NOVARTIS

Clinical Development

Panobinostat (LBH589)

Clinical Trial Protocol CLBH589D1201 / NCT02290431

A phase II, multi-center, single arm, open label study to evaluate the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone in Japanese patients with relapsed/refractory multiple myeloma

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute Myeloid Leukemia
aPTT	activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BSA	Body surface area
BTZ	bortezomib
BUN	Bllod urea nitrogen
CR	complete response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome p450
DAC	deacetylase
DACi	Deacetylase inhibitor
DDI	Drug-drug interaction
Dex	dexamethasone
DLT	Dose Limiting Toxicity
DOR	Duration of response
DS&E	Drug Safety and Epidemiology
EBMT	European Bone Marrow Transplant organization
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FAS	Full analysis set
FISH	fluorescence in situ hybridization
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
Gr 3,Gr 4	Grade 3, grade 4
i.v.	intravenous(ly)
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMiD	Immuno-modulatory Drug(s)
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
ISS	International Scoring System
LDH	Lactate dehydrogenase
LEN	lenalidomide
LLN	Lower limit of normal values
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities

[redacted]

MM	Multiple myeloma
MR	Minimal response
MRR	Minimal response rate
msec	milliseconds
MTD	Maximum Tolerated Dose
MUGA	Multiple uptake gated acquisition scan
NC	No change
NCI-CTC	National Cancer Institute – common toxicity criteria
nCR	Near Complete Response
ORR	Objective response rate
OS	Overall survival
PAN	Panobinostat
PD	Progressive disease
PEP	Protein electrophoresis
PFS	Progression free survival
PK	Pharmacokinetics
PLT	Platelets
[redacted]	[redacted]
PR	Partial Response
PRO	Patient-reported outcome
PT	Prothrombin time
QoL	Quality of life
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event
[redacted]	[redacted]
SCT	Stem Cell Transplant
T4	thyroxine
TIW	three times in/per week
TP1, TP2	Treatment phase 1, treatment phase 2
TSH	Thyroid stimulation hormone
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal values
[redacted]	[redacted]
WBC	White Blood Cells
WBC/HPF	White Blood Cells per High Power Field
WOCBP	Woman of child-bearing potential

[redacted]

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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
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
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further study related contact

Amendment 3 (27-Feb-2018)

Amendment rationale

As of Jan 15 2018, 31 patients have been enrolled to receive treatment in this trial.

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

The major changes to the selection criteria are as follows:

1. 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 5 prior lines of therapy to be included in this protocol.
2. 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 and CLBH589D1201 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.

Changes to the protocol

- Table of contents: current page numbers and changes to section headings.
- Protocol Summary: changes in the main body of the protocol (see bullet points below) are also implemented in the relevant sections of the protocol synopsis.
- Section 1.2.1.2: Update the number of studies and total number of patient as of 22 February 2017.
- Section 3.1: Clarify the primary endpoint
- Section 4.1: Update Figure 4-1 to change prior lines of therapy from "1 to 3" to "1 to 5".
- Section 5.1:
  - Patient population: Changed prior lines of therapy from “1 to 3” to “1 to 5”. Changed bortezomib (BTZ) to proteasome inhibitors to correct throughout the protocol.
- Section 5.2:
  - Inclusion criteria 3: Changed prior lines of therapy from “1 to 3” to “1 to 5”. Changed BTZ to proteasome inhibitors to correct throughout the protocol.
  - Inclusion criteria 7: Changed Absolute neutrophil count from “$\geq 1.5 \times 10^9$ /L” to “1.0×10^9 /L” and Platelet count from “$\geq 100 \times 10^9$ /L” to “$\geq 75 \times 10^9$ /L”.
- Section 5.3:
  - Exclusion criteria 10 a: Added “Use of Dex as supportive treatment (e.g. for pain relief) is allowed”.
  - Exclusion criteria 15 a: Changed LVEF from “LLN of institutional norm” to “40%, as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA)”.

- Section 7.1.1: Added the following sentence 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.
  "If the plasma cell count 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"
- Section 10.4: Clarify the primary objective
- Section 14.1.2: Updated table 14-1 to consist with the latest LBH589 study.

IRBs/IECs

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.

Summary of previous amendments

Amendment 2 (15-Nov-2015)

Amendment rationale

As of Sep 30 2015, 14 patients have been enrolled to receive treatment in this trial.

This amendment will introduce the following changes to the study protocol:

1. Update combination therapy – dosing modifications.
2. Introduce follow up on potential Drug-Induced Liver Injury cases.
3. Update inclusion and exclusion criteria.

1. Update combination therapy – dosing modifications

As of Sep 30 2015, 8/14 patients have discontinued study treatment due to adverse events, mainly fatigue, anorexia and nausea. Most patients discontinued study treatment at Cycle 4 or Cycle 5 (6/8 patients) and have experienced dose reductions of panobinostat before treatment discontinuations. 2/8 patients have changed bortezomib schedule from a twice-weekly to a once-weekly. 6/8 patients have had dose reduction of PAN and/or BTZ. On the other hand, 4/14 patients have continued study treatment more than Cycle 5. 3/4 patients have dose reduction of PAN and changed to once-weekly BTZ or have skipped BTZ on D11 at every cycle. 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). In addition, a safety analysis of patients enrolled in PANORAMA-1 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). This amendment will implement a dose modification approach; the early change of BTZ from twice a week to weekly BTZ administration to improve tolerability of PAN+BTZ+Dex combination over a longer treatment duration.

2. Introduce follow up on potential Drug-Induced Liver Injury cases

This amendment provides follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug-Induces Liver Injury cases in order to optimize patient safety.

3. Update inclusion and exclusion creitera

Different degree of renal impairment (mid, moderate and severe) did not alter panobinostat plasma exposure based on results from the renal impairment study [CLBH589X2106]. Therefore, criteria of renal functions were updated.

Contraception duration was updated as following reasons.

- Terminal half-life of panobinostat is 15-18 hours
- Genotoxic potential was shown in bacterial and eukaryotic systems
- Oral administration of panobinostat to rats and rabbits is associated with embryo-fetal toxicity (increased resorptions/decreased live litters). Although no major malformations were observed, the incidence of fetal skeletal variations and anomalies was increased.
- Male reproductive effects were observed in the testes, epididymides and prostate in 4- and 13-week repeated dose oral toxicity studies in the dog.

These changes do not impact efficacy and safety assessment for patients who have been enrolled.

Changes to the protocol

- Table of contents: current page numbers and changes to section headings.
- Protocol Summary: changes in the main body of the protocol (see bullet points below) are also implemented in the relevant sections of the protocol synopsis.
- Section 5.2:
  - Inclusion criteria 7: deleted criterion of serum creatinine levels and changed calculated creatinine clearance criterion from ≥ 60 to ≥30 with alliance of CLBH589D2222 study protocol which is the latest protocol for MM.
  - Inclusion criteria 13: added criterion related to CYP3A4 interaction to introduce new protocol template.
- Section 5.3:
  - Exclusion criteria 10: added criterion of Stem cell therapy with alliance of CLBH589D2222 study protocol which is the latest protocol for MM.
  - Exclusion criteria 20: updated criterion of contraception methods and period for female subjects with alliance of CLBH589D2222 study protocol which is the latest protocol for MM.

[redacted]

- Exclusion criteria 21: updated criterion of contraception period for male subjects.

- Section 6.3.1 and 6.3.2: update this section for safety management with dose modifications.
- Section 6.3.2.1: Updated management of grade 2 non-hematologic toxicity to allow dose reduction of study treatment (PAN/BTZ/Dex) at treatment restarting.
- Section 6.3.3: updated Table 6-6, Table 6-7, Table 6-8 and Table 6-9 to early switch from twice a week to weekly BTZ administration.
- Section 6.3.4: added this section to introduce follow up on potential drug-induced liver injury cases.
- Table 7-1: added 3rd annotation in a footnote.
- Section 7.1.1: updated this section to introduce new protocol template.
- Section 7.1.3: updated this section to introduce new protocol template.
- Section 7.1.5.2: added visit allowance for disease assessment.
- Section 7.1.5.3: added visit allowance for survival information.
- Section 8.2.2: updated this section to introduce new protocol template.

IRB/IEC

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.

Amendment 1 (23-Jun-2015)

Amendment rationale

As of May 20 2015, 12 patients have been enrolled to receive treatment in this trial.

This amendment will introduce the following changes to the study protocol:

1. Interim report.
2. Extension of study treatment period as an optional extension of the study.
3. Discontinuation of Clinical Trial Protocol Elements guideline
4. Update exclusion criteria.

The rationale for these changes is presented below:

1. Introduce interim report

In the review process of panobinostat submission for indication of relapsed or refractory MM in Japan, [redacted] requested sponsor to conduct additional interim report to present the key efficacy and safety information in public per approximately 6 months basis.

[redacted]

2. Study treatment period

Based on the expected favorable tolerability under longer treatment of PAN + BTZ (weekly administration) + Dex in treatment phase 2 in PANORAMA1 study (San-Miguel JF et al ASH 2014), the amendment will implement longer treatment beyond 12 cycles until disease progression under the careful risk/benefit assessment of the treating physicians.

3. Introduce Discontinuation of Clinical Trial Protocol Elements guideline

Discontinuation of Clinical Trial Protocol Elements provides guidance on how to effectively manage patients who discontinue Clinical Trial Protocol element(s) to maximize data captured.

Discontinuation of Clinical Trial Protocol Elements guidance helps to differentiate between patients who:

- Discontinue certain CTP elements (e.g., discontinue study treatment, or some or all visits etc.)
- Withdraw consent
- Are lost to follow-up

4. Update exclusion criteria

- Extend the exclusion criterion of ‘’patients who have been refractory to prior BTZ’’to ‘’patents who have been refractory to prior BTZ and other proteasome inhibitors”. Recently, additional proteasome inhibitors have been developed and may gain marketing authorization. Given the identical mode of action of these newer drugs as BTZ, patients failing treatment with any representative of this class of drugs (proteasome inhibitors) shall be excluded from participation in this protocol.
- Exclude patients have a known history of HIV seropositivity or history of active/treated hepatitis B or C.

Clarification/Inconsistencies:

Clarification was provided through edited text and inconsistent language was corrected throughout the protocol.

- Sample size calculation was corrected to clarify the test statistics value-based p-value is used to reject or accept null hypothesis, the sentences regarding 90% confidence interval were deleted.
- Exclusion criterion 21 was added to clarify the excludable condition of sexually active males.
- Chemo-, biologic or immunologic therapy and/or other investigational agents are added as prohibited medications to be consistent with Appendix 1

Changes to the protocol

- Table of contents: current page numbers and changes to section headings.
- Protocol Summary: changes in the main body of the protocol (see bullet points below) are also implemented in the relevant sections of the protocol synopsis.

[redacted]

- Section 2.2: updated rationale for study design to introduce optional extension of study treatment period as an option.
- Section 4.1: update Figure 4-1 to extend treatment period.
- Section 4.1.2: changed 2nd and 3rd bullets to allow extension of treatment period until disease progression.
- Section 5.3:
  - Exclusion criteria 2: changed BTZ to Proteasome inhibitors.
  - Exclusion criteria 18: added criterion that exclude patients have a known history of HIV seropositivity or history of active/treated hepatitis B or C.
  - Exclusion criteria 20: changed contraception period from during doing and for 28 days to during and for 1 month.
  - Exclusion criteria 21: added criterion of contraception for sexually active males.
- Section 6.1.1: corrected to change orange to Seville orange
- Section 6.4.3: corrected for consistency with Appendix 1
- Table 7-1: remove thyroid function test on day 1 between Cycle 2 to 8
- Section 7.1: changed Section 7.1.3 and added Section 7.1.4 and 7.1.5 to introduce DOCE guideline
- Section 7.2.2.6: specified urinary pregnancy test during study treatment period and at EOT visit
- Section 10: added background pertaining to newly introduced interim analysis
- Section 10.4.2: deleted a sentence regarding 90% confidence interval
- Section 10.7: added information regarding interim analysis
- Section 10.8: deleted a sentence regarding 90% confidence interval
- Section 11.5: added a sentence regarding interim reports
- Section 14.4: corrected Figure 14-1, 14-2, 14-3, 14-5, 14-6, 14-7, 14-8, 14-9 and 14-10

[redacted]

Protocol summary:

Protocol number	CLBH589D1201
Title	A phase II, multi-center, single arm, open label study to evaluate the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone in Japanese patients with relapsed/refractory multiple myeloma
Brief title	Study of efficacy and safety LBH589 in combination with bortezomib and dexamethasone in Japanese patients with relapsed/refractory multiple myeloma
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	[CLBH589D2308] (PANORAMA-1) study demonstrated panobinostat (PAN, LBH589) in combination with bortezomib (BTZ) and dexamethasone (Dex) was superior to BTZ, Dex and placebo (PBO) in patients with relapsed or relapsed and refractory multiple myeloma. The safety profile was generally manageable with dose reduction and supportive care. In PANORAMA-1 study, 34 Japanese patients were enrolled and the median PFS in Japanese population was longer in PAN+BTZ+Dex arm as compared to PBO+BTZ+Dex as well as in overall population. The near complete response (nCR)/complete response (CR) rate was higher in the PAN arm than the placebo arm. Also, the safety profile in Japanese population was not much different to the one of overall population and was generally manageable and predictable. As for detail, please refer to Section 1.2 The purpose of this study is to collect additional efficacy and safety of oral PAN treatment in combination with BTZ and Dex in Japanese patients with relapsed/refractory multiple myeloma.
Primary Objective(s) and Key Secondary Objective	**Primary objective**: Evaluate nCR/CR rate after all patients have been treated for 8 cycles or discontinued treatment (as per investigator on modified EMBT 1998 criteria) **Key secondary objective**: Evaluate progression free survival
Secondary Objectives	Evaluate overall response rate (ORR) comprising CR, nCR and PR Evaluate minimal response rate (MRR) Evaluate time to response (TTR) Evaluate time to progression/relapse (TTP) Evaluate duration of response (DOR) Assess safety of the combination therapy HRQoL as measured by: FACTGOG-NTX Assess the Pharmacokinetics (PK) of PAN and BTZ in patients who agree to blood samplings for the PK assessments
Study design	A total of 33 eligible patients will be enrolled. PAN will be administered in combination with BTZ and Dex 2 weeks on/1 week off. Total duration of treatment will be 48 weeks, divided into two phases. Treatment Phase 1 will consist of 8 three-week (21 days) cycles for a total of 24 weeks. Patients with clinical benefit at the end of cycle 8 as per investigator assessment may continue to receive study treatment in treatment Phase 2 for 4 additional six-week (42 day) cycles of therapy. After 4 additional six-week cycles of therapy, patients who investigators will judge continuous treatment provide benefit based on risk/benefit assessment may continue in the study until disease progression or the End of study whichever comes first as an optional extension. Post-treatment efficacy evaluations will continue up to progression, relapse, death or withdrawal of consent.
Population	Adult (at least 18 years of age) male and female, with relapsed multiple myeloma or relapsed and refractory multiple myeloma. 33 patients will be enrolled.

