) is that it has a beta distribution with parameters a_0 and b_0. If there are x responders out of n patients at the interim analysis, then the posterior distribution for π is beta with parameters $a_1=a_0+x$ and $b_1=b_0+n-x$. Now let Y represent the number of successes (i.e. responders) from m future observations at the primary analysis, then the (posterior) predictive distribution of Y conditioned on the observed data at the interim analysis (x responders out of n patients) is a betabinomial distribution described by

$$p(Y = y|x,n) = \binom{m}{y} \frac{B(a_0+x+y, b_0+n-x+m-y)}{B(a_0+x, b_0+n-x)} \quad (1)$$

where B (a, b) is the beta function.

A weakly informative Beta (0.82, 1) prior distribution for ORR is used for each treatment arm. This prior distribution has mean 45% and 95% probability interval from 1.1% to 97.0%.

Assuming exactly 120 (40 in each arm) patients have been included in the interim:

- The PAN 10 mg TIW and/or PAN 20 mg BIW arm will be stopped, if observed ORR <= 42.5% (number of observed responders <=17 out of 40 in the respective arm) which corresponds to predictive probability (ORR of PAN 10 mg >= 55% at FA) <4%
- Predictive probability of 4.4% corresponds to observed number of responders of 18 out of 40 patients which is equivalent to a 45% ORR. Given that the observed ORR up to 8 cycles in the Placebo arm from D2308 is 46%, the POS cut-off of 4% seems a reasonable assumption.

In addition to the criteria based on predictive probability, the decision to choose an appropriate regimen at IA will also be based on overall safety.

The decision rules at interim analysis based on ORR are presented below in Table 10-2. However, the cut-off for the number of responders needed in each of the 2 arms will be determined at the time of interim analysis based on the actual number of patients who completed up to 8 cycles of study treatment.

Table 10-2 Predictive probability of observing ORR at least 55% at the primary analysis (n=80) in the FAS under different interim results (n=40 patients)

Observed response rate at IA		Predictive probability of observing ORR ≥ 55% at the primary analysis (%)	Decision at IA if predictive probability is <4%
# of responses	%		
17	42.5	1.5	Not recommended to continue
18	45.0	4.4	Recommended to continue
19	47.5	10.4	Recommended to continue
20	50.0	20.9	Recommended to continue
21	52.5	35.8	Recommended to continue
22	55.0	53.3	Recommended to continue
23	57.5	70.2	Recommended to continue
24	60.0	83.6	Recommended to continue
25	62.5	92.3	Recommended to continue
26	65.0	96.9	Recommended to continue

10.7.2 Interim safety analysis

Review of safety data will include, but is not limited to, assessment of the nature and frequency of deaths during treatment, serious adverse events, Grade 3 or 4 adverse events, key laboratory abnormalities, abnormal results from electrocardiogram (ECG) assessments and distribution of safety-related reasons for treatment discontinuation.

10.7.3 Interim PK analysis

Review of pharmacokinetic data will include, but is not limited to, assessment of the PK parameters (AUC0-8h, Cmax, Tmax, C24h and Cmin) for PAN and/or BTZ, as applicable and also assessment of exposure response (efficacy and safety) relationship.

10.8 Sample size calculation

The study design allows randomization of up to 240 patients in order to obtain up to 80 patients in each arm.

The operating characteristics of the design based on the primary endpoint (ORR per IMWG criteria as determined by IRC assessment) under different true ORR is provided in Table 10-3. This assessment is based on 80 patients per arm in the FAS at the primary analysis. The proposed study design has reasonable operating characteristics. At the time of interim analysis, probability of success at the primary analysis is 54.2% if the true ORR is 55% and the risk of recommending an arm is 4.6% if the true ORR is 45%.

Table 10-3 Operating characteristics for an individual treatment group – Interim analysis (40 patients)

True ORR (%)	Operating characteristics		
	Probability of not recommending the arm at IA (%)	Probability of recommending the arm at IA and positive conclusion at primary analysis (80 patients/arm) (%)	Probability of recommending the arm at IA and negative conclusion at primary analysis (80 patients/arm) (%)
40.0	68.9	0.5	30.7
45.0	43.9	4.6	51.5
50.0	21.5	21.5	57.0
55.0	7.7	54.2	38.1
60.0	1.9	84.5	13.6

10.9 Power for analysis of key secondary variables

Not applicable.

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 protocol and to give access to all relevant data and records to Secura Bio monitors, auditors, Secura Bio Clinical Quality Assurance representatives, designated agents of Secura Bio, 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.

Secura Bio 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 Secura Bio before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Secura Bio 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.

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

11.4 Discontinuation of the study

Secura Bio 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

Secura Bio 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.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this study, 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 Secura Bio-

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 study necessary for the reconstruction and evaluation of the study. 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 study.

Data collection is the responsibility of the clinical study 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 study 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 previously or to Secura Bio. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Secura Bio 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 Secura Bio 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 Secura Bio 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 Secura Bio, 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, Secura Bio 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.

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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
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: https://CredibleMeds.org/.

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 14-4) has been associated with Torsades de pointes and QT prolongation but has not been shown to cause Torsades de pointes. Therefore, if use of ondansetron cannot be avoided, more frequent ECG monitoring should be performed.

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 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
* regular orange juice is 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.

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 study 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.

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.	

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)

Hidaka M, Fujita K, Ogikubo T, et al. (2004). Potent inhibition by star fruit of human cytochrome P450 3A (CYP3A) activity, Drug Metab Dispos 2004; 32: 581.

Synold TW, Takimoto CH, Doroshow JH, et al. (2007). Escalating and Pharmacological Study of Oxaliplatin in Adult Cancer Patients with Impaired Hepatic Function: A National Cancer Institute Organ Dysfunction Working Group Study, Clin Cancer Res. 2007 13; 3660.

Woosley RL, Heise CW and Romero KA, www.CredibleMeds.org QTdrugs list, AZCERT, Inc. 1822 Innovation Park Dr. Oro Valley, AZ 85755.

14.2 Appendix 2: Guidelines for response assessment in multiple myeloma

14.2.1 Introduction and scope

This document provides working definitions and specifications for consistent and efficient analyses of efficacy for Secura Bio clinical studies assessing anti-neoplastic activity in multiple myeloma (MM).

This document is based on the uniform response criteria as proposed by the International Myeloma Working Group (IMWG; International Myeloma Workshop Consensus Panel I, Rajkumar et al 2011). These response criteria will be referred to as IMWG criteria. Other references were used to add recommendations. With the release of this document, newly developed study protocols in MM should use the IMWG criteria as described in this document.

The objectives of this document are:

- to ensure that the definitions of responses in a clinical study protocol correctly reflect the IMWG criteria in the target patient population
- to provide guidance for the response assessment and clinical monitoring to ensure consistency with the IMWG's criteria for response in multiple myeloma

The assessment and analysis of MM-specific patient reported outcomes will be covered in a subsequent version of this guideline or in an attachment.

14.2.2 Efficacy assessments

14.2.2.1 Assessments – general

The following should be addressed/considered while designing a study:

1. frequency of response assessments should be adapted to the type and schedule of treatment, phase of the study (e.g. treatment phase, post-treatment follow-up phase)
2. schedule and time window for response assessments should be included in the protocol
3. guideline on following-up patients for PD or survival after completion or discontinuation of study treatment should be provided in the protocol

All data associated with response assessments should be captured in the CRF (i.e. not merged from several sources), if possible.

14.2.2.1.1 Measurable disease

For the IMWG criteria, measurable disease based on protein assessment is defined as at least one of the following conditions present at baseline (Durie et al 2006, Dimopoulos et al 2015):

- Serum M-protein by PEP ≥ 1.0 g/dL (for protocols including relapsed and refractory patients a threshold of ≥ 0.5 g/dL can be considered)
- 24h-urine M-protein by PEP ≥ 200 mg/24h
- Involved serum FLC level ≥ 10 mg/dL provided the FLC ratio is abnormal (Section 14.2.2.2.2)

In case of none of the criteria applies, the patient is considered to have non-measurable disease.

14.2.2.1.2 Eligibility

In general, patients with measurable disease according to Section 14.2.2.1.1 should be included in a study. In case a patient with non-measurable disease was enrolled, disease assessment should be continued with bone marrow aspiration / biopsy and a protocol deviation should be documented if measurability is mandated by the protocol.

14.2.2.1.3 Definition of lines of therapy

A line of therapy is defined as one or more planned cycles of either single agent or combined therapy, as well as a sequence of treatments administered in a planned manner (e.g. a autologous stem cell transplant, followed by maintenance, is considered only one line of therapy).

A line of therapy ends at the planned treatment completion, disease progression, relapse, discontinuation of treatment due to toxicity, start of an unplanned anti-MM therapy or death (Rajkumar et al 2011).

14.2.2.1.4 Baseline assessments

The following baseline assessments are mandatory:

- M-protein in serum and urine by PEP (Section 14.2.2.2.1)
- M-protein in serum and urine by immunofixation (IF) (Section 14.2.2.2.1)
- Serum FLC ratio (Section 14.2.2.2.2)
- Plasma cell count in bone marrow (Section 14.2.2.2.3)
- Clinical assessment for soft tissue plasmacytomas. In case of known or detectable soft tissue plasmacytoma at baseline, further confirmation and measurements are required at baseline by imaging techniques (CT/MRI) (Section 14.2.2.2.5)
- Full body skeletal survey by X-ray: full body CT scan and full body MRI are also accepted if X-rays cannot be performed (Section 14.2.2.2.6)
- Routine biochemistry including ionized calcium or total serum calcium and albumin (Section 14.2.2.2.7)

For baseline assessments, no confirmation measurement is required.