[redacted]

Inclusion criteria	1. Age 18 years or older at time of consent 2. Patient has a previous diagnosis of multiple myeloma, [redacted] 3. Patient with 1 to 5 prior lines of therapy who requires retreatment of myeloma [redacted] for one of the 2 conditions below: a. Relapsed, defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy for up to 60 days of last dose of this therapy. Patients previously treated with BTZ are eligible For regimen that are administered until progression, for example maintenance therapies, the documentation of a minimal duration of 60 days of MR or better is considered sufficient for a patient to qualify for the study. b. Relapsed-and-refractory defined as therapy that meets both of the following: ● patient has relapsed to at least one prior line; ● and patient was refractory to another line (except proteasome inhibitors), by either not reaching a MR, or progressed while under this therapy, or within 60 days of its last dose; 4. Patient has measurable disease at study screening [redacted] 5. Patient treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, is eligible. Two weeks must have elapsed since last date of radiotherapy, which is recommended to be a limited field. Patient who requires 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 6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 7. Patient has the following laboratory values within 3 weeks before starting study drug (lab tests may be repeated, as clinically indicated, to obtain acceptable values before failure at screening is concluded but supportive therapies are not to be administered within the week prior to screening tests for ANC or platelet count) a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 /L b. Platelet count ≥ 75 x 10^9 /L c. Serum potassium, magnesium, phosphorus , within normal limits (WNL) for Institution d. Total calcium (corrected for serum albumin) or ionized calcium greater or equal to lower normal limits (> LLN) for institution, and not higher than CTCAE grade 1 in case of elevated value **Note:** Potassium, calcium, magnesium, and/or phosphorus supplements may be given to correct values that are < LLN e. AST/SGOT and ALT/SGPT ≤ 2.5 x ULN f. Serum total bilirubin ≤ 1.5 ULN (or ≤ 3.0 x ULN if patient has Gilbert syndrome) g. Calculated creatinine clearance ≥ 30 ml/min

[redacted]

	8. Patient has provided written informed consent prior to any screening procedures 9. Patient is able to swallow capsules 10. Patient must be able to adhere to the study visit schedule and other protocol requirements 11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at baseline 12. Written informed consent for the main study must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness 13. Patients must avoid consumption of grapefruit, 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.
Exclusion criteria	1. Patients who have progressed under all prior lines of anti-multiple myeloma therapy (primary refractory) 2. Patients who have been refractory to prior Proteasome inhibitors (i.e. did not achieve at least a MR, or have progressed under it or within 60 days of last dose) 3. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression 4. Patient has shown intolerance to BTZ or to dexamethasone (Dex) or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information 5. Patient has grade ≥ 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination within 14 days before enrollment 6. Patient needing valproic acid for any medical condition during the study or within 5 days prior study treatment 7. Patient received prior treatment with DAC inhibitors including PAN 8. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted. Anti-RANKL antibody (Denosumab) can be also maintained if commenced prior to screening period.) 9. Patient has secondary primary malignancy < 3 years of first dose of study treatment (except for treated basal or squamous cell carcinoma, or in situ cancer of the cervix). 10. Patient who received at least one of the following: a. prior anti-myeloma chemotherapy or medication including IMiDs and Dex ≤ 3 weeks prior to first dose 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 first dose of study treatment c. prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior first dose of study treatment d. Stem cell transplant ≤ 3 weeks prior to start of study treatment 11. Patient has ≥ grade 2 CTCAE from all therapy-related toxicities associated with above listed treatments 12. Patients who have not recovered from side effect of prior surgery to < grade 2 CTCAE 13. Patients with evidence of mucosal or internal bleeding 14. Patient has unresolved diarrhea ≥ grade 2 CTCAE 15. Patient has impaired cardiac function, including any one of the following: a. Known LVEF < 40%, as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA) b. obligate use of a permanent cardiac pacemaker c. congenital or acquired long QT syndrome d. presence of uncontrolled ventricular tachyarrhythmia

[redacted]

	e. resting bradycardia defined as < 50 beats per minute f. QTcF > 450 msec on screening ECG g. complete left bundle branch block (LBBB), bifascicular block h. any clinically significant ST segment and/or T-wave abnormalities i. presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria j. myocardial infarction or unstable angina pectoris ≤ 12months prior to starting study drug k. symptomatic congestive heart failure (New York Heart Association class III-IV) l. other clinically significant heart disease and vascular disease (e.g. uncontrolled hypertension 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 PAN (e.g. ulcerative disease, uncontrolled nausea, vomiting, malabsorption syndrome, obstruction, or stomach and/or small bowel resection) 18. Patient has a known history of HIV seropositivity or history of active/treated hepatitis B or C. 19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping all study treatment. 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). For female subjects on the study 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. 21. 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 in order to prevent delivery of the drug via seminal fluid.
Investigational and reference therapy	Panobinostat is the investigational drug in this study. Investigational treatment refers to combination treatment with PAN, BTZ and Dex.

[redacted]

Efficacy assessments	Efficacy will be evaluated based on modified EBMT 1998 criteria. Throughout the trial, efficacy will be evaluated by the following parameters: Serum M-protein (M-spike by PEP, by central laboratory assessment), urine M-protein (M-spike by PEP, M-spike is measured at a central laboratory), serum immunofixation, urine immunofixation, serum calcium level, evaluation of soft tissue plasmacytoma (by CT scans or MRI), skeletal surveys and plasma cell count in bone marrow (by bone marrow aspiration/biopsy). Efficacy parameters will be measured at screening and at every 3 weeks during treatment phases and at every 6 weeks during follow-up phase for response assessment.
Safety assessments	Safety will be evaluated by monitoring the frequency, duration and severity of adverse events and laboratory abnormalities, and assessing the physical examinations, vital signs and electrocardiograms. Severity of adverse events and laboratory abnormalities will be assessed using CTCAE 4.03. Concomitant medications and significant non-drug therapies will be assessed during the study.
Other assessments	Pharmacokinetic Plasma samples from patients who agree to blood samplings for pharmacokinetic assessment of PAN and BTZ will be collected on Cycle 1 Day1 and Day 8. Plasma concentrations of PAN (and its metabolite BJB432, if feasible) and BTZ will be measured, and the pharmacokinetic parameters (Cmax, Tmax, AUC, T1/2, etc) will be assessed.
Data analysis	Sample size assumptions in this trial are based on the data from the PANORAMA-1 study, which enrolled a similar patient population; i.e. patients with relapsed multiple myeloma or relapsed-and-refractory myeloma. Considering BTZ is currently widely used in newly diagnosed MM and relapsed/refractory MM in Japan, it is expected that most patients in this study have BTZ containing regimen. Based on the data from the PANORAMA-1 study, for patients previously treated with BTZ, the nCR+CR rate for PAN is expected to be around 25 %. nCR+CR rate of 10 % or less is considered as an insufficient level of activity for the proposed patient population. Based on the normal distribution, approximately 33 patients are required to reject a null hypothesis of the nCR+CR rate ≤ 10% vs. a target the nCR+CR rate of 25% or more, with a one-sided alpha of 0.05 and at least 80% power.
Key words	Panobinostat, Phase II, relapsed/refractory multiple myeloma

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Multiple myeloma (MM) is a malignant proliferation of plasma cells and plasmacytoid cells. It is the second most common hematological malignancy and is invariably fatal (Raab et al 2009; Kyle et al 2008). The median age at diagnosis is 61 years for females and 62 years for males. The most common presenting symptoms are fatigue and bone pain (Kyle et al 2003). Osteolytic bone lesions and/or compression fractures are the hallmark of the disease and cause significant morbidity. Anemia occurs in 66% of patients at diagnosis and is the primary cause of fatigue. Renal dysfunction occurs in 20% and hypercalcemia in 15-20% of patients. The annual incidence of MM is approximately 2.0 per 100,000 in Japan (MHLW database 2011).

Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines such as interleukin-6 (IL-6), macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival (Klein et al 1989; Vidriales et al 1996). Processes that change the bone marrow microenvironment either retard the growth of the tumor or cause myeloma cells to undergo apoptosis.

Although outcomes for patients with multiple myeloma (MM) have improved over the past decade, the disease remains incurable and even patients who respond well to induction therapy ultimately relapse and require additional treatment. Conventional chemotherapy and high-dose therapy with stem cell transplantation (SCT) have historically been utilized in the management of relapsed MM, but in recent years the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide (LEN), as well as the proteasome inhibitor bortezomib (BTZ), have assumed a primary role in this setting. These agents have not only improved overall response, but emerging data suggest that these agents also have doubled patient survival from 3-4 years to 7-8 years as a direct result (Kumar et al 2008). The use of these targeted therapies to treat relapsed and refractory MM and relapsed MM has transformed MM therapy and patient outcome. However, there is still a high unmet need for patients with relapsed and refractory disease who have received prior targeted therapies. Patients who are refractory to BTZ and have failed LEN have a very poor progression free survival (PFS) of 5 months and overall survival (OS) of 9 months (Kumar et al 2011).

Relapsed and/or refractory MM represents an important focus of ongoing research efforts. Characterization of the molecular events underlying this disease at the level of the MM cell and the bone marrow microenvironment has provided the platform for development of the novel agents as well as various emerging compounds in MM, including new IMiD and proteasome inhibitors, as well as DAC inhibitors. It is anticipated that drug combinations that target different oncogenic pathways will deliver greater anti-MM activity and add to progress made in the treatment of patients with relapsed and/or refractory disease, for which there remains a clear medical need to improve outcomes.

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

1.2.1 Overview of panobinostat (LBH589)

Panobinostat (LBH589, PAN) belongs to a structurally novel cinnamic hydroxamic acid class of compounds and is a pan-inhibitor of Class I, II and IV histone deacetylases (DACs). DACs are involved in the deacetylation of histone and non-histone cellular proteins, targeting lysine groups on chromatin and transcription factors and various non-histone proteins such a p53, tubulin, heat shock protein 90 (Hsp90), and retinoblastoma protein (Rb). PAN has shown antitumor activity in preclinical models and in cancer patients and has been formulated as an oral capsule and as a solution for intravenous (i.v.) injection. Both the i.v. and oral formulations have been investigated in Phase IB/II studies in advanced solid tumors and hematological malignancies.

1.2.1.1 Non-clinical experience

PAN has been developed as an anticancer agent based on its potential to act:

- by exhibiting differential antiproliferative activity against a broad range of solid tumor cell lines and high sensitivity in lymphomas and hematologic malignancy cell lines, including acute myeloid leukemia (AML) and multiple myeloma (MM).
- by inducing consistent tumor growth control in various tumor-bearing xenografted mice and by increasing histone-H3 and H4 acetylation in excised tumors.
- by showing synergistic or additive anti-tumor effect in combination with other anti-cancer agents such as trastuzumab, docetaxel, BTZ or standard cytotoxic agents e.g., doxorubicin, fludarabine, Ara-C.

The potent anticancer effects of PAN seen in experimental models may result from two distinct mechanisms of action, both related to pan-DAC inhibition. PAN was shown to affect epigenetic mechanism of gene expression via inhibition of Class I HDACs, as shown by induction of histone acetylation and consequent induction of cell cycle control genes (i.e. p21) and to inhibit HDAC6 through abrogation of Hsp90-mediated stabilization of client oncoproteins, resulting in their depletion and in reduced downstream oncogenic signaling (Atadja 2011).

Proteasome and DAC inhibition in multiple myeloma

BTZ is a reversible inhibitor of the chymotrypsin-like activity of the 20S proteasome in mammalian cells. The 20S proteasome is a large protein complex that degrades ubiquinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 20S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. BTZ is cytotoxic to a variety of cancer cell types in vitro and causes a delay in tumor growth in vivo in non-clinical tumor models, most notably MM.

The microtubule-associated histone deacetylase HDAC6 is a component of aggresomes and recruits misfolded proteins for transport to aggresomes. Unfolded or misfolded proteins exceeding proteasomal degradation form aggregates and are transported to the microtubule

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organizing center (MTOC) for degradation. This transport requires HDAC6 which deacetylates alfa-tubulin and binds both polyubiquitinated proteins and dynein. Inhibiting HDAC6 with tubacin, whether or not combined with the proteasome inhibitor BTZ, accumulates misfolded or unfolded proteins and leads to apoptosis.

Pei et al (2004) were the first to demonstrate in vitro that DACi in combination with BTZ resulted in an improved cytotoxic effect compared to their effects as single agents. Sequential exposure of U266 and MM1S cells to BTZ and suberoylanilide hydroxamide acid (SAHA) potently induced caspase-3, -8 and -9 activation and release of the pro-apoptotic mitochondrial proteins cyto-c and Smac, resulting in a synergistic induction of apoptosis indicating that several molecular mechanisms may contribute to the synergy between BTZ and DACi. (Feng et al 2007)

The well-characterized model of synergy between proteasome inhibitors and DACi are the dual inhibition of the proteasome and aggresome pathways (Figure 1-1, Hideshima et al 2011). Targeting both the proteasome with BTZ and the aggresome with HDAC6 inhibitors in tumor cells induces greater accumulation of polyubiquitinated proteins, resulting in increased cellular stress and apoptosis (Catley 2006, Hideshima 2005). More specifically, proteasome inhibition drives the formation of aggresomes, which are dependent on the interaction of HDAC6 with tubulin and dynein complex (Catley et al 2006). Moreover, the proteasome inhibitor (BTZ) and HDAC6 inhibitors (tubacin or PAN) lead to increased hyperacetylation of tubulin and generation of polyubiquitinated proteins, thus increasing cellular stress response (i.e., c-Jun *N*-terminal protein kinase activation) and leading to apoptosis, which is, in part, dependent on caspase activity (Catley 2006, Hideshima 2005). Therefore the combined use of BTZ and of PAN could lead to the blockage of known pathways of cytotoxic protein clearance from MM cells.

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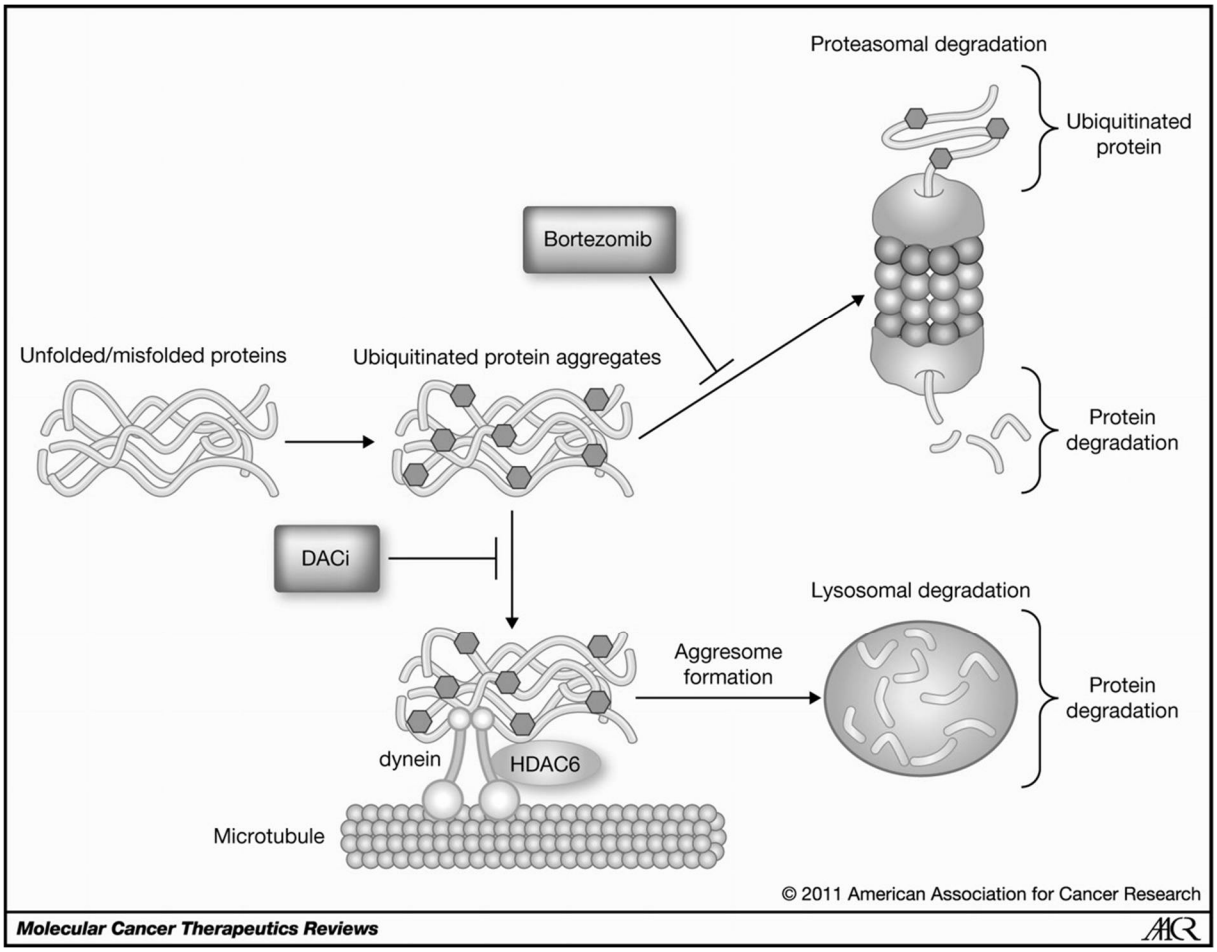
Figure 1-1 Inhibition of the proteasome by bortezombib and aggresome pathways by panobinostat and deacetylase inhibitors (DACi)



Atadja et al (2007) demonstrated PAN to induce growth inhibition and apoptosis in MM cells, and to potentiate the activity of other drugs, such as BTZ, in vitro. Furthermore, PAN produced significant anti-tumor activity with protection from bone damage in an in vivo mouse model of MM. In this model PAN inhibited growth of MM cells sensitive or resistant to standard steroid or chemotherapeutic treatment as well as plasma cells isolated from MM patients. In particular, significant synergistic cytotoxicity was observed with PAN in combination with BTZ without additional toxicity to normal bone marrow stromal cells. Comparable single-agent anti-tumor activity, evidenced by reduced tumor burden was observed with PAN, BTZ, and melphalan in vivo. Importantly, PAN alone appeared to demonstrate preservation of bone integrity in this model. Enhanced anti-MM activity of the PAN/BTZ combination could not only be observed in primary human MM cells but also in co-culture conditions and conditions with exogenous growth factors IL-6 or IGF-1 (Atadja et al 2007). Moreover, a combination of PAN and BTZ and with the addition of dexamethasone, resulted in strong synergistic effects seen on growth inhibition and apoptosis in both in vitro and in vivo models (Ocio et al 2010).

For the latest information on the pre-clinical pharmacology and toxicity of PAN, please refer to the current [Investigator Brochure].

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1.2.1.2 Clinical experience

As of 22 February 2017, 40 clinical studies, including clinical pharmacology (CP), Phase I and Phase II trials, as well as two randomized Phase III studies have either been completed or are ongoing. A total of 2592 patients were enrolled; of which 2202, 235 for i.v. and 1967 for oral, received at least one dose of PAN either as a single agent or in combination with other agents.

The most frequent non-hematologic toxicities included GI events (diarrhea, nausea, vomiting) and fatigue, which were mild to moderate in severity and generally reversible.

The most common ECG findings were sinus tachycardia, T-wave abnormalities and depressed ST segment. QTcF above 500 msec is uncommon and noted only with the weekly oral dosing regimen. No torsade de pointes have been reported in clinical trials with oral PAN.

1.2.1.2.1 Overview on human pharmacokinetics

Following oral administration, PAN was rapidly absorbed with a rate of absorption (Ka) of 0.3 $hour^{-1}$, peak plasma concentration was reached within 1 hour; systemic clearance was 33 L/hour and central volume of distribution was 25 liters. Half-life associated with the distribution, initial elimination and terminal elimination phases were 0.14, 2.3 and 37 hours, respectively. Observed drug accumulation was approximately 1.14 fold with TIW schedule. This is consistent with an effective half-life of 15 hours. Absolute oral bioavailability estimated for the Final Market Image (FMI) formulation was 21%.The compound can be administered regardless of food intake as the variability and overall systemic exposure remained unchanged in patients taking PAN with or without food (Lewis et al 2009). AUC increased linearly and proportionally with doses up to 50 mg. The inter-individual variability (CV%) in systemic exposure is 60%. The plasma protein binding of PAN (mainly to albumin) is moderate (89.6% at 37°C) and independent of concentration. Elimination half-lives averaged 15 hours. Steady state is achieved by the third dose following days 1, 3, and 5 (TIW) weekly (QW) dosing. On day 5, PAN has an observed AUC accumulation ratio (R_A) of ~1.4 fold over a single dose AUC which is consistent with the estimated R_A based on linear pharmacokinetic processes.

PAN was extensively metabolized in patients, with the parent compound accounting for 6-9% of the drug-related exposure in plasma with the remainder accounted for by approximately 40 metabolites. Metabolites formed via the primary metabolic pathways were all inactive for DAC inhibitory activity *in vitro*.

CYP3A4 is the main oxidative metabolizing enzyme of PAN (70-98%) with minor involvement of CYP2D6 and CYP2C19. PAN is a competitive CYP2D6 inhibitor with a K_i value of 0.17µM in human liver microsomes. It is also a weak time-dependent inhibitor of CYP3A4 with K_i value of 12.0 µM and k_{inact} value of 0.0228 min^{-1}. PAN is not an inducer of CYP enzymes, UGT1A1, Pgp or MRP2 and does not inhibit Pgp efflux activity *in vitro*.

A strong CYP3A inhibitor, ketoconazole, increased PAN systemic exposure by 80% in cancer patients. This clinical drug interaction is deemed weak, and consistent with *in vitro* findings. Co-administration of a strong CYP3A inhibitor with PAN is feasible when medically necessary with close monitoring.

Population PK analysis was performed using plasma concentrations obtained from intravenous and oral administration of PAN. Among the covariates investigated, body surface area, age at baseline and race were statistically significant covariates on clearance and volume of

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distribution in the central compartment. However, the extent of these covariate effects were small as compared to the large inter-individual variability and were not deemed clinically relevant.

For further details, please refer to the current [PAN Investigator Brochure].

1.2.1.2.2 Interactions with other drugs

Based on *in vitro* data, PAN is a CYP3A4 and CYP2D6 substrate and a CYP2D6 inhibitor (IC_{50} 0.17 μM). Thus, two clinical DDI studies were conducted using ketoconazole as a potent CYP3A inhibitor [CLBH589B2110] and PAN as CYP2D6 inhibitor with dextromethorphan as CYP2D6 substrate [CLBH589B2109].

Study [CLBH589B2110] was conducted in 14 patients with advanced cancer. Multiple ketoconazole doses at 400 mg increased Cmax and AUC of PAN by 1.6- and 1.7-fold, respectively, but with no change in Tmax (de Jonge et al 2009). The less than 2-fold increase in PAN AUC upon co-administration suggests that CYP3A contribution to the total clearance is low (Ohno et al 2008). The observed effect of ketoconazole on PAN CYP3A mediated metabolic pathways is considered weak and not clinically relevant, as doses at least 2-fold greater than 20 mg (i.e., 40 mg and 60 mg) have been safely administered in patients. Clinical monitoring of signs of possibly PAN related adverse events is recommended when long-term (≥ 1 week) concomitant administration of potent CYP3A inhibitors and PAN at doses > 20 mg is medically indicated.

Study [CLBH589B2109] was conducted in 17 patients with advance cancer. Multiple PAN doses at 20 mg (TIW) increased Cmax and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold, respectively, but with no change in Tmax. An approximately 2-fold increase in Dextromethorphan AUC upon co-administration with PAN indicated that *in vivo* CYP2D6 inhibition of PAN is weak. As the study was conducted using a sensitive CYP2D6 substrate resulting in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally considered safe to be co-administered with PAN. Caution is to be exercised when PAN is co-administered with medications that are exclusively metabolized by CYP2D6 and have a narrow therapeutic window (e.g., tamoxifen, anti-arrhythmics). Please refer to //druginteractioninfo.org for a more detailed reference list.

Study PANORAMA-1- Phase III placebo-controlled study in combination with bortezomib and dexamethasone in MM

The Study [PANORAMA-1] was a multi-center, randomized, double-blind, placebo-controlled Phase III study of PAN in combination with BTZ and Dexamethasone (Dex) in 768 patients with relapsed or relapsed and refractory MM Study.

In the treatment phase 1, patients received 20 mg PAN or placebo (PBO) TIW with a 2 weeks on/1 week off schedule, and 1.3 mg/m^2 iv BTZ on Days 1, 4, 8 and 11, and 20 mg Dex on each day of and after BTZ dosing in a 21 day cycle. PK samplings were conducted in only Japanese population in this study. Serial dense blood samples to characterize the PK of PAN (Day 1 and Day 8 of Cycle 1) and BTZ (Day 8 of Cycle 1) were collected in a subset of 13 Japanese patients.

Geometric mean PAN plasma exposure, AUC0-48h (CV%) was 76.01 (45.6%) and 118.9 (29.5%) ng*hr/mL, respectively on Cycle 1 Day 1 and Cycle 1 Day 8. Peak plasma

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concentration of PAN (Cmax) showed similar increase from Cycle 1 Day 1 to Cycle 1 Day 8, and was 9.16 (74.8%) ng/mL on Cycle 1 Day 1 and 15.33 (39%) ng/mL on Cycle 1 Day 8. The apparent increase in plasma exposure of PAN on Cycle 1 Day 8 is most likely a reflection of not only drug accumulation based on the effective half-life of approximately 15 hours, but also the large variability.

PAN exposure was moderately variable, and was considerably lower than that from single-agent trials likely due to induction of CYP3A4 by Dex.

1.2.1.2.3 Clinical experience in multiple myeloma with PAN combination therapy

The safety and efficacy data of oral PAN treatment in combination with BTZ (iv) and Dex in adult patients with relapsed or relapsed/refractory (RR) multiple myeloma is based on the results of three independent studies. These studies are summarized below and include the following: 1). LBH589B2207 a phase 1b dose escalation (n=47) and expansion (n=15) study establishing the MTD/DLTs and the RP2D; 2). LBH589DUS71 a phase 2 exploratory study (n=55) demonstrating efficacy in the relapsed and BTZ refractory myeloma patient population; and 3). PANORAMA-1, a phase 3 international randomized study (n=768) conducted in 34 countries including Japan demonstrating superiority of the addition of PAN to the combination of BTZ and Dex.

Study LBH589B2207

Study [LBH589B2207] is an open-label Phase Ib dose-escalation/dose-expansion trial of oral PAN and IV BTZ that enrolled patients with relapsed or relapsed-and-refractory MM, following at least one prior line of therapy and who were suitable for treatment (or re-treatment) with BTZ (not mandatory for inclusion into the study). A total of 62 patients were enrolled: 47 patients in the dose escalation phase at five different dose levels in six consecutive dose-cohorts and 15 patients in the dose-expansion phase.

The dose-escalation component of the trial consisted of a single treatment arm where escalating doses of oral PAN (3 times weekly) were administered in combination with escalating doses of intravenous BTZ. An adaptive Bayesian logistic regression model was used to guide the dose escalation. The observed safety profile and the Bayesian model based on DLTs from cycle one as defined in the protocol declared the PAN 20 mg (3 times weekly) + BTZ 1.3 mg/m^2 dose level to be the maximal tolerated dose (MTD) on the continuous dosing schedule. Review of the long term safety and tolerability of the dose-escalation phase dose-level cohorts, resulted in modifying the dosing schedule of PAN to introduce a treatment rest week, to proceed simultaneously with that for BTZ (2-weeks on and 1-week off). To optimize clinical responses in the dose-expansion phase and conform to current standard-of-care (Jagannath et al 2006; Mikhael et al 2009), oral Dex (20 mg daily) was given to all dose-expansion patients starting at Cycle 2.

Promising results from the analysis of the dose-expansion phase (n=15) are reported here (data cut-off date of 10-Aug-2011) (San-Miguel et al 2013). Patients had received a median of 2 prior lines of anti-myeloma therapy (range: 1-7) and 46.6% of patients had received 3 or more prior lines of treatment. The majority of patients (53.3%) were relapsed-and-refractory at study entry.

In the Full Analysis Set (n=15, defined as all patients who received at least one dose of study treatment), the overall response rate [redacted]

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[redacted] was 73.3% (95% CI, 44.9-92.2), [redacted] in 3 patients (20.0%). In addition, half of patients (53.3%) achieved a partial response (PR), 2 patients (13.3%) achieved a minimal response (MR), and one patient (6.7%) had a best response of stable disease. The median time to response (≥ PR) was 44.0 days (range: 22-1393). Median exposure to study treatment was 159 days (range: 45-353). Most patients (86.7%) received treatment for ≥ 3 months with one-third (33.3%) having received ≥ 6 months of treatment by the data cut-off date.

AEs ≥ grade 3 were experienced by most patients (86.7%) in the dose-expansion cohort with; thrombocytopenia (66.7%), neutropenia (46.7%), lymphopenia (33.3%), and hypophosphatemia (26.7%) the most commonly observed grade 3-4 events. One patient (6.7%) experienced ≥ grade 3 PN. There were two (13.3%) on-treatment deaths, attributed to 'injury' and 'ischemic stroke'; none of the deaths were assessed as related to study treatment. Six patients (40.0%) had at least one serious AE (SAE); the most common SAEs were thrombocytopenia (26.7%) and dehydration (13.3%). Five patients (33.3%) had at least one AE that led to study drug discontinuation, and the most common AE in this category was peripheral neuropathy (13.3%). A hemorrhagic event was reported in one patient, a grade 4 cerebral hemorrhage (6.7%). No major changes in vital signs and ECG parameters were observed.

The promising efficacy (an ORR of 73.3%) and manageable safety of Study [LBH589B2207] allowed the PAN clinical development program to move the triple combination regimen into a pivotal Phase III trial for relapsed or relapsed-and-/refractory MM.

Study LBH589DUS71

Study [LBH589DUS71] illustrates the efficacy of PAN in combination with BTZ and Dex in patients with relapsed or relapsed-and-refractory MM, including BTZ-refractory patients. Given that BTZ is a current standard-of-care for relapsed/refractory MM, either as a single agent or in combination, the possibility of rescuing a response in patients who have become refractory to BTZ is of high clinical relevance.

Patients that had received ≥ 2 prior lines of therapy including an IMiD and who had progressed on or within 60 days of their last BTZ-based therapy were treated in a single-arm, Phase II trial with PAN/BTZ/Dex (Richardson et al 2013). The main purpose of this study was to assess whether patients refractory to BTZ would regain responsiveness to the drug if given in combination with PAN.

Treatment phase 1 (TP1) consisted of eight 3-week cycles of oral PAN (20 mg three times weekly, 2-weeks on and 1-week off) + IV BTZ (1.3 mg/m^2 on Days 1, 4, 8, and 11) + oral Dex (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12). Patients demonstrating clinical benefit (≥ no change in disease status) could proceed to treatment phase 2 (TP2), which consisted of 6-week cycles until disease progression. The primary endpoint was ORR (≥ PR) in TP1, as defined by 1998 modified European Society for Blood and Marrow Transplant (mEBMT) criteria.

Patients (n=55) with BTZ-refractory MM were enrolled (median age: 61 years, range: 41-88 years). This was a heavily pretreated population; patients had received a median of four prior lines of anti-myeloma therapy (range: 2-11). Most patients (67.3%) had received more than three prior lines of previous therapy. In the most recent prior line, almost half of patients (49.1%) had received BTZ. All patients were previously treated with BTZ, Dex, and at least

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one IMiD (BTZ: 100%, lenalidomide: 98.2%, thalidomide: 69.1%). The majority of patients had received prior stem cell transplantation (63.6%).

The median duration of exposure to study treatment was 139.0 days (range: 2-735 days). Nineteen of the 55 patients completed TP1 and all 19 entered TP2.

The primary endpoint, ORR based on investigator's assessment, was observed in 19 patients (34.5%) (95% CI: 22.2%, 46.7%). One patient (1.8%) achieved near Complete Response (nCR), 18 patients (32.7%) achieved a PR. In addition, 10 patients (18.2%) had a MR, and 20 patients (36.4%) had no change as best response. For all patients, median PFS and OS were 5.4 months and 17 months, respectively. Thus, the PAN/BTZ/Dex regimen recaptured clinical responses in heavily pretreated BTZ-refractory patients.

Most patients (89.1%) experienced ≥ grade 3 AEs; thrombocytopenia (63.6%), diarrhea (20.0%), and fatigue (20.0%) were the most commonly observed ≥ grade 3 events. One patient (1.8%) experienced grade 3 PN. Thirty-nine patients (70.9%) had at least one SAE; the most common SAEs were thrombocytopenia (29.1%), pneumonia (14.5%) and pyrexia (9.1%). Four (7.3%) on-treatment deaths occurred; of these four deaths, three (5.5%) were due to study indication and the remaining patient died of multi-organ failure in the context of pneumonia and disease progression. Ten patients (18.2%) had at least one AE that led to study drug discontinuation, and the most common AE in this category was fatigue (7.3%).