14.2.2.1.5 Time frame of response assessments

For the baseline assessment, the last available measurement for a variable prior to first intake of study treatment/randomization has to be used. Baseline assessments should be done prior to the first intake of study treatment/randomization and within a time window defined by the protocol.

All measurements required for a response assessment post-baseline should be performed within a predefined time window. It is recommended to align this time window with the treatment cycle length for the treatment period. The time window(s) should be specified in the study protocol.

In case there is more than one measurement of any variable in the predefined time window, the latest non-missing measurement of this variable will be used. Exception: In case of one

measurement qualifying for PD, this will be used for the response assessment irrespective of subsequent measurements of the same variable.

14.2.2.1.6 Response assessment by time point

Response is to be assessed based on the response assessment criteria (Table 14-5) and on data collected for scheduled response assessment. Confirmation of response 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). For confirmation of response see Section 14.2.2.4.1 and Section 14.2.2.4.2.

14.2.2.1.7 Response assessment date

The response assessment date is defined as the last of all dates of measurements which are required to qualify for a response category (excluding PD). In case of PD, the first of all measurement dates associated with a disease assessment will be used as assessment date. The assessment date will be used for the derivation of the time-to-event endpoints.

14.2.2.1.8 Mandatory assessments

For every patient the following assessments have to be performed at every scheduled post baseline visits for response assessment:

1. M-protein in serum and urine by PEP (Section 14.2.2.2.1)
2. M-protein in serum and urine by IF (Section 14.2.2.2.1)
3. Serum FLC assessment if patient has non-measurable disease in serum and urine M-protein at baseline (Section 14.2.2.2.2)
4. Soft tissue plasmacytomas (Section 14.2.2.2.5)
5. Lytic bone lesion assessment if clinically indicated (Section 14.2.2.2.6)
6. Serum calcium and albumin or ionized calcium (Section 14.2.2.2.7)
7. Plasma cell count in bone marrow by aspirate or biopsy in patients who met all criteria for CR by serum and urine M-protein with no indication of disease progression by STP, lytic bone lesions and hypercalcemia or in case of non-measurable disease by M-protein in serum and urine by PEP and by FLC (Section 14.2.2.2.3)
8. Residual disease by flow cytometry / immunohistochemistry in bone marrow plasma cells in case CR criteria are met (Section 14.2.2.2.4)

14.2.2.1.9 Nadir

The nadir is defined as the lowest value of a variable including baseline measurements excluding the measurement of the respective visit. This rule implies that the time point of determination of the lowest value of a patient may be different for each variable.

14.2.2.1.10 Use of a central laboratory

Laboratory to laboratory variability could potentially be high. So, the use of a central laboratory is recommended for the assessments defined in Table 14-5.

Table 14-5 Recommended use of a central or local laboratory

Assessment	Recommendation
Serum and urine M protein by PEP	Central laboratory
FLC	Central laboratory
Bone marrow assessments plasma cell counts	Local laboratory; keep archival slides for subsequent potential central review of BM pathology
Bone marrow flow cytometry and immunohistochemistry	Central laboratory
Bone marrow for ASO-PCR or equivalent	Central laboratory
Serum calcium variables	Local laboratory

For pivotal efficacy studies phase II and III, central laboratories for measurement of M-protein by PEP are strongly recommended. If local laboratories are used for M protein measurement by PEP in such studies, this choice should be justified in the study protocol. Any use of a local laboratory should be addressed during the site selection process, and ability of the local laboratories to perform and report the protocol required measurements needs to be verified. Adequate measures for local laboratory selection and monitoring should be taken and specifically described in the study monitoring plan. The same laboratory should be used throughout the study.

14.2.2.1.11 Staging of Multiple Myeloma

Staging of MM should be done according the International Staging System (ISS, Greipp et al 2005, Figure 14-1). To compare patient staging across studies, the Durie-Salmon staging system (Durie, Salmon 1975; Kyle et al 2009) can be used additionally (Table 14-6).

Figure 14-1 International Staging System

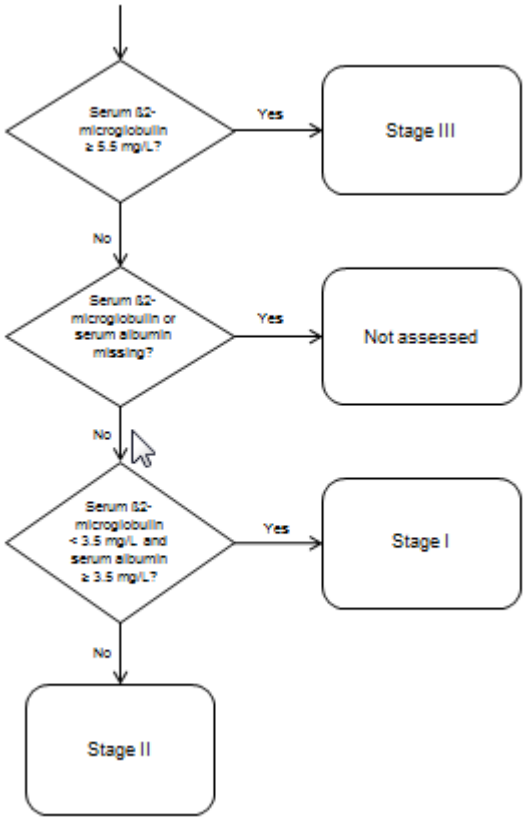

Table 14-6 Durie-Salmon staging system

Stage	Criteria
Stage I	All of the following: Hemoglobin value >10 g/dL Serum calcium value normal or <10.5 mg/dL Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only Low M-component production rates (IgG value <5 g/dL; IgA value <3 g/dL) Urine light chain M-component on electrophoresis <4 g/24h
Stage II	Fitting neither stage I nor stage III
Stage III	One or more of the following: Hemoglobin value <8.5 g/dL Serum calcium value >12 mg/dL Advanced lytic bone lesions (scale 3) High M-component production rates (IgG value >7 g/dL IgA value >5 g/dL) Bence Jones protein >12 g/24h
Sub-classification	A: relatively normal renal function (serum creatinine value) <2.0 mg/dL B: abnormal renal function (serum creatinine value) >2.0 mg/dL

14.2.2.2 Tests required for response assessment

14.2.2.2.1 Assessment of M-protein in serum and urine

The assessment of the M-protein levels in serum and urine is the basis for the response assessments for multiple myeloma. The following two methods are used to assess M-protein in serum as well as in urine

1. Protein electrophoresis (PEP): Provides quantitative measurements. Techniques other than electrophoresis are not acceptable unless specifically mentioned in this document.
2. Immunofixation (IF): Provides qualitative measurements (Present/absent). This is a more sensitive method than PEP and is used to confirm the absence of M-protein by PEP.

For M-protein in urine by PEP, a 24h urine collection is required.

The PEP has to be performed to assess serum and urine M-protein levels at baseline and post baseline. Even if the disease is non-measurable, both, serum and urine M-protein should be measured by PEP routinely at post.

In case no M-protein is found by protein electrophoresis, this should be confirmed by serum/urine immunofixation.

In case urine/serum M-protein was not assessed by PEP and the corresponding urine/serum immunofixation indicates absence of M-protein, it can be concluded that there is no M-protein identifiable by PEP in serum/urine.

14.2.2.2.2 Assessment of free light chain proteins (FLC)

The free light chain (FLC) assessment was introduced by the IMWG using serum FLC assay (FREELITE, The Binding Site Ltd., Birmingham, UK), which is performed by immunonephelometry (Dispenzieri et al 2009).

The serum FLC assay measures:

1. Free kappa light chain (also known as kappa serum level) (reference interval, 0.33-1.94 mg/dL) and
2. Free lambda light chain (also known as lambda serum level) (reference interval, 0.57-2.63 mg/dL)

The FLC ratio is defined as the kappa serum level divided by the lambda serum level.

Involved light chain is determined based on the following criteria (Snozek et al 2008):

1. Lambda is the involved light chain if FLC ratio < 0.26
2. Kappa is the involved light chain if FLC ratio of > 1.65

The FLC ratio is considered to be

- Normal if FLC ratio is within [0.26-1.65]
- Abnormal if FLC ratio is <0.26 or >1.65

The FLC serves as monitoring indicator of disease status when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met (Table 14-7).

14.2.2.2.3 Assessment of bone marrow for percentage of plasma cells

Bone marrow should be assessed for percentage of plasma cells. Either bone marrow aspirate or biopsy can be used for this assessment. The same method (aspirate versus biopsy) should be used throughout the study, if possible. In case both aspirate and biopsy were done, the response criteria need to be satisfied by both assessments. In case both aspirate and biopsy are performed, the highest of both percent values should be used for the assessment.

Bone marrow samples are usually drawn from either sternum or iliac crest. Percentage of plasma cells will be determined by using cytological/histological examination.

In case of inadequate/uninterpretable bone marrow sample, the sampling must be repeated in a timely manner but no later than within the protocol-defined time window (Section 14.2.2.1.5).

Bone marrow aspirate and/or biopsy should be performed for every patient at baseline.