Study PANORAMA-1

PANORAMA-1 study is a Phase III randomized, double blind, placebo controlled, multicenter global registration study to evaluate LBH589 in combination with BTZ and Dex vs BTZ, Dex and placebo in patients with relapsed or relapsed and refractory multiple myeloma having received 1 to 3 prior line of therapy. Treatment phase 1 (TP1) consisted of eight 3-week cycles of oral PAN (20 mg three times weekly, 2-weeks on and 1-week off) + IV BTZ (1.3 mg/m^2 on Days 1, 4, 8, and 11) + oral Dex (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12). Patients demonstrating clinical benefit (≥ no change in disease status) could proceed to treatment phase 2 (TP2), which consisted of 6-week cycles until 48 weeks. The primary endpoint of the trial was progression-free survival (PFS) and the key secondary endpoint is overall survival (OS). Other secondary endpoints include overall response rate, nCR+CR rate, time to progression, time to response, duration of response and safety.

A total of 768 patients with relapsed or relapsed and refractory MM were enrolled in Study PANORAMA-1, and randomized to receive either PAN arm (n=387 patients) or PBO arm (n=381 patients). Treatment arms were well-balanced by baseline treatment history. In this trial, 51.4% of all patients had received one prior line of anti-MM therapy and 48.3% of all patients had received 2-3 prior lines. The proportion of patients receiving BTZ as prior antineoplastic therapy was similar between the two treatment arms (PAN arm, 43.7%; PBO arm, 42.3%). The proportion of patients in both arms receiving thalidomide for prior antineoplastic therapy (PAN arm, 53.0%; PBO arm, 49.3%) was higher than in patients who received lenalidomide for prior antineoplastic therapy (PAN arm, 18.6%; PBO arm, 22.3%).

The primary endpoint of the study was met with median PFS of 12.0 months vs. 8.1 months (HR, 0.63; 95% CI: 0.52 to 0.76, p<0.0001) for patients treated on the PAN arm vs. PBO arm. The PFS benefit of PAN+BTZ+Dex per investigator assessment was consistent across a series

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of preplanned analyses in clinically relevant subgroups. Hazard ratios within all major subgroups are in favor of the PAN arm, demonstrating patient benefit independent of: sex, race, prior therapies (i.e BTZ, IMiDs, stem cell transplantation), renal impairment, clinical staging by International Scoring System (ISS), relapsed or relapsed and refractory disease, age, and cytogenetic risk. Overall response rate (ORR) was higher in the PAN arm (60.7%) compared to the PBO arm (54.6%) arm with a higher rate of complete and nCRs. The nCR+CR rate was almost two-fold higher in the PAN arm (27.6%) vs. the PBO arm (15.7%) indicating higher quality responses in the PAN arm. Of note, this tendency was observed in patients with having BTZ-containing therapy as a prior line of therapy (PAN arm: 24.9%, PBO arm: 10.2%). In the PANORAMA-1 study, 34 Japanese patients were enrolled. The median PFS in Japanese population was also longer in PAN arm (10.6 months vs. 9.0 months) as well as in overall population. In Japanese population, although the ORR was higher in PBO arm (75.0%) than PAN arm (61.1%), nCR+CR rate was also higher in the PAN arm (33.3%) vs. the PBO arm (12.5%).

The most frequently reported AEs in Study PANORAMA-1 are presented in Table 1-1. Patients in the PAN arm generally had higher frequencies of common AEs. The most notable AEs with a frequency ≥ 30% for the PAN arm include diarrhea, thrombocytopenia, anemia, fatigue, nausea and peripheral neuropathy. Similarly the most notable grade 3/4 AEs with a frequency ≥ 10% for the PAN arm include thrombocytopenia, diarrhea, neutropenia, hypokalemia, fatigue, anemia, pneumonia and lymphopenia.

Table 1-1 AEs by PT and severity, irrespective of causality (with an incidence greater than 10% in either group)

	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
AEs by preferred term	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Diarrhoea	260 (68.2)	97 (25.5)	157 (41.6)	30 (8.0)
Thrombocytopenia	246 (64.6)	217 (57.0)	154 (40.8)	94 (24.9)
Anaemia	158 (41.5)	63 (16.5)	126 (33.4)	60 (15.9)
Fatigue	157 (41.2)	65 (17.1)	110 (29.2)	33 (8.8)
Nausea	138 (36.2)	21 (5.5)	78 (20.7)	2 (0.5)
Neuropathy peripheral	117 (30.7)	26 (6.8)	133 (35.3)	21 (5.6)
Neutropenia	114 (29.9)	92 (24.1)	40 (10.6)	30 (8.0)
Oedema peripheral	109 (28.6)	8 (2.1)	72 (19.1)	1 (0.3)
Decreased appetite	107 (28.1)	12 (3.1)	47 (12.5)	4 (1.1)
Hypokalaemia	104 (27.3)	73 (19.2)	53 (14.1)	24 (6.4)
Constipation	102 (26.8)	4 (1.0)	123 (32.6)	4 (1.1)
Pyrexia	99 (26.0)	5 (1.3)	56 (14.9)	7 (1.9)
Vomiting	98 (25.7)	28 (7.3)	49 (13.0)	5 (1.3)
Asthenia	84 (22.0)	36 (9.4)	55 (14.6)	14 (3.7)
Cough	81 (21.3)	4 (1.0)	70 (18.6)	0
Insomnia	73 (19.2)	0	61 (16.2)	1 (0.3)
Dizziness	71 (18.6)	11 (2.9)	62 (16.4)	9 (2.4)
Upper respiratory tract infection	68 (17.8)	9 (2.4)	55 (14.6)	6 (1.6)
Pneumonia	65 (17.1)	48 (12.6)	48 (12.7)	39 (10.3)
Leukopenia	62 (16.3)	35 (9.2)	31 (8.2)	12 (3.2)

[redacted]

	PAN+BTZ+Dex N=381		PBO+BTZ+Dex N=377	
AEs by preferred term	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Dyspnoea	56 (14.7)	9 (2.4)	44 (11.7)	9 (2.4)
Hypotension	53 (13.9)	11 (2.9)	35 (9.3)	5 (1.3)
Headache	52 (13.6)	3 (0.8)	40 (10.6)	1 (0.3)
Lymphopenia	52 (13.6)	47 (12.3)	35 (9.3)	28 (7.4)
Abdominal pain	51 (13.4)	9 (2.4)	40 (10.6)	3 (0.8)
Hyponatraemia	49 (12.9)	37 (9.7)	19 (5.0)	13 (3.4)
Nasopharyngitis	49 (12.9)	0	47 (12.5)	2 (0.5)
Back pain	48 (12.6)	3 (0.8)	47 (12.5)	5 (1.3)
Dyspepsia	47 (12.3)	1 (0.3)	43 (11.4)	1 (0.3)
Abdominal pain upper	44 (11.5)	3 (0.8)	36 (9.5)	1 (0.3)
Weight decreased	44 (11.5)	7 (1.8)	17 (4.5)	2 (0.5)
Hypophosphataemia	43 (11.3)	33 (8.7)	32 (8.5)	24 (6.4)
Platelet count decreased	43 (11.3)	35 (9.2)	17 (4.5)	13 (3.4)
Peripheral sensory neuropathy	42 (11.0)	9 (2.4)	46 (12.2)	7 (1.9)
Pain in extremity	40 (10.5)	1 (0.3)	54 (14.3)	3 (0.8)
Blood creatinine increased	38 (10.0)	4 (1.0)	22 (5.8)	6 (1.6)
Neuralgia	38 (10.0)	5 (1.3)	44 (11.7)	3 (0.8)
Herpes zoster	18 (4.7)	4 (1.0)	40 (10.6)	7 (1.9)

Preferred terms are sorted in descending frequency of all grades, as reported in PAN treatment group.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

The incidence of AEs leading to discontinuation of study treatment was 36.2% in the PAN arm and 20.4% in the PBO arm. Grade 3/4 AEs leading to discontinuation were reported in 25.5% of patients in the PAN arm and 13.3% in the PBO arm. The single most frequent AEs leading to treatment discontinuations were diarrhea (4.5% and 1.6%, respectively), fatigue (2.9% both arms), asthenia (2.9% and 0, respectively), and peripheral neuropathy (3.7% and 1.9%, respectively). While the overall frequency of treatment discontinuation in the combination studies appears to be high, AEs leading to discontinuation of study treatment were relatively low in frequencies with no more than 5% of patients who discontinued due to one single AE. This indicates that AEs have been effectively managed with dose interruption, dose modification, and/or supportive medical intervention. In Japanese population, the safety profile was not much different to the one of overall population and was generally manageable similar to overall population.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to assess efficacy and safety of oral PAN treatment in combination with BTZ and Dex in Japanese patients with relapsed/refractory multiple myeloma to collect additional efficacy and safety data in Japanese patients.

In PANORAMA-1 study, a clinically meaningful and statistically significant median PFS prolongation was observed with higher nCR/CR rate in the PAN arm. This is particularly

[redacted]

relevant given that higher quality responses have been shown to be associated with longer PFS and OS in patients with relapsed or refractory MM (Lonial and Anderson 2014). Based on these data, the primary objective was set as nCR plus CR rate after 8 cycles, when most of patients reached confirmed nCR or CR in PANORAMA-1, to assess efficacy [redacted] in this single-arm phase II study.

2.2 Rationale for the study design

This study is open-label, single arm, multi-center phase II evaluating efficacy PAN in combination with BTZ and Dex in Japanese patients with relapsed/refractory multiple myeloma. PAN will be administered in combination with BTZ and Dex 2 weeks on/1 week off. Total duration of treatment will be 48 weeks, divided into two phases. Treatment Phase 1 will consist of 8 three-week (21days) cycles for a total of 24 weeks. Patients with clinical benefit at the end of cycle 8 as per investigator assessment may continue to receive study treatment in Treatment Phase 2 for additional six-week (42 day) cycles of therapy. The treatment periods were set with reference to PANORAMA-1, which demonstrated that PAN in combination with BTZ/Dex provides a meaningful and robust clinical benefit in relapsed or relapsed-and-refractory multiple myeloma with the safety profile that was generally predictable and manageable with dose reduction/interruption and supportive care.

After amendment 1, it is allowed that patients will be treated with study treatment as treatment phase 2 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 Pomalidomide + Bortezomib + Dex vs Bortezomib + Dex) have been conducted using BTZ treatment until progression. The longer administration of BTZ in this study as compared to a maximum 12 cycles used in PANORAMA-1 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 PANORAMA-1 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 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 weekly BTZ administration after cycle 8 is expected to further improve tolerability of PAN+BTZ+Dex combination over longer treatment duration.

[redacted]

2.3 Rationale for dose and regimen selection

The selection of the dose levels of PAN 20 mg TIW and BTZ 1.3 mg/m^2 on days 1, 4, 8 and 11 is supported by the results of the Phase Ib study [CLBH589B2207] where 15 evaluable patients in the dose escalation phase receiving this dose remained longest on therapy and exhibited the best overall tolerability when compared to the other cohorts.

In addition, the review of efficacy, safety, and tolerability of this MTD dose, resulted in modifying the dosing schedule of PAN to introduce an on/off treatment strategy similar to that already used for BTZ (2 weeks on and 1 week off) in an effort to further improve tolerability. This dose level and intermittent regimen investigated in the dose expansion phase (N=15) of [CLBH589B2207], was the one adopted in studies [PANORAMA-1] and [CLBH589DUS71]. Based on the results of these studies which demonstrated the safety profile that was generally predictable and manageable with dose reduction/interruption and supportive care, it has been determined to be the safest and most efficacious dosing regimen, and therefore will be utilized for this trial.

2.4 Rationale for choice of combination drugs

To collect additional efficacy and safety data in Japanese patients, same combination drug (BTZ and Dex) used in the trial will be used. In this study, BTZ will be administered by subcutaneously (sc). BTZ sc injection was approved and is widely used as an alternative to iv therapy based on the results of the phase III study to compare the use of sc vs. iv BTZ in patients with relapsed MM, which demonstrated similar efficacy with improved tolerability (Moreau et al 2011). Intravenous BTZ administration was not found to alter panobinostat PK in B2207 study dose escalation phase. Comparing intravenous BTZ administration, subcutaneous BTZ administration will have little impact on AUC of BTZ, but will decrease Cmax of BTZ. Therefore, in terms of PK drug-drug interaction, subcutaneous BTZ will not alter panobinostat PK as well. Based on these data, it is reasonable to expect that the use of BTZ sc in this combination may demonstrate similar efficacy results with potential benefit in tolerability compared to the combination with BTZ iv.

2.5 Rationale for choice of comparators drugs

Not applicable.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate nCR/CR rate after all patients have been treated for 8 cycles or discontinued treatment	nCR plus CR rate after all patients have been treated for 8 cycles or discontinued treatment is based on modified EBMT criteria per investigator assessment	
Key secondary		Refer to Section 10.5.1
To evaluate progression free survival (PFS)	PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed by investigator	
Other secondary		Refer to Section 10.5.2
To evaluate overall response rate (ORR) comprising CR, nCR and PR	ORR is defined as the proportion of patients with CR or nCR or PR based on modified EBMT criteria per investigator assessment	
To evaluate overall survival (OS)	OS, defined as time from first dose of study treatment to death	
To evaluate minimal response rate (MRR)	MRR is based on modified EBMT criteria per investigator assessment	
To evaluate time to response (TTR)	TTR is defined as the time from the date of first dose of study treatment to first documented response (PR or nCR or CR) per modified EBMT criteria as assessed by investigator	
To evaluate time to progression/relapse (TTP)	TTP is defined as the time from the date of the first dose of study treatment to the date of the first documented disease progression or relapse	
To evaluate duration of response (DOR)	DOR is defined as the time from date of the first documented CR/nCR or PR to the date of the first documented progression or relapse or death due to MM	
To assess safety of the combination therapy	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events and for laboratory assessments (v4.03) that include biochemistry, hematology, urinalysis; special safety assessments that include LVEF, Thyroid function Creatinine clearance and ECGs.	
To assess QoL as measured by FACT/GOG-NTX	Calculated scores and changes from baseline will be summarized by visit.	
To assess the PK of Panobinostat and bortezomib in patients who agree to blood samplings for the PK assessments	Cmax, Tmax, AUC, T1/2, etc	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

[redacted]

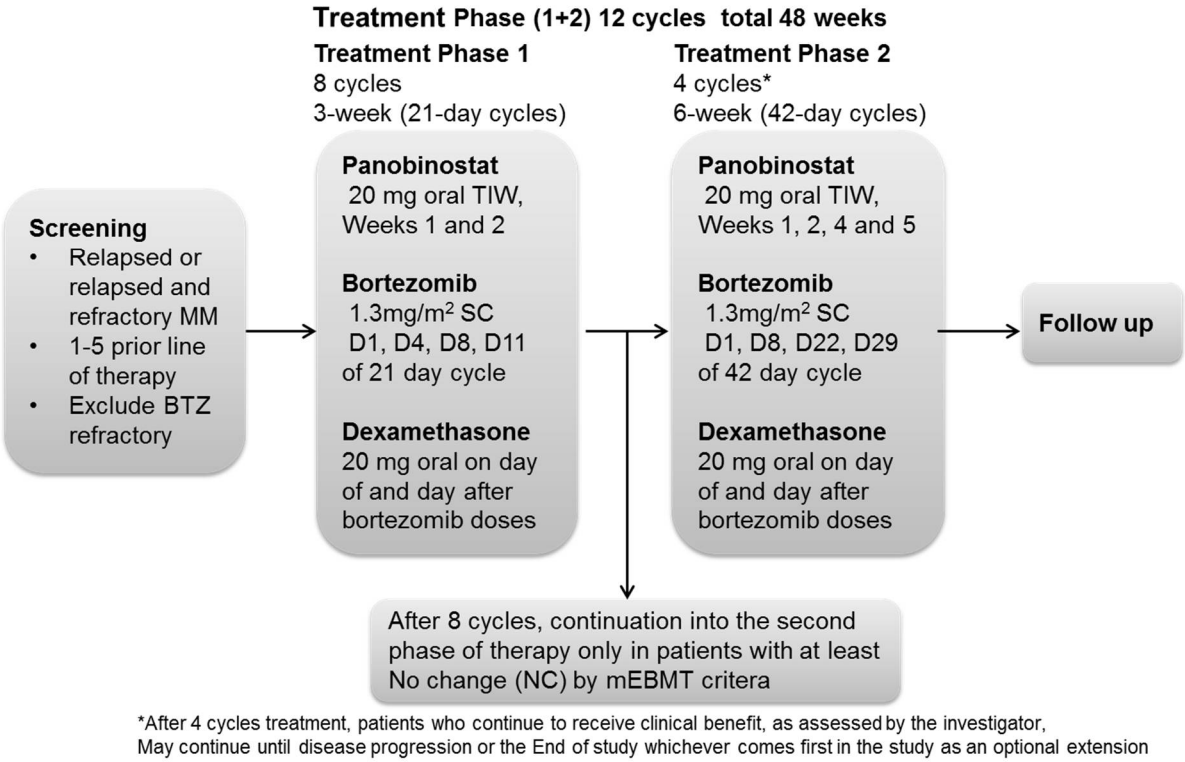
4 Study design

4.1 Description of study design

This study is an open-label, single arm, multi-center phase II evaluating efficacy panobinostat (PAN) in combination with bortezomib (BTZ) sc and dexamethasone (Dex) in Japanese patients with relapsed/refractory multiple myeloma. A total of 33 eligible patients will be enrolled. The primary objective is to evaluate nCR plus CR after 8 cycles of study treatment.