Bone marrow aspirate and biopsy are invasive procedures. Standard practice is to perform post-baseline bone marrow assessment only when it is essential. Therefore, recommendation is for performing bone marrow assessments under the following conditions:

1. to confirm complete response
2. in case of non-measurable disease by M-protein in serum and urine as well as by FLC, bone marrow plasma cell count is used to assess response

14.2.2.2.4 Assessment of aberrant plasma cells

The two most widely used methods for assessing residual neoplastic plasma cells (PCs) in the bone marrow are 1) flow cytometry and 2) immunohistochemistry.

1) Flow cytometry

IMWG criteria require assessment of clonal plasma cells for assessment of sCR, by standard flow cytometry (using 2 to 4 colors). If the protocol requires determining iCR, which is a more strict criterion, PCs should only be assessed by multiparametric flow cytometry (using >4 colors), counting a minimum of $1x10^6$ PCs.

If there are no bone marrow elements and no plasma cells in the sample, this will be considered not to be suitable for analysis and will need to be repeated.

2) Immunohistochemistry

Immunohistochemistry is used to differentiate normal from clonal PCs in the bone marrow for assessment of sCR. Presence/absence of clonal cells is based upon the kappa/lambda (k/l) ratio. An abnormal k/l ratio by immunohistochemistry 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 (Durie et al 2006).

3) Molecular assessment

Assessment of mCR in the bone marrow will be done by quantitative nested polymerase chain reaction (PCR) with a minimal sensitivity of 10^{-5} using patient-specific primers to identify rearrangements of immunoglobulin-heavy-chain sequences (ASO-primers), or equivalent methods.

IMWG refers to the ASO-PCR method only to identify mCR. However, the rapidly developing area of sequencing-based methods with high concordance to ASO-PCR justifies the use of equivalent methods, such as B-cell receptor (BCR) sequencing (Lopez et al 2014). However, the same method should be used and detailed in the study protocol.

14.2.2.2.5 Assessment of soft tissue plasmacytomas

General definitions:

- The size of the soft tissue plasmacytoma (STP) is defined as the sum of the products of the cross-diameters (SPD) of each STP using the longest perpendicular diameters.
- A definite increase in the size is defined as a ≥ 50% increase (and at least 10mm^2) of this sum from the nadir.

Assessment of STPs:

1. Each patient should be clinically assessed for STP(s) at each visit for response assessments.
2. For STP(s) present at baseline (per clinical assessment):
   - imaging by CT or MRI must be performed at baseline (screening or C1D1) for suspected STP to confirm and to determine size and location of the soft tissue plasmacytoma.
   - size and location of the STP(s) will be monitored by imaging at regular intervals according to the requirements of the individual study protocol.
3. In case of clinical suspicion of (re-)appearance of STP(s) post-baseline, imaging by CT or MRI must be performed as soon as possible to confirm and to determine size and location of the STP(s).
4. Size and location of identified STP(s) should be captured on the CRF.
   a. The size should be captured in terms of longest perpendicular diameters
   b. If any of the perpendicular diameters cannot be reliably measured because of its small size, the minimum limit of detection as the diameter size (e.g. 7.5 mm for CT) should be entered.
   c. A value of 0 mm x 0 mm should be entered in case of disappearance of a STP

The same imaging technique must be used throughout the course of the study to monitor an existing soft tissue plasmacytoma.

CT and MRI should be performed with slice thickness ≤ 7.5 mm.

If soft tissue plasmacytomas become confluent over time, then these should be measured as one soft tissue plasmacytoma. The overall diameters should be recorded for one of the soft tissue plasmacytomas, and 0 mm x 0 mm should be recorded for the rest of the soft tissue plasmacytomas.

If a soft tissue plasmacytoma splits during the study, each part of the soft tissue plasmacytoma should be measured separately for all subsequent assessments and all parts of the soft tissue plasmacytoma should contribute to the SPD.

14.2.2.2.6 Assessment of lytic bone lesions

Full body skeletal survey using conventional X-rays (preferred method) or CT or MRI should be performed on every patient prior to study treatment start/randomization. Based on the currently available evidence, PET is not recommended to be used for the assessment of lytic bone lesions (Dimopoulos et al 2009, Rajkumar et al 2014).

Interpretation of full body skeletal survey (in terms of presence or absence of lytic bone lesion, number and location of lesions) will be captured on the CRF.

Targeted post baseline assessments using bone X-ray/CT/MRI on location(s) should be performed if there is any medical indication (e.g. bone pain) as determined by the investigator. The following information will be captured on the CRF: absence/ presence, lesion location, unchanged, new lesion(s) or increase in size of existing lesion(s).

The same imaging technique at baseline and post-baseline should be used for comparison of lytic bone lesion assessments. In case of newly symptomatic areas with no finding by X-ray a targeted MRI or CT assessment(s) should be performed.

14.2.2.2.7 Assessment of hypercalcemia

For each response classification, the assessment of hypercalcemia by determination of corrected or ionized serum calcium is required.

In case total serum calcium is measured, the value needs to be corrected for serum albumin according to the following formula (Ladenson et al 1978):

Corrected serum calcium [mg/dL] = measured total serum calcium [mg/dL] + (3.5 - serum albumin [g/dL]) x 0.8.

It is not acceptable to use uncorrected total calcium to assess hypercalcemia.

Corrected serum calcium values > 11.5 mg/dL indicate hypercalcemia.

In case ionized serum calcium is measured, no correction for serum albumin is required and values > 6.0 mg/dL indicate hypercalcemia.

In case corrected serum calcium and ionized calcium are measured at the same visit, the ionized calcium value will be used for response assessment. It is recommended to use the same method throughout the study.

14.2.2.3 Capturing response classification

Response classification can be obtained/determined from different sources:

1. Investigator assessment
2. Assessment by independent review committee (IRC)
3. Response derived from data collected in the CRF

The source of response classification to be used in the protocol, defined efficacy analyses associated with protocol objectives needs to be pre-specified in the protocol (investigator, IRC, derived response).

For assessment of disease progression it is recommended to collect the variable(s) on which progression is documented on the CRF (investigator and IRC, if applicable).

It is recommended to use IRC assessments for registration studies with an efficacy endpoint.

14.2.2.4 Response assessment per IMWG criteria

Response assessment according to IMWG criteria is described in Table 14-7 and Table 14-8. 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 14.2.2.4.1 and Section 14.2.2.4.2.

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.

Table 14-7 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 (see Section 14.2.2.2.5) 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.

Response category	Definition*
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 (see Section 14.2.2.2.5) is required.
Stable disease (SD)	Not meeting the criteria for mCR, sCR, CR, VGPR, PR, PD
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 (Section 14.2.3.2.7) 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 14-8.

Table 14-8 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).

14.2.2.4.1 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. 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.

14.2.2.4.2 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.

14.2.3 Derivation rules

14.2.3.1 Best overall response and overall response

Best overall response is the best post baseline confirmed overall response observed in a given patient, among the confirmed response categories, excluding “unknown” and “not assessed”. Best overall response is determined based on overall responses observed at all post-baseline response assessments, recorded from the start of the study treatment/randomization until PD, death, start of new therapy, withdrawal of consent or end of study, whichever comes first.

If the first complete post-baseline response assessment indicates, for example, PR or better (VGPR, CR, sCR or mCR) and no confirmation response assessment available then SD will be considered as best overall response.

Best overall response will be assigned according to the following ascending order (Table 14-9).

Table 14-9 Best overall response

Rank	Best overall response category
1	Molecular complete response (mCR)
2	Immunophenotypic complete response (iCR)
3	Stringent complete response (sCR)
4	Complete response (CR)
5	Very good partial response (VGPR)
6	Partial response (PR)
7	Minimal response (MR)
8	Stable disease (SD)
9	Unknown
10	Progressive disease (PD)

In case no post-baseline assessment is available or assessments with only unknown response status are available, the category “unknown” will be assigned as best overall response.

Based on the patients' best overall response during the study, the following rate is calculated:

Overall response rate (ORR) is the proportion of patients with best overall response of PR or better. For the calculation of the ORR, the denominator should include all patients in the targeted patient population. Additional analysis sets can be defined in the study protocol.

MR can be an indicator of drug activity in certain patient populations, and in particular for patients with relapsed, as well as, relapsed and refractory MM. In case MR is used, the rate of patients with MR should be reported separately from the ORR (Rajkumar et al 2011).

The clinical benefit rate (CBR) is defined as the proportion of patients with best overall response of MR, PR, VGPR, CR, sCR, iCR or mCR (Anderson et al 2008).

14.2.3.2 Calculation of time-to-event variables

General rule for the calculation of the time to event interval is:

Time to event = end date - start date + 1 (in days)

When no post-baseline response assessment is available, the date of randomization/ start of study treatment will be used as end date (duration = 1 day), i.e. time to event variables will never be negative.

14.2.3.2.1 Adequate response assessment

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than "unknown" or PD.

14.2.3.2.2 Overall survival

Overall survival (OS) is defined as the time from date of randomization/start of study treatment to the date of death due to any cause.

If a patient is alive or his/her survival status is unknown, OS will be censored at the date of last contact.

14.2.3.2.3 Progression-free survival

Progression-free survival (PFS) is defined as time from date of randomization/start of study treatment to date of (1) death due to any cause or (2) PD.

If a patient has not had an event, PFS is censored at the last adequate response assessment date.