The study design is shown on Figure 4-1.

Figure 4-1 Study design



4.1.1 Screening period

Patient's screening evaluation will commence after the patient signs informed consent and will be concluded within 21 days prior to first day of dosing.

4.1.2 Treatment period

PAN will be administered in combination with BTZ and Dex 2 weeks on/1 week off. Treatment period will be divided into two phases:

- **Treatment phase 1**: 24 weeks of combined treatment with PAN + BTZ s.c / Dex (8 cycles of 3 weeks duration each)

[redacted]

- **Treatment phase 2**: 24 weeks of combined treatment with PAN + BTZ s.c / Dex (4 cycles of 6 weeks duration each) After 24 weeks treatment, patients who investigators will judge continuous treatment provide benefit based on risk/benefit assessment may continue in the study as an optional extension. They will follow the same assessments with the same frequency until disease progression or the End of study whichever comes first.
- All patients will receive study treatment until completion of week 24 (eight 21-day cycles). Patients with clinical benefit (achieving ≥ No Change at cycle 8 day 1, as assessed per modified EBMT criteria) will continue study treatment in Treatment phase2.

4.1.3 Follow-up period

All patients enrolled into the study will be followed through the treatment period and until relapse/progression after treatment discontinuation, and thereafter every 3 months for survival, except those who are lost to follow-up or withdraw consent.

Patients who discontinue study treatment due to reasons other than relapse or progression of disease will be followed for relapse/progression until 1 year after the last patient completed 24 weeks of treatment, except those who are lost to follow-up or withdraw consent.

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of the study

The End of study is defined as 1 year after the last patient completed 24 weeks of treatment.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.3.1 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The eligible patient population will consist of adult patients with relapsed multiple myeloma or relapsed and refractory multiple myeloma. The target population includes patients with all of the following:

- relapsed multiple myeloma having received 1 to 5 prior lines of therapy, or relapsed-and-refractory multiple myeloma, but who are not refractory to prior proteasome inhibitors
  - A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by

[redacted]

autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar et al 2011).

[redacted]

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

5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures

1. Age 18 years or older at time of consent
2. Patient has a previous diagnosis of multiple myeloma, [redacted]
3. Patient with 1 to 5 prior lines of therapy who requires retreatment of myeloma [redacted] for one of the 2 conditions below:
   a. Relapsed, defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy for up to 60 days of last dose of this therapy. Patients previously treated with BTZ are eligible
      For regimen that are administered until progression, for example maintenance therapies, the documentation of a minimal duration of 60 days of MR or better is considered sufficient for a patient to qualify for the study.
   b. Relapsed-and-refractory defined as therapy that meets both of the following:
      - patient has relapsed to at least one prior line;
      - and patient was refractory to another line (except proteasome inhibitors), by either not reaching a MR, or progressed while under this therapy, or within 60 days of its last dose;
4. Patient has measurable disease at study screening [redacted]
5. Patient treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, is eligible. Two weeks

[redacted]

must have lapsed since last date of radiotherapy, which is recommended to be a limited field. Patient who require concurrent radiotherapy should have entry to the protocol deferred until the radiotherapy is completed and 2 weeks have passed since the last date of therapy

6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
7. Patient has the following laboratory values within 3 weeks before starting study drug (lab tests may be repeated, as clinically indicated, to obtain acceptable values before failure at screening is concluded but supportive therapies are not to be administered within the week prior to screening tests for ANC or platelet count)
   a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 /L
   b. Platelet count ≥ 75 x 10^9 /L
   c. Serum potassium, magnesium, phosphorus , within normal limits (WNL) for Institution
   d. Total calcium (corrected for serum albumin) or ionized calcium greater or equal to lower normal limits (> LLN) for institution, and not higher than CTCAE grade 1 in case of elevated value

Note: Potassium, calcium, magnesium, and/or phosphorus supplements may be given to correct values that are < LLN

   e. AST/SGOT and ALT/SGPT ≤ 2.5 x ULN
   f. Serum total bilirubin ≤ 1.5 ULN (or ≤ 3.0 x ULN if patient has Gilbert syndrome)
   g. Calculated creatinine clearance ≥ 30 ml/min
8. Patient has provided written informed consent prior to any screening procedures
9. Patient is able to swallow capsules
10. Patient must be able to adhere to the study visit schedule and other protocol requirements
11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at baseline
12. Written informed consent for the main study must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness
13. Patients must avoid consumption of grapefruit, 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.

5.3 Exclusion criteria

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

1. Patients who have progressed under all prior lines of anti-multiple myeloma therapy (primary refractory)
2. Patients who have been refractory to prior Proteasome inhibitors (i.e. did not achieve at least a MR, or have progressed under it or within 60 days of last dose)
3. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression

[redacted]

4. Patient has shown intolerance to BTZ or to dexamethasone (Dex) or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information
5. Patient has grade ≥ 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination within 14 days before enrollment
6. Patient needing valproic acid for any medical condition during the study or within 5 days prior to study treatment
7. Patient received prior treatment with DAC inhibitors including PAN
8. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted. Anti-RANKL antibody (Denosumab) can be also maintained if commenced prior to screening period.)
9. Patient has secondary primary malignancy < 3 years of first dose of study treatment (except for treated basal or squamous cell carcinoma, or in situ cancer of the cervix).
10. Patient who received at least one of the following
    a. prior anti-myeloma chemotherapy or medication including IMiDs and Dex ≤ 3 weeks prior to first dose 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 first dose of study treatment
    c. prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior first dose of study treatment
    d. Stem cell transplant ≤ 3 weeks prior to start of study treatment
11. Patient has ≥ grade 2 CTCAE from all therapy-related toxicities associated with above listed treatments
12. Patients who have not recovered from side effect of prior surgery to < grade 2 CTCAE
13. Patients with evidence of mucosal or internal bleeding
14. Patient has unresolved diarrhea ≥ grade 2 CTCAE
15. Patient has impaired cardiac function, including any one of the following:
    a. Known LVEF < 40%, as determined by echocardiogram (ECHO) or Multiple Gated acquisition (MUGA)
    b. obligate use of a permanent cardiac pacemaker
    c. congenital or acquired long QT syndrome
    d. presence of uncontrolled ventricular tachyarrhythmia
    e. resting bradycardia defined as < 50 beats per minute
    f. QTcF > 450 msec on screening ECG
    g. complete left bundle branch block (LBBB), bifascicular block
    h. any clinically significant ST segment and/or T-wave abnormalities
    i. presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria
    j. myocardial infarction or unstable angina pectoris ≤ 12months prior to starting study drug

[redacted]

k. symptomatic congestive heart failure (New York Heart Association class III-IV)
l. other clinically significant heart disease and vascular disease (e.g. uncontrolled hypertension

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 PAN (e.g. ulcerative disease, uncontrolled nausea, vomiting, malabsorption syndrome, obstruction, or stomach and/or small bowel resection)
18. Patient has a known history of HIV seropositivity or history of active/treated hepatitis B or C (a test for screening is not required)
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping all study treatment. 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). For female subjects on the study 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.

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.

21. 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 in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

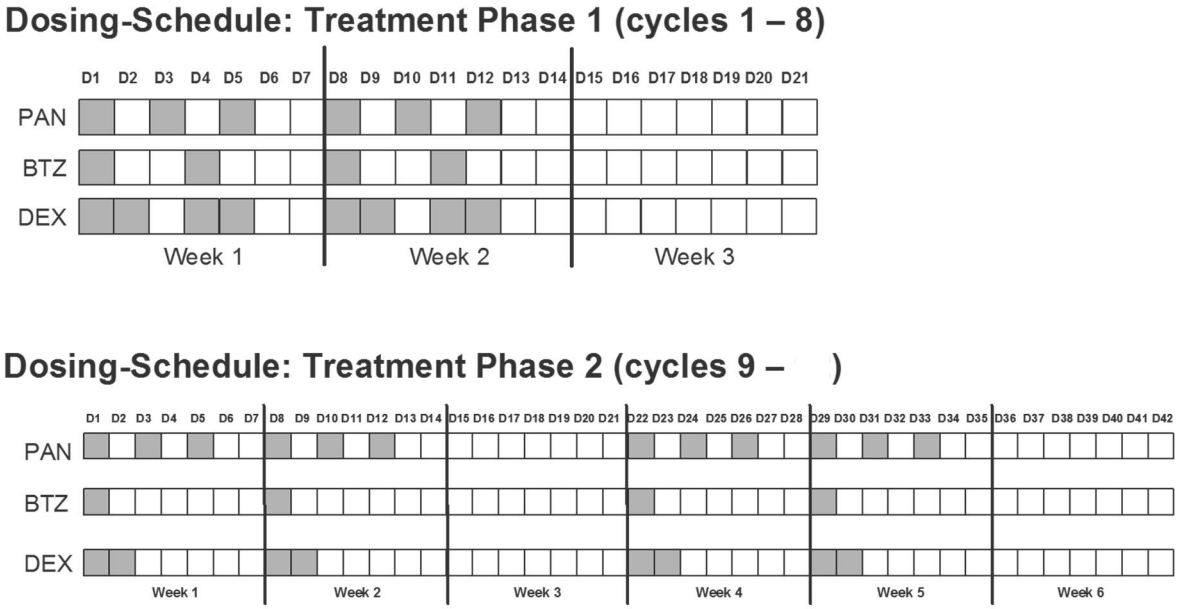
Panobinostat (PAN) is the study drug in this trial. Study treatment refers to combination treatment with PAN, Bortezomib (BTZ) sc and dexamethasone (Dex).

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Treatment Phase 1: Cycles 1- 8, 3 week cycle (21 days)			
Drug	PAN	BTZ s.c	Dex
Dose	20 mg	1.3 mg/m^2	20mg
Regimen	Days: 1, 3, 5 8, 10, 12	Days: 1, 4 8, 11	Days: 1, 2, 4, 5 8, 9,11, 12
Treatment Cycle duration	21 Days	21 Days	21 Days
Treatment Phase 2: Cycles 9 -			
Drug	PAN	BTZ s.c	Dex
Dose	20 mg	1.3 mg/m^2	20mg
Regimen	Days: 1, 3, 5 8, 10, 12 22, 24, 26 29, 31, 33	Days: 1 8 22 29	Days: 1, 2 8, 9 22, 23 29, 30
Treatment Cycle duration	42 Days	42 Days	42 Days
Note: For PAN / BTZ/Dex dose modifications due to toxicity during a treatment cycle, please refer to Section 6.3			

Figure 6-1 Dosing schedules in the treatment period 1 and treatment period 2



In both, TP 1 and TP2, every effort must be made to dose the patient with PAN on the same 3 days of the week consistently throughout the study (e.g. if Cycle 1 day 1, 3, 5 is a Monday, Wednesday, Friday; for subsequent cycles/weeks dosing must again be on Monday, Wednesday, Friday). To allow for some flexibility (e.g. scheduled dose day is a Monday which happens to be a holiday or patient forgets to take the dose), it is permitted to change the original weekly schedule if necessary on any given week throughout the study, and to then return to the original schedule once appropriate as long as there is no dosing on consecutive days.

Treatment delays due to toxicities and/or scheduling issues are allowed but consecutive doses of PAN must be separated by a minimum of 30 hours. Continuous day dosing (e.g. Day 1 and Day 2 or Day 8 and Day 9 etc.) is not permitted. If a patient experiences an adverse event that leads to a dose delay, in order to ensure adequate exposure to panobinostat for restarting the drug, patients should be monitored at least weekly for resolution of adverse events that have led to dose delays.

Dose of PAN may be taken with or without food except for on Day 1 and Day 8 of Cycle 1 in case PK sampling will be conducted.

In the event that the patient does not take the daily dose at the specified routine time, unrelated to toxicity (for example, the patient forgets), but the dose can be taken within 12 hours of the specified time, then s/he may take the daily dose at that time. If more than 12 hours have passed, that day's dose must be withheld, and the patient must wait to take the dose until the next scheduled treatment day. The patient will then continue treatment with the original dosing schedule.

Each dose of PAN should be taken with a large glass (approximately 240 mL) of non-carbonated water. Patients should be instructed to swallow the capsules whole and not chew them.

[redacted]

If vomiting occurs during the course of treatment, then no re-dosing of the patient is allowed before the next scheduled dose.

Patients must avoid grapefruits, grapefruit juice, Seville oranges and Seville orange juice during the entire study period.

6.1.2 Ancillary treatments

Not Applicable

6.1.3 Rescue medication

Not Applicable

6.1.4 Guidelines for continuation of treatment

Patients may continue treatment provided no tolerability issues are present (See Section 6.3) and criteria for discontinuation are not met (see Section 7.1.3)

6.1.5 Treatment duration

All patients will receive study treatment until completion of Treatment Phase 1 at week 24 (eight three-week cycles). Patients may be discontinued from study treatment earlier due to disease progression, unacceptable toxicity and/or study treatment discontinued at discretion of the investigator. Patients with clinical benefit at the end of Cycle 8 as per investigator assessment (achieving ≥ NC at the end of Cycle 8) may continue study treatment for up to week 48 (four additional six-week cycles) as Treatment Phase 2. After week 48, patients who investigators will judge continuous treatment provide benefit based on risk/benefit assessment may continue in Treatment Phase 2 as an optional extension. They will follow the same assessments with the same frequency until disease progression or the End of study whichever comes first.

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Study drug compliance and accountability

6.2.1.1 Study drug compliance

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.

6.2.1.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of PAN 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

[redacted]

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 Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.2.1.3 Handling of other study treatment

Not applicable.

6.2.2 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study treatment. These dose adjustments may consist of withholding dosing and/or reductions in the dose being administered. Dosing should be withheld if the physician determines it is in the best interest of the patient.

All dose modifications must be recorded on the Dosage Administration Record form.

Patients unable to tolerate the minimum dose level of Dex may continue on rest of therapy without Dex.

Patients requiring discontinuation of BTZ s.c due to peripheral neuropathy may continue on PAN and Dex (or without Dex) BTZ s.c may be restarted at any time during treatment phases 1 and 2 if clinically indicated and in accordance with the local prescribing instructions for BTZ.

Patients requiring permanent discontinuation of BTZ s.c due to any other reason or permanent discontinuation of PAN must discontinue study treatment and be followed for PD/relapse and survival.

Before starting a next cycle, patient monitoring should be performed and dose delay may be considered by investigator in case patients experience AEs which are not recovered. If a patient requires a dose delay > 21 days from the intended day of the next scheduled dose, the patient should be discontinued from the study treatment. If, however, the patient was clearly benefiting from study treatment and the cause of delay has resolved, the patient may be able to restart study treatment upon agreement of the Investigator and the Sponsor. This option should be used with highest amount of caution keeping the safety of the patient in mind and evaluate if the benefit for the patient outweighs the risks.

6.3.2 Panobinostat - dosing modifications and delay

Patients should continue to receive therapy until progressive disease or relapse is documented, or study treatment is not tolerated. If study drug-related toxicities are observed, treatment can

[redacted]

be resumed only if these toxicities have resolved to the baseline level or to CTCAE ≤ grade 1, or as otherwise specified in the protocol.

The dose of PAN may be modified for a patient as per the dosing tables below (Table 6-2, Table 6-4) during any cycle. Dose levels lower than 10 mg three times a week in combination with a minimum of 0.7 mg/m^2 BTZ s.c, with or without Dex, are not permitted at any time of the study. When and if it is determined that a patient would require a dose below 10 mg three times week in combination with the minimum dose of BTZ s.c, the patient should be discontinued from study treatment. Continuation of dosing with PAN without BTZ s.c at any dose is not permitted in TP1, nor in TP2 except in case BTZ s.c is interrupted due to peripheral neuropathy.

Table 6-2 Dosing level reductions for re-initiation of panobinostat

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

Table 6-3 is recommended for PAN - dosing modifications and delay. Investigators may use their discretion when making temporary dose interruption or dose-reduction decisions unless otherwise specified in the guidelines below.

Table 6-3 Criteria for panobinostat dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related toxicity (excluding QT prolongation)

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)		Dose Modification Guidelines At any time during a cycle of therapy (including intended day of dosing)
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia (PLT)	Grade 3 (PLT < 50 x 10^9/L) uncomplicated	No change in dosing
	Grade 4 (PLT < 25 x 10^9/L) or Grade 3 (PLT < 50 x 10^9/L) with bleeding	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then, restart at reduced dose level as per Table 6-2
In PANORAMA-1, thrombocytopenia typically recovered to baseline by the start of the next 21-day cycle. The median time to onset was one month and the median time to recovery was 12 days. Platelet transfusions may be required, if clinically indicated		
Neutropenia (ANC)	Grade 3 uncomplicated ANC < 1.0 - 0.5 x 10^9/L	Temporarily discontinue dosing until resolved to ≤ Grade 2 or baseline, then, restart at same dose level
	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue dosing until resolved to ≤ Grade 2 or baseline, then, restart at reduced dose level as per Table 6-2
	Grade 3 febrile neutropenia	Temporarily discontinue dosing until fever resolved and ANC ≤ Grade 2, then restart at reduced dose level as per Table 6-2
In case of grade 3 or 4 neutropenia, physicians should consider the use of growth factors (e.g. G-CSF) according to local guidelines.		
Anemia	Grade 2 (Hgb < 10.0 g/dL)	No change in dosing - Consider supportive measures

[redacted]

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
	Grade 3 (Hgb < 8.0 - 6.5 g/dL) or Grade 4 (Hgb < 6.5 g/dL)	Temporarily discontinue dosing and use supportive measures until resolved to ≤ Grade 2, or baseline, then, restart at reduced dose level as per Table 6-2, if required
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		Please refer to Section 6.3.2.6 and Section 7.2.2.7
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc) persisting despite the use of optimal antidiarrheal medications	Temporarily discontinue dosing until resolved to ≤ Grade 1, or baseline, then restart at unchanged dose level
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue dosing until resolved to ≤ Grade 1, or baseline, then restart reduced by one dose level
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc) despite the use of optimal antidiarrheal medications	Discontinue dosing
Note: At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication (e.g. loperamide). Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice. Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances Replacement i.v. fluids and electrolytes may be used as appropriate. Please also see Section 6.3.2.6		
Vomiting/Nausea	Grade 1 & 2 not requiring treatment or controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue dosing until resolved to ≤ grade 1, or baseline, then restart reduced by one dose level
Note: Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice. Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances		
Fatigue	Grade 3	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then: ● If resolved within 7 days after suspending dosing, then restart at an unchanged dose level ● If resolved in more than 7 days after suspending dosing, then restart dosing reduced by one dose level

[redacted]

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
	Grade 4	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then restart dosing reduced by one dose level
Note: Most of the treatments for fatigue in cancer patients are for treating symptoms and providing emotional support because the causes of fatigue that are specifically related to cancer have not been determined. Some of these symptom-related treatments may include adjusting the dosages of pain medications, administering red blood cell transfusions or blood cell growth factors, diet supplementation with iron and vitamins, and antidepressants or psychostimulants.		
HEPATIC		
Total Bilirubin	Grade 3 or 4	Temporarily discontinue dosing until resolved to ≤ Grade 2, or baseline, then restart dosing reduced by one dose level
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.		
AST/SGOT, ALT/SGPT	> 5-20 x ULN	Temporarily discontinue dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor is present), or baseline, then: ● If resolved within 7 days restart at unchanged dose level ● If resolved in more than 7 days, then reduce dosing by one dose level
	> 20 x ULN	Temporarily discontinue dosing until resolved to ≤ grade 1, or baseline, then restart dosing reduced by one dose level
All dose modifications should be based on the worst preceding toxicity. * Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)		

General guidelines for PAN dose modifications due to adverse events related to study drug are provided below. If such adverse event(s) are considered possibly related to BTZ s.c or Dex, the relevant dose-modification guidelines for each should be followed (see Section 6.6.3).

6.3.2.1 Grade 2 non-hematologic toxicity

Patients experiencing CTCAE grade 2 non-hematologic adverse event(s), 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 study treatment (PAN/BTZ/Dex), 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. Study treatment may then be restarted at the same dose and schedule or one dose level lower. If the same intolerable grade 2 adverse event(s) occurs again, PAN treatment must again be temporarily discontinued until the toxicity resolves to ≤ CTCAE grade 1 and be restarted at one dose level lower. At the discretion of the Investigator and in consultation with the Sponsor, patients with grade ≥ 2 adverse events of

[redacted]

major organs (e.g., heart, lungs, CNS) may be discontinued from further study therapy without being retreated with a dose reduction.

6.3.2.2 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 6-3, must have their treatment temporarily discontinued until the adverse event resolves to ≤ CTCAE grade 1 or baseline unless otherwise specified in Table 6-3. If the AE was considered related to PAN, the drug should then be restarted at one dose level lower. If the AE was considered not related to PAN, then therapy may be restarted (when the AE resolves to ≤ grade 1 or baseline) at the current dose.

6.3.2.3 Management of diarrhea

Patients must be instructed to contact their physician at the onset of diarrhea. Patients should be encouraged to maintain adequate oral hydration (at least 240 ml every 2 hours,) with the onset of diarrhea. Also, patients should be instructed to stop all lactose-containing products and alcohol consumption. Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. At the beginning of each cycle, each patient should be asked if they experienced any diarrhea. If symptoms were experienced, the site should question the patient regarding the actions taken for these symptoms.

Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours, not to exceed a total of 16 mg in 24 hours. Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt treatment with PAN as described in Table 6-3. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated. 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.

The use of drugs with laxative properties must be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

6.3.2.4 Infection

Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including hepatitis B virus and herpes simplex, have been reported in patients taking PAN. Of note, in PANORAMA-1, whereas grade 3 and grade 4 neutropenia were observed in 28% and 7% of patients respectively, febrile neutropenia was observed in 1% of patients. Physicians and patients should be aware of the increased risk of infection with PAN.

PAN should not be initiated in patients with active infections. Treat pre-existing infections prior to starting treatment with PAN. Monitor patients for signs and symptoms of infections during treatment with PAN; if a diagnosis of infection is made, institute appropriate anti-infective treatment.

[redacted]

6.3.2.5 Dose re-escalation

Patients receiving a reduced dose level of PAN due to toxicity 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 at least 9 scheduled doses at the reduced level have been administered and tolerated.

or

the adverse event due to which the dose was omitted/reduced is determined to be not related to PAN

Should this guidance be met, then the patient may be dose escalated as per Table 6-4.

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.

Table 6-4 Dosing re-escalation for panobinostat treatment

Current dosing level	Dose re-escalation
20 mg/day	No dose escalation allowed
15 mg/day	Increase to 20 mg/day
10 mg/day	Increase to 15 mg/day

6.3.2.6 Dose modifications of PAN 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. 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 local sites.

Patients must have QTcF < 450 msec to be eligible for the trial. If QTcF is ≥ 480 msec or above 60 msec from baseline on a pre-dose ECG patients should be followed with triplicate ECGs. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient must be discontinued from study treatment.

[redacted]

Table 6-5 Dose reductions for QTc prolongation

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

6.3.3 Combination Therapy - dosing modifications and delay

Dose modifications for bortezomib and dexamethasone may be performed based on Table 6-6 and Table 6-7 below.

Table 6-6 Dose reduction steps for BTZ s.c

Drug		Starting Dose	1st Dose Reduction	2nd Dose Reduction	3nd Dose Reduction	4th Dose Reduction
BTZ s.c.	Cycles 1-8 (TP1)	1.3 mg/m^2 twice a week 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
	Cycles 9 -12* (TP2)	1.3 mg/m^2 once a week (OW) D 1, 8, 22 & 29	1.0 mg/m^2 OW D 1, 8, 22 & 29	0.7 mg/m^2 OW D 1, 8, 22 & 29	Discontinue	
Total BTZ dose to be administered is calculated using weight determined on Day 1 of each cycle * TP2 therapy is started at dose level tolerated at completion of Cycle 8.						

Table 6-7 Dose reduction steps for Dex

Starting Dose Cycles 1-8 on Days 1, 2, 4, 5, 8, 9, 11, 12	**1st Dose Reduction**	**2nd Dose Reduction**
Cycles 1-8 on Days 1, 2, 4, 5, 8, 9, 11, 12*		
20 mg/day of administration	8 or 12 mg/day of administration	Discontinue Dex
Cycles 9-12** (TP2) on Days 1, 2, 8, 9, 22, 23, 29 and 30		
20 mg/day of administration	8 or 12 mg/day of administration on Days 1, 2, 8, 9, 22, 23, 29 and 30	Discontinue Dex
* In case of weekly BTZ administration, Dex should be administered on Day 1, 2, 8 and 9. ** TP2 therapy is started at dose level tolerated at completion of Cycle 8		

[redacted]

6.3.3.1 Dose modification guidelines

Each Adverse Event must be attributed to a study drug if possible so that modifications can be made accordingly. Reduction of one agent and not the others is appropriate if toxicity is related primarily to one of the agents. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity guidelines. Investigators can use their discretion when making dose-reduction decisions unless otherwise specified in the guidelines below.

Table 6-8 Drug related adverse events dose modification guidelines for BTZ s.c

CTCAE Category	**Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)**
Uncomplicated Gr 3 Neutropenia (ANC < 1.0 x 10^9/L) or uncomplicated Gr 3 Thrombocytopenia (PLT < 50 x 10^9/L)	No change in dosing
≥ Febrile neutropenia or Neutropenia Gr 4 (ANC < 0.5 x 10^9/L) and/or Thrombocytopenia Gr 3 (PLT < 50 x 10^9/L) with bleeding, or Gr 4 (PLT < 25 x 10^9/L)	Hold therapy until neutropenia and/or thrombocytopenia both resolve to ≤ Gr 2 ; if only one dose was omitted prior to correction to these levels, BTZ s.c should be restarted at same dose, if two or more doses were omitted - consecutively, or within the same cycle - then BTZ s.c should be restarted at a reduced dose by one dose.
Peripheral Neuropathy	See Table 6-9
Herpes Zoster reactivation any grade	Hold therapy until lesions are dry.
Other BTZ s.c related non-hematologic toxicity ≥ Gr 3	Determine attribution of toxicity and hold therapy. If toxicity resolves to ≤ Gr 2, resume therapy with one level dose reduction.

6.3.3.2 Management of patients with bortezomib-related neuropathic pain and/or peripheral sensory neuropathy

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

[redacted]

Table 6-9 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 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Gr 1 with pain or Gr 2 (interfering with function but not with activities of daily living)	Reduce by one dose level
Gr 2 with pain or Gr 3 (interfering with activities of daily living)	Hold BTZ s.c therapy until toxicity resolves to < Gr 2 When toxicity resolves, reinitiate with a reduction by one dose levels During TP2 cycles discontinue BTZ s.c
Gr 4 (Permanent sensory loss that interferes with function)	Discontinue BTZ s.c
Grading based on NCI Common Terminology Criteria CTCAE v4.03	

Table 6-10 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, decrease Dex dose by 1 dose level
	> Gr 3 (requiring hospitalization or surgery)	Hold Dex until symptoms adequately controlled. Restart and decrease one dose level of current dose 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 decrease Dex dose by 1 dose level; if edema persists despite above measures, discontinue Dex and do not resume.
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. If symptoms persist despite supportive medical intervention, discontinue Dex and do not resume.
Musculoskeletal	Muscle weakness > Gr 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease Dex dose by one dose level. If weakness persists despite supportive medical intervention, decrease dose by one 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, decrease dose by one dose level until levels are satisfactory

[redacted]

6.3.4 Follow-up for toxicities

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

Patients with transaminase increase combined with 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 PK sample, as close as possible to last dose of study drug, 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

[redacted]

"potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4 Concomitant medications

All medications (excluding study treatment components and/or any prior chemotherapy and biologic or immunologic) and significant non-drug therapies (including physical therapy and blood or platelet transfusions) administered within 14 days prior to the administration of study treatment through 30 days after the last treatment of study drug, with reasons for therapy use, will be recorded in the Prior and Concomitant medication /Surgical and Medical Procedure eCRF. Medications include not only physician prescribed medications, but also all over-the-counter medications, vitamins, herbals and alternative therapies.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study treatment. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study treatment must be listed on the Prior and Concomitant medication /Surgical and Medical Procedure after start of study treatment eCRF.

6.4.1 Permitted concomitant therapy

6.4.1.1 Growth factors

G-CSF may be initiated for an individual patient in accordance with local guideline of each site, if the patient experiences febrile neutropenia and/or grade 3 or 4 neutropenia for > 7 days. Growth factors may then be administered prophylactically in all subsequent cycles for that patient.

Patients who were receiving available recombinant erythropoiesis stimulating agents such as epoetin and darbepoietin prior to starting study treatment may continue to receive it throughout the study. Likewise these can be introduced during the study.

6.4.1.2 Bisphosphonate and anti-RANKL antibody therapy

Bisphosphonate therapy can be maintained if commenced prior to screening period. Mouth care is recommended in these patients. Anti-RANKL antibody (Denosumab) can be also maintained if commenced prior to screening period.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Anti-coagulant therapy

PAN therapy, especially in combination with BTZ, is commonly associated with moderate to severe degree of thrombocytopenia. This may lead to an increase in the risk of bleeding especially if with concomitant administration of long acting anticoagulation, such as sodium warfarin (Coumadin®). It is recommended that patients who require anticoagulation therapy while on PAN 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 PAN but for such patients, a close and frequent monitoring of the coagulation parameters, including PT/INR should be followed and they should be

maintained within a therapeutic range (suggested INR 2-3). Warfarin should be used with caution and the dose of sodium warfarin may be adjusted as needed while on study treatment. It is recommended that if the platelet count falls below 50 x 10^9 /L, withholding of thromboprophylaxis be considered to minimize the risk of bleeding.

6.4.2.2 CYP2D6 substrates

In *in vitro* assays, PAN was shown to inhibit the cytochrome P450 isoenzyme CYP2D6 at low micromolar ranges, thereby suggesting a potential risk of drug-drug interactions with concomitant medications that are also metabolized by CYP2D6. Clinical DDI study was conducted in patients where multiple PAN doses at 20 mg three-times-a-week increased Cmax and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in Tmax in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with PAN indicated that *in vivo* CYP2D6 inhibition of PAN is weak. In general, drugs that are CYP2D6 substrates and have large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are safe to be co-administered with PAN. However, caution is to be exercised when PAN is co-administered with medications that are exclusively metabolized by CYP2D6 and have a narrow therapeutic window (e.g., tamoxifen, anti-arythmics, oxycodone). Patients should be carefully monitored for potential signs of toxicity and may require dose titration or dose reduction of a CYP2D6 substrate which have narrow therapeutic window.