14.2.3.2.4 Time to progression

Time to progression (TTP) is defined as time from date of randomization/start of study treatment to date of (1) death due to multiple myeloma or (2) PD.

If a patient has not had an event, TTP is censored at the last adequate response assessment date.

14.2.3.2.5 Duration of response

Duration of response (DOR) is defined as the duration from the first documented onset of PR or better response to the date of PD or death due to multiple myeloma.

In case a patient does not have PD or death due to multiple myeloma, DOR will be censored at the date of the last adequate assessment.

In general patients without PR or better response are excluded from this analysis. However, there are several ways to address this issue. Clear instruction on this should be included in protocol.

14.2.3.2.6 Time to response

Time to response (TTR) is defined as the time between date of randomization/start of study treatment to the date of first onset of PR or better response.

Patients without experiencing any PR or better response will be censored according to the following events:

- Patients experiencing a PD will be censored at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients (i.e. either progressed or died due to any cause).
- Patients not experiencing PD will be censored at their last adequate response assessment date which is different from “unknown” or “not done”.

Table 14-10 Censoring rules for time to response

Situation		Start-date	End-date	Outcome
A	PR or better	Date of randomization/ start of study treatment	Date of first onset of confirmed PR or better (before cut-off date and before start of new anti-neoplastic therapy)	Event
B	PD/Death	Date of randomization/ start of study treatment	Date of maximum follow-up of all patients in study	Censor
C	No PR or better and no PD/death	Date of randomization/ start of study treatment	Date of last adequate response assessment before cut-off date and before start of new anti-neoplastic therapy	Censor

14.2.3.2.7 Time to next treatment

Time to next treatment (TNT) is defined as the time from the date of randomization/start of study treatment to the date of next treatment for multiple myeloma or death due to any cause. The need to start the next treatment should be defined clearly in the protocol. According to the IMWG criteria, this should be in case of either clinical relapse or significant paraprotein relapse. Start of new treatment without meeting the relapse criteria is also considered as a relapse.

In case a patient does not experience a relapse event and does not start new anti-neoplastic therapy, time to next treatment will be censored at the last adequate response assessment.

Clinical relapse is defined as one or more of the following indicators that are related to the underlying MM:

- Development of new soft tissue plasmacytomas or lytic bone lesions on skeletal survey, MRI, or other imaging.

- Definite increase in size of existing plasmacytomas or lytic bone lesions.
- Hypercalcemia (ionized serum calcium > 6 mg/dL and if missing corrected serum calcium >11.5 mg/dL)
- Decrease in hemoglobin of ≥ 2 g/dL (1.25 mmol/L) or to less than 10 g/dL (6.2 mmol/L)
- Rise in serum creatinine by ≥ 2 mg/dL from nadir
- Hyperviscosity (as reported as Adverse Event)

A significant paraprotein relapse is defined as one or more of the following indicators:

- Doubling of the M-component in two consecutive measurements separated by ≤ 2 months.
- Increase in the absolute level of serum M protein by ≥ 1 g/dL in two consecutive measurements separated by ≤ 2 months
- Increase in the absolute level of urine M protein by ≥ 500 mg/24h in two consecutive measurements separated by ≤ 2 months
- Increase in involved FLC level by ≥ 20 mg/dL (plus an abnormal FLC ratio) in two consecutive measurements separated by ≤ 2 months.

As it is difficult to compare across studies, TNT is preferably to be used in randomized studies.

14.2.3.3 Event and censoring date, sensitivity analysis

This section outlines the possible event and censoring dates for PD (Table 14-11), as well as addressing the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed. Using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-11 Options for event dates used in PFS and TTP

Situation		Options for end-date[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment	Censor
B	PD at scheduled assessment date or before next scheduled assessment	(1) Date of PD (2) Date of next scheduled assessment	Event Event
C1	PD or death after **exactly one** missing assessment	(1) Date of PD (or death) (2) Date of next scheduled assessment[1]	Event Event
C2	PD or death after **two or more** missing assessments	(1) Date of last adequate assessment[1] (2) Date of next scheduled assessment[1] (3) Date of PD/ (or death)	Censor Event Event
D	No PD and no death	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease PD' without documented PD, i.e. clinical PD based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical PD was determined)	Ignored Event
F	New anticancer therapy given	(1) Date of last adequate assessment prior to start of new anti-cancer therapy (2) Date of new anti-cancer therapy (3) Date of new anti-cancer therapy (4) N/A	Censor Censor Event Not considered as event
G	Deaths due to reason other than multiple myeloma	(1) Date of last adequate assessment	Censor (only TTP and TNT)
[1] PFS: death due to any reason; TTP: death due to MM			

In case a patient does not have an adequate assessment, the date of randomization/start of study treatment is used as end date.