6.4.2.3 Drugs that can inhibit CYP3A4/5

PAN is metabolized *in vitro* by CYP3A4/5. A clinical drug-drug interaction study with ketoconazole and PAN has recently been completed. The less than 2-fold increase in PAN AUC upon co-administration with ketoconazole suggests that CYP3A contribution to the total clearance of PAN is low (40%). The observed interaction is not considered clinically relevant, as PAN doses at least 2-fold greater than 20 mg (40 and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of PAN and may be co-administered when medically necessary.

6.4.2.4 Analgesics

Baseline analgesics for tumor-related (bone) pain should be maintained during the study. However, an increase in analgesic use for control of bone pain may indicate disease progression. If an increase in analgesic medication from baseline is required during the study, the patient should be evaluated for progression of disease/bone lesions.

6.4.2.5 Anti-emetics and anti-diarrheal medications

Prophylactic anti-emetics such as granisetron can be administered at the discretion of the Investigator. Granisetron is the preferred 5HT3 antagonist, due to the possibility of QT prolongation with the other 5HT3 antagonists (e.g. ondansetron, dolasetron, etc). Their use is prohibited (see Appendix1).

At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication. See Section 6.3.2.3.

[redacted]

6.4.2.6 Medications that have the potential to alter serum electrolytes

Patients taking concomitant medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias. Electrolyte abnormalities should be corrected prior to dosing.

Other treatments, described in Section 6.4.1.2 and Section 6.4.2.7 are allowed as medically indicated and apply to the entire study duration or defined parts of the study.

6.4.2.7 Vitamin Supplements

Vitamin supplements are suggested in the event of peripheral neuropathy or for those patients deemed to be at risk, at the discretion of the investigator.

6.4.3 Prohibited concomitant therapy

See Appendix 1 for a full list of prohibited medications

- Investigational agents
- Chemo-, biologic or immunologic therapy and/or other investigational agents
- DAC inhibitors
- Strong CYP3A4/5 inducers

6.5 Patient numbering

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

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.6.1 Study drug panobinostat

Oral PAN will be supplied as 10-mg and 15-mg hard gelatin capsules and will be given on a flat scale of mg on a given day. The capsules are packaged in HDPE bottles with plastic child resistant closures or boxes. Each study site will be supplied by Novartis with study drug in identically-appearing packaging. Medication labels will be in the local language and comply with the legal requirements of Japan. They will include storage conditions for the drug (For details, see study drug handling procedure which is provided by Novartis)

[redacted]

6.6.2 Bortezomib s.c.

Bortezomib (Velcade®) is a commercially available product that will be prescribed by the investigator and will be administered by site personnel at the study site.

Refer to the Product information sheet of Velcade® (bortezomib) for detailed information on handling and precautions (Velcade® Product information sheet and applicable health authority recommendations).

6.6.3 Dexamethasone oral

Dexamethasone (LenaDex®) will be sourced locally by each investigational site. Refer to the Dexamethasone LenaDex® product information for detailed information on handling and precautions regarding the use of tablets of dexamethasone for oral administration. On days when BTZ is administered, Dex should be taken prior to BTZ administration.

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. For most visits, there is a ± 3days window on assessments to take into account scheduling over public holidays if not explicitly specified otherwise. Assessments that are required at screening visit and on cycle 1 day 1 do not have to be repeated if performed ≤ 7 days prior to cycle 1 day 1 unless otherwise specified. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Table 7-1 Visit evaluation schedule

	Category	Reference to Section	Screening	Treatment Phase																	Follow-up Phase			
				Treatment Phase 1													Treatment Phase 2				End of Treatment				
				Cycle 1 (day 1 to 21)									Cycle 2 - 8 (day 1 to 21)				After Cycle 9 (day 1 to 42)					30 day safety Follow-up	Disease Follow-up	Study Evaluation Completion	Survival
Day of cycle			**- 21 to - 1**	**1**	**2**	**3**	**4**	**5**	**8**	**9**	**10**	**11**	**1**	**4**	**8**	**11**	**1**	**8**	**22**	**29**					
Informed consent	D	7.1.1	X																					
Patient history																								
Demography	D	7.1.1	X																					
Inclusion/exclusion criteria	D	5.2, 5.3	X																					
Medical history/ current medical conditions	D	7.1.1	X																					
Diagnosis & history of MM	D	7.1.1	X																					
Prior antineoplastic therapy	D	7.1.1	X																					
Bone Marrow FISH	D	7.2.1	X																					
Administration																								
Bortezomib (BTZ)	D	6.1		X			X		X			X	X	X	X	X	X	X	X	X				
Panobinostat (PAN)	D	6.1		Days 1-3 -5 + 8-10-12 (3 times weekly, 2 weeks on & 1 week off, 3 weeks cycle)													Days 1-3-5, 8-10-12 & 22-24-26, 29-31-33 (6 weeks cycle)								

[redacted]

	Category	Reference to Section	Screening	Treatment Phase																	Follow-up Phase			
				Treatment Phase 1													Treatment Phase 2				End of Treatment				
				Cycle 1 (day 1 to 21)									Cycle 2 - 8 (day 1 to 21)				After Cycle 9 (day 1 to 42)					30 day safety Follow-up	Disease Follow-up	Study Evaluation Completion	Survival
Day of cycle			**- 21 to - 1**	**1**	**2**	**3**	**4**	**5**	**8**	**9**	**10**	**11**	**1**	**4**	**8**	**11**	**1**	**8**	**22**	**29**					
Dexamethasone (Dex)	D	6.1		Days 1-2-4-5 + 8-9-11-12													Days 1-2-8-9 + 22-23-29-30								
Physical assessments																									
Vital signs	D	7.2.2	X	X			X						X				X				X				
Height	D	7.2.2	X																						
Weight / BSA	D	7.2.2	X	X									X				X				X				
Physical examination	S	7.2.2	X	X									X				X				X				
ECOG PS	D	7.2.2	X	X									X				X				X				
Efficacy assessments																									
Investigator response assessment	D	7.2.1											X				X		X		X		X		
Electrophoresis (Serum and urine)	D	7.2.1	X	X									X				X		X		X		X		
Immunofixation (Serum and urine)	D	7.2.1	X										X				X		X		X		X		
Serum immunogloblin	D	7.2.1	X	X									X				X		X		X		X		
[redacted]																									
Skeletal survey	D	7.2.1	X																						

[redacted]

	Category	Reference to Section	Screening	Treatment Phase																		Follow-up Phase			
				Treatment Phase 1														Treatment Phase 2				End of Treatment				
				Cycle 1 (day 1 to 21)									Cycle 2 - 8 (day 1 to 21)				After Cycle 9 (day 1 to 42)					30 day safety Follow-up	Disease Follow-up	Study Evaluation Completion	Survival
Day of cycle			**- 21 to - 1**	**1**	**2**	**3**	**4**	**5**	**8**	**9**	**10**	**11**	**1**	**4**	**8**	**11**	**1**	**8**	**22**	**29**					
Evaluation of soft-tissue plasmacytomas	D	7.2.1	X										X				X		X		X		X		
CT or MRI [2]	D	7.2.1	X										X				X				X		X		
Bone Marrow	D	7.2.1	X																						
Safety assessments																									
Hematology[3]	D	7.2.2	X	X			X		X			X	X	X	X	X	X	X	X	X	X				
Coagulation	D	7.2.2	X																		X				
Biochemistry	D	7.2.2	X	X								X	X			X	X		X		X		X		
Urinalysis	D	7.2.2	X																		X				
Thyroid function	D	7.2.2	X																		X				
Pregnancy test	D	7.2.2	X	X									X				X				X				
12-lead ECG	D	7.2.2	X	X				X					X												
LVEF	D	7.2.2	X	X																					
Adverse Events	D	8.1, 8.3	X	Continuous																					
Prior/Concomitant medications	D	6.4	X	Continuous																					
Pharmacokinetics																									
PAN Blood samples	D	7.2.7		X	X	X			X	X	X														
BTZ Blood samples	D	7.2.7							X	X	X														

[redacted]

	Category	Reference to Section	Screening	Treatment Phase																	Follow-up Phase			
				Treatment Phase 1													Treatment Phase 2				End of Treatment				
				Cycle 1 (day 1 to 21)									Cycle 2 - 8 (day 1 to 21)				After Cycle 9 (day 1 to 42)					30 day safety Follow-up	Disease Follow-up	Study Evaluation Completion	Survival
Day of cycle			**- 21 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**9**	**10**	**11**	**1**	**4**	**8**	**11**	**1**	**8**	**22**	**29**					
PRO																									
QoL questionnaires	D	7.2.5	X	X									X				X							X	
Other																									
Post antineoplastic therapy	D																				X	Continuous			
Survival	D																							X	

[redacted]
2. In case of plasmacytoma is/are present at screening, assessment of that lesion(s) by MRI or CT is required at screening, and thereafter every 6 weeks during treatment phase, end of treatment and follow-up, i.e.: at day 1 of cycle 3, cycle 5, cycle 7, cycle 9, 10, 11, and 12.
3. In case of once week BTZ administration, hematology test at Day4 and Day 11 and biochemistry at day11 are not mandatory between cycle 2 to cycle 8.

[redacted]

7.1.1 Screening

Screening examination (Visit 1) is to include the procedures found in Table 7-1 and should occur within 21 days prior to baseline (C1D1). The informed consent must be signed prior to ANY screening procedure being performed.

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

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. 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. If the plasma cell count 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.

7.1.1.1 Eligibility screening

Patient eligibility will be checked by the Sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the Sponsor for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed eligibility check form to the site. The investigator site will then be allowed to assign treatment to the patient.

7.1.1.2 Information to be collected on screening failures

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

7.1.1.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. Baseline assessments will be collected as per Table 7-1.

7.1.2 Treatment period

The maximum duration of the study treatment period is 48 weeks or until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessments, refer to Table 7-1. For most visits, there is a ± 3days window on assessments.

If a patient requires a dose delay > 21 days from the intended day of the next scheduled dose, the patient should be discontinued from the study treatment. If, however, the patient was clearly benefiting from study treatment and the cause of delay has resolved, the patient may be able to restart study treatment upon agreement of the Investigator and the Sponsor.

7.1.3 Discontinuation of study treatment

Patients may voluntarily withdraw from 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 to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF 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, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Pregnancy
- Use of prohibited treatment, as described in Appendix 1
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision
- Lost to follow-up
- Death

Patients may permanently stop the study treatment for one of the following reasons:

- Technical Problems
- Protocol deviation

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1. If they fail to return for unknown reasons, every effort (e.g., telephone, email, letter) should be made to contact them as specified in Section 7.1.5.

Patients who become pregnant during the trial must be withdrawn (Section 8.3). Patients who become pregnant must cease all efficacy assessments regardless of whether or not they developed Progressive Disease.

Patients who discontinue study treatment during the treatment phase should be scheduled for a visit as soon as possible and within 7 days after the last dose of study treatment, at which time

[redacted]

all of the assessments listed for the EOT visit will be performed. If a patient withdraws from treatment at a study visit, EOT assessments do not need to be repeated. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, be contacted for safety evaluations within 30 days after the last dose of study treatment. The investigator should inquire about any AE observed/concomitant medication taken during this 30-day period. This can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last study treatment.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the survival status.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a patient discontinues study treatment, but continues study assessments, (e.g. during post treatment follow up phase as detailed in Table 7-1), the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the End of Post Treatment Phase Disposition (Study Phase Completion) eCRF page.

Patients who discontinue study treatment should enter the survival follow-up period or continue tumor assessments when appropriate. For patients who discontinue treatment for reasons other than documented disease progression, relapse 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, withdrawal of consent or End of study.

7.1.3.1 Additional guidance for premature withdrawal

If a patient will have no further study data collected because he/she withdraws from the study completely, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment Phase Completion eCRF as applicable. The investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. If the patient was still taking study medication at the time of the withdrawal, the End of Treatment eCRF should also be completed.

Patients may voluntarily withdraw from the study or be discontinued from the study at the discretion of the investigator at any time.

7.1.4 Withdrawal of Consent

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

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

If a patient withdraws consent, the investigator should make a reasonable effort to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

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

7.1.5 Follow up period

7.1.5.1 Safety follow up

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of study treatment at the end of treatment phase.

The investigator should inquire about any AE observed/concomitant medication taken during this 30-day period. This can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last study treatment.

7.1.5.2 Post-Treatment Follow-up

If a patient completes or discontinues study treatment in the absence of PD or relapse, disease assessments every 6 weeks +/- 3 days should continue to be performed from the EOT visit until PD/relapse(by investigator), death, lost to follow-up, withdrawn consent to efficacy follow-up occurs or End of study; however, safety assessments do not need to continue to be performed. If a patient decides to discontinue from the study treatment, they must be asked if they agree for continuation of efficacy assessments in absence of dosing with study treatment. Antineoplastic therapies since completion or discontinuation of study treatment will continue to be collected.

Once the patient ceases disease follow-up, the reason for completion should be recorded on the Study Phase Completion Disposition eCRF page.

7.1.5.3 Survival follow-up

All patients who had PD/relapse as per investigator assessment or withdrew consent from further study assessments will subsequently be followed for survival information every 12 weeks +/- 14 days until death, lost to follow-up, withdrawal of consent for survival follow-up or the End of study. The investigator or his designee will collect this survival information and any new anti-neoplastic therapies for all patients until the final survival analysis.

Follow-up can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last dose of the study treatment.

7.1.5.4 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 M-protein, immunoglobulins fractions (serum and urine)

M-protein and immunoglobulins fractions (measured by Protein Electrophoresis) must be performed at visits indicated in Table 7-1. A 24hr urine sample must be collected for the assessments. More frequent assessments may be performed if medically indicated as determined by the Investigator, and these evaluations should be recorded on the Unscheduled Visit eCRF.

Per modified EBMT criteria any assessment indicating a response needs to be repeated after 6 weeks to confirm the response level.

If progressive disease is suspected based on M-protein result a repeat assessment is required to confirm PD. No time window applies for the confirmation of PD. It is recommended to repeat the assessment as soon as possible.

Assessments are to be performed at the central laboratory, [redacted]

7.2.1.2 Immunofixation (serum and urine)

Immunofixation assessment will be performed to qualify and to confirm any response better than PR at visits indicated in Table 7-1. Assessments are to be performed at the central laboratory, [redacted]

7.2.1.3 Serum immunoglobulins

Serum immunoglobulins assessment will be performed at visits indicated in Table 7-1. Assessments are to be performed at the central laboratory, [redacted]

[redacted]

7.2.1.5 Bone Marrow

A bone marrow (BM) aspirate will need to be collected for a plasma cell (PC) count, FISH and standard cytogenetics at visit indicated in Table 7-1 and at the following times. PC count will be performed at each trial center at:

[redacted]

- Screening, to determine eligibility
- On study, a repeat bone marrow aspirate for PC count is required, within 3 weeks of other disease assessments results suggestive of CR per EBMT criteria (not nCR), in order to qualify CR, [redacted] by flow cytometry at the central laboratory, LSI. All efforts should be taken to not delay BM aspirate PC count when other criteria for CR are met

Standard cytogenetics will be assessed at each trial center at screening visit.

[redacted]

7.2.1.6 Skeletal survey (bone X- ray)

Skeletal survey should be performed at screening. If results of a skeletal survey performed within 8 weeks prior to screening visit are available, and if there is no clinical indication to repeat, then skeletal survey need not to be repeated at screening visit.

Bone X-ray oriented by symptom location (e.g. bone pain), are to be performed if medically indicated and to assess PD as determined by the Investigator, and these evaluations should be recorded on the Unscheduled Visit eCRF.

7.2.1.7 Evaluation of soft- tissue plasmacytomas

Soft tissue plasmacytoma must be assessed by clinical examination at visit indicated in Table 7-1. In case of findings at any time, assessment by MRI or CT is required.

7.2.1.7.1 Plasmacytoma present at screening

If plasmacytoma(s) is already known or detected at screening, in addition to repeating clinical assessment as described above, assessment by CT or MRI is required every 6 weeks as mentioned Table 7-1. The same imaging technique should be used throughout the trial.