Situations C (C1 and C2): PD or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual PD or death date, in the case of only one missing assessment.

- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or more missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'PD' without documented PD: By default, option (1) is used for situation E as patients without documented PD should be followed for PD after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If PD is claimed based on clinical deterioration instead of response assessment by e.g. sPEP, option (2) may be used for indications with high early PD rate or difficulties to assess response due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-11 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition: **Date of previous scheduled assessment (from baseline)** is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.
- By considering any appearance or recurrence of clinical indicators not part of the criteria list but mentioned in the IMWG criteria, in particular "bone pain".

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the Study Protocol or RAP documentation.

14.2.4 Medical review of response assessment

In case the investigator assesses response in the CRF, this assessment needs to be checked in terms of calculated response according to the rules provided in this document. Discrepancies between investigator's assessment and calculated response will be clarified via a query.

For any discontinuation due to disease progression, the respective patients' response needs to qualify the criteria for this category as defined in this document.

In case IRC data are checked, the detailed process needs to be planned in advance to avoid a time lag between the independent review and the check.

14.2.5 References (available upon request)

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14.3 Appendix 3: 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 14-12 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.

14.4 Appendix 4: New York Heart Association (NYHA) functional classification

The NYHA function classification provides a simple way classifying the extent of heart failure.

Table 14-13 NYHA functional classification

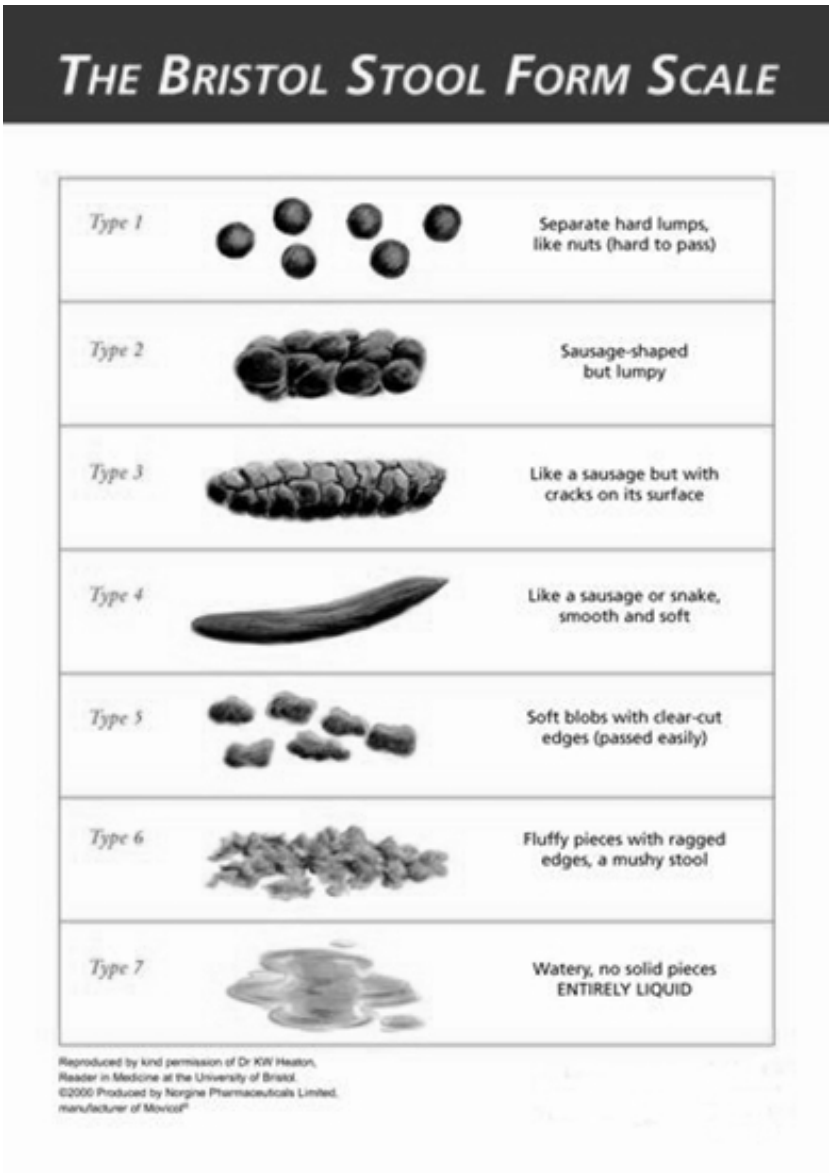
NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

As published in: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

14.5 Appendix 5: The Bristol Stool Form Scale

The Bristol Stool Form Scale provides a simple method of monitoring intestinal function and will be used in the electronic diary for diarrhea management.

Figure 14-2 The Bristol Stool Form Scale



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