More frequent assessments should be performed in case of findings or if medically indicated as determined by the Investigator. These evaluations should be recorded on the Unscheduled Visit eCRF. The same imaging technique should be used throughout the trial.

7.2.1.8 Serum calcium variables

Hypercalcemia will be assessed for disease evaluation during study until end of follow-up. The total serum calcium, serum albumin or ionized serum calcium assessment as part of the biochemistry assessments is to be performed at visit indicated in Table 7-1. Assessments are to be performed at each trial center.

7.2.2 Safety assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 8.

[redacted]

7.2.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study center. For the assessment schedule refer to Table 7-1.

7.2.2.2 Vital signs

Vital signs include body temperature, respiratory rate, sitting blood pressure and sitting pulse measurements. For the assessment schedule refer to Table 7-1.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. BSA will be calculated as defined by the institution or as published in (Mosteller et al 1987). Height will be measured at screening only. For the assessment schedule for weight refer to Table 7-1.

7.2.2.4 Performance status

ECOG performance status will be assessed as per the assessment schedule (refer to Table 7-1).

Assessment of ECOG performance status (Table 7-2) will be performed within the time windows described above of the scheduled assessment, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-2 ECOG performance status scale

Score	Performance Status
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 housework, 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

7.2.2.5 Laboratory evaluations

The standard clinical laboratory analyses described Table 7-3 are to be performed by the study site's local laboratories according to Table 7-1. Laboratory tests will be collected and analyzed on the scheduled day, even if study medication is being withheld. More frequent examinations may be performed at the investigator's discretion if medically indicated and these results should be recorded on the Unscheduled Visit eCRFs as applicable.

[redacted]

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (Local)	Hemoglobin, Platelets, Red blood cells, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Biochemistry (Local)	BUN, β-2 Microglobulin, creatinine, sodium, potassium, Fasted glucose, total calcium (corrected for serum albumin) or ionized calcium, albumin, total protein, total bilirubin, LDH, alkaline phosphatase, AST/SGOT, ALT/SGPT, phosphorous and magnesium. If total bilirubin > ULN, direct and indirect bilirubin should be performed.
Coagulation (Local)	Prothrombin time (PT) or International normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen
Urinalysis (Local)	Dipstick examination includes: protein, glucose, blood, and specific gravity Microscopic examination is only required if dipstick result is abnormal, it includes: WBC/HPF, RBC/HPF
Thyroid (Local)	T3 [free], T4 [free], TSH

7.2.2.6 Pregnancy and assessments of fertility

During screening, all pre-menopausal women who are not surgically sterile will have a serum hCG-β pregnancy test. On Cycle 1 Day 1 prior to dosing and at subsequent cycles and at EOT, serum or urinary pregnancy test will be performed. A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study treatment.

7.2.2.7 Electrocardiogram (ECG)

12-lead ECGs will be performed at a minimum at visits indicated in Table 7-1 as indicated in Table 7-4. With regard to Cycle1 day5, pre-dose ECGs can be done on Cycle1 Day 4 visit when patient is at the site for BTZ s.c administration but not post-dose ECGs of Day 5 as relative to PAN dosing. All ECGs will be read at each trial center.

Table 7-4 ECG assessment monitoring schedule

Cycle	Day of cycle	ECG monitoring
	Screening	3 sequential ECGs separated by at least 5-10 minutes
Cycle 1	1, 5	Pre-dose: Single ECG Post-dose at 3 hours ± 0.5 hour: Single ECG
Cycle 2-8	1	Pre-dose: Single ECG
QTcF interval, QTcB interval, QT interval, RR interval, PR interval, QRS duration and ventricular rate are collected to eCRF. QTc F: Heart rate corrected QT interval using the Fredericia formula: QTc=QT/RR0.33		

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

A baseline MUGA scan or echocardiogram to assess LVEF will be performed at visits indicated in Table 7-1. At day 1 Cycle 1 unless the above screening assessment was correct and obtained ≤ 7 days prior to first administration of study treatment. If the result from this MUGA/ECHO shows a clinically relevant change (e.g. a reduction of >5% or as defined by the institution), a formal cardiac evaluation should be sought and a repeat MUGA/echo be conducted at the

[redacted]

beginning of every-other treatment cycle (or at the discretion of the cardiologist/investigator). More frequent assessments may be performed if medically indicated as determined by the Investigator, and these evaluations should be recorded on the Unscheduled Visit eCRF.

7.2.3 Tolerability

In addition to general safety data, information on dose reductions will be collected.

7.2.4 Resource utilization

Not applicable

7.2.5 Patient reported outcomes

The Functional Assessment of Cancer Therapy Gynecology Oncology Group Neurotoxicity scale (FACT/GOG-NTX) is an 11 item measure to assess neurotoxicity from systemic chemotherapy. The recall period for this measure is the past 7 days.

Patient questionnaires should be completed before any study drug administrations at the visits indicated in Table 7-1. Questionnaires should be completed in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. Attempts should be made to collect all questionnaires for all patients, including those who discontinue prior to the study evaluation completion visit.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, should be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

7.2.6 Pharmacokinetics

PK sample collection will be performed in patients who agree to blood samplings for the PK assessments of PAN and BTZ.

The following conditions are to be followed on the days of PK: Each patient should have a meal (breakfast) shortly before administration of any components of study treatment. The order of administration of the three study treatment components will be 1) PAN, 2) Dex and 3) BTZ.

PK sampling schedule is as follows, i.e. at:

- C1 D1, prior to dosing of PAN, BTZ s.c and Dex
- C1 D1, serial blood collection following dosing of PAN, BTZ s.c and Dex
- C1 D2 and D3, 2 samples (24 hrs and 48 hrs post C1D1 dose)
- C1 D8, prior to dosing of PAN, BTZ s.c and Dex
- C1 D8, serial blood collection following dosing of PAN, BTZ s.c and Dex
- C1 D9 and D10, 2 samples (24 hrs and 48 hrs post C1D8 dose)

PK collections for both BTZ and PAN may be collected at the same time (6 mL of whole blood at the common collection time points) provided that dose administration of BTZ s.c and PAN

[redacted]

is in tandem. Please record dosing time for each drug and collection times on the appropriate eCRF pages.

At specified time points (Table 7-5 and Table 7-6), 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 and BTZ, 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. Plasma will be aliquoted and transferred to a polypropylene screw-cap tube, the tube capped, and the sample mixed briefly and then immediately placed in a freezer set at ≤ -60ºC until shipment to the central laboratory for both PAN and BTZ plasma PK samples. Refer to the [LBH589D1201 PK Laboratory Manual] for detailed instructions for the collection, handling, and shipping of samples.

Residual plasma samples after drug concentration measurement may be used for further pharmacokinetic investigations for PAN and BTZ (e.g., protein binding, metabolism, etc).

Table 7-5 Pharmacokinetic blood collection log for panobinostat

Dose Reference ID		PK Sample number	Cycle (Period number)	Study day	Time	Blood volume (mL)
1		1	1	1	0 (pre-dose)	2
1		2	1	1	0.5 h	2
1		3	1	1	1 h	2
1		4	1	1	2 h	2
1		5	1	1	3 h	2
1		6	1	1	4 h	2
1		7	1	1	8 h	2
1		8	1	2	24 h	2
1		9	1	3	48 h (before day 3 dosing)	2
2	201*	10	1	8	0 (pre-dose)	2
2		11	1	8	0.5 h	2
2		12	1	8	1 h	2
2		13	1	8	2 h	2
2		14	1	8	3 h	2
2		15	1	8	4 h	2
2		16	1	8	8 h	2
2		17	1	9	24 h	2
2		18	1	10	48 h (before day 10 dosing)	2
Total volume						36
Unscheduled samples						
NA	NA	100x	NA	NA	Unscheduled	2

[redacted]

Dose Reference ID	PK Sample number	Cycle (Period number)	Study day	Time	Blood volume (mL)
*: Dose reference ID to collect previous dose information Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002,…(for panobinostat) Note: The plasma samples collected for PAN PK will be also used for measurement of the metabolite BJB432, if feasible.					

Table 7-6 Pharmacokinetic blood collection log for bortezomib

Dose Reference ID		PK Sample number	Cycle (Period number)	Study day	Time	Blood volume (mL)
3	301*	101	1	8	0 (pre-dose)	4
3		102	1	8	0.083 h	4
3		103	1	8	0.25 h	4
3		104	1	8	0.5 h	4
3		105	1	8	1 h	4
3		106	1	8	2 h	4
3		107	1	8	3 h	4
3		108	1	8	4 h	4
3		109	1	8	8 h	4
3		110	1	9	24 h	4
3		111	1	10	48 h (before day 10 dosing)	4
Total volume						44
Unscheduled samples						
NA	NA	200x	NA	NA	Unscheduled	4
*: Dose reference ID to collect previous dose information Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002,…(for bortezomib)						

7.2.7 PK sample labelling

The pharmacokinetic samples will be labeled as Table 7-7.

Table 7-7 PK sample labelling

Study Code:	CLBH589D1201
Study drug	panobinostat (PAN) or bortezomib (BTZ)
Subject Number:	_____ (e.g. 0501-00001)
Date of Collection: dd/mm/yr	Day____ Month _____ Year_____
Sample Number:	See Table 7-5 and Table 7-6
Cycle and study day	See Table 7-5 and Table 7-6

All label information should be prepared on the label.

7.2.8 Analytical method

7.2.8.1 Panobinostat

Plasma samples for PAN PK will be assayed for concentrations of PAN (and the metabolite, BJB432, if feasible) using a validated liquid chromatography-tandem mass spectrometry assay

[redacted]

(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.

7.2.8.2 Combination agent - bortezomib

The plasma samples for BTZ PK will be assayed for concentrations of BTZ with a validated LC-MS/MS assay with LLOQ of approximately 0.1 ng/mL. Values below LLOQ will be reported as zero. Missing values will be labeled accordingly.

7.2.9 PK analysis

PK parameters listed in Table 7-7 will be calculated from concentration-time data for PAN (and the metabolite BJB432, if feasible) and BTZ using Phoenix WinNonlin (Pharsight, Mountain View, CA).

Table 7-8 Noncompartmental pharmacokinetic parameters of panobinostat and bortezomib

AUClast	The AUC from time zero to the last measurable concentration sampling time (Tlast) (ng*h/mL)
AUC0-24h	The AUC from time zero to 24 h (ng*h/mL)
AUC0-48h	The AUC from time zero to 48 h (ng*h/mL)
AUCinf	The AUC from time zero to infinity (ng*h/mL)
Cmax	The maximum (peak) observed plasma concentration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration (h)
Lambda_z	The terminal elimination rate constant (h^{-1})
T1/2	The elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (h)
CL/F	The apparent total body clearance of drug from the plasma (L/h)
Vz/F	The apparent volume of distribution during terminal phase (associated with Lambda_z) (L)
These parameters will be calculated if feasible. For a metabolite BJB432, the same parameters will be calculated, except for CL/F and Vz/F, if feasible.	

8 Safety monitoring and reporting

8.1 Adverse events (AEs)

8.1.1 Definitions and reporting

An AE 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 AEs 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).

AEs that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded

[redacted]

in the Medical History page of the patient's eCRF. AE monitoring should be continued for at least 30 days following the last dose of study treatment. AEs (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 AE.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death eCRF. The occurrence of AEs 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. AEs 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:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study drug (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study drug (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

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

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 (for example, as per EBMT criteria for MM), 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 drug.

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 eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - 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

[redacted]

8.2.2 Reporting

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

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form within 24 hours Novartis. 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 sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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

8.3 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment

of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

8.4 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.

8.5 Data Monitoring Committee

Not applicable.

8.6 Steering Committee

Not applicable.

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

[redacted]

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

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

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

9.4 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification

[redacted]

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 relating to protein electrophoresis, immunofixation, immunoglobulin and PK will be processed centrally and the results will be sent electronically to Novartis.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. Once 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.

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

10 Statistical methods and data analysis

The primary analysis of study data will be performed when all patients have been treated for 24 weeks or discontinued treatment. Additionally, follow-up efficacy and safety data will also be summarized in a separate report.

In the review process of panobinostat submission for indication of relapsed or refractory MM in Japan, [redacted] requested sponsor to conduct additional interim report to present the key efficacy and safety information in public per approximately 6 months basis. Prior to the primary analysis time point, no statistical testing will be conducted as key efficacy in the interim report.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who took at least one dose of study treatment.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication.

10.1.3 Pharmacokinetic analysis set

The pharmacokinetic analysis set for PAN (PAS-PAN) consists of all patients with at least one evaluable PK data of PAN. PAS-BTZ consists of all patients with at least one evaluable PK data of BTZ.

10.2 Patient demographics/other baseline characteristics

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

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

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

Data on the study treatment administration will be summarized. The duration of treatment and relative dose intensity of each of the components of study treatment will be summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized.

10.4 Primary objective

The primary objective of the study is to assess efficacy of panobinostat (PAN) by nCR+CR rate after all patients have been treated for 8 cycles or discontinued treatment. The nCR+CR rate is based on modified EBMT criteria per investigator assessment in patients with relapsed multiple myeloma or relapsed and refractory multiple myeloma.

10.4.1 Variable

The proportion of patients with a near Complete Response (nCR) or complete response (CR) as their best overall response is definition for nCR+CR rate. The nCR+CR rate will be assessed according to modified EBMT criteria.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be based on a single-sample binomial test (normal approximation) at the one-sided 5% significance level, analyzed in the FAS.

The study targets the nCR+CR rate of 25%. A response rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. Therefore the null and the alternative hypothesis are defined as follows: Ho: nCR+CR rate $\leq$ 10%, Ha: nCR+CR rate > 10%.

10.4.3 Handling of missing values/censoring/discontinuations

For the purposes of the primary analysis, patients with a best overall response of ‘Unknown’ (UNK) will be treated as non-responders in estimating the nCR+CR rate in the FAS.

10.5 Secondary objectives

The key secondary objective is to evaluate progression free survival (PFS), defined as time from first dose of study treatment to progression or death due to any cause per investigator in patients with relapsed multiple myeloma or relapsed and refractory multiple myeloma.

Other secondary efficacy objectives are to evaluate overall response rate (ORR), overall survival (OS), minimal response rate (MRR), time to response (TTR), time to progression/relapse (TTP) and duration of response (DOR).

The secondary safety objective is to assess safety of the combination therapy.

The secondary pharmacokinetic objective is to assess the PK of PAN and bortezomib (BTZ) in a subset of patients.

[redacted]

Population and grouping for the analyses

The secondary efficacy variables will be analyzed using the FAS. For all safety analyses, the safety set will be used. For all PK analyses, pharmacokinetic analysis sets will be used.

10.5.1 Key secondary objective(s)

Progression free survival (PFS) is defined as the time from first dose of study treatment to progression or death due to any cause.

Survivorship functions will be estimated by using the Kaplan-Meier product-limit method and displayed as graphs. Median PFS time and its two-sided 95% confidence intervals will be reported.

A patient who has not progressed/ relapsed, or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy would have his/her PFS censored at the time of the last adequate response assessment before or at the cut-off date or before start of further anti-cancer therapy. An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

10.5.2 Other secondary efficacy objectives

Other secondary efficacy variables include overall response rate (CR, nCR or PR), minimal response rate (MRR), time to response (TTR), time to progression/relapse (TTP) and duration of response (DOR). The assessment of these endpoints will be based on modified EBMT criteria per investigator assessment.

Overall response rate (ORR) is defined as the proportion of patients with CR or nCR or PR.

Overall survival (OS) is defined as time from first dose of study treatment to death.

Time to response (TTR) is the time between date of first dose of study treatment until first documented response (CR or nCR or PR).

Duration of response (DOR) is defined as the time from the first documented occurrence of response (PR or nCR or CR) until the date of the first documented disease progression or relapse or death due to multiple myeloma.

Time to progression/relapse (TTP) is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression or relapse.

Estimated ORR along with corresponding 95% confidence intervals will be presented.

Estimated MRR along with corresponding 95% confidence intervals will be presented.

Median TTR, DOR and TTP along with corresponding 95% confidence intervals will be presented.

ORR, MRR, TTR and TTP will be analyzed based on the FAS. However, DOR will be analyzed based on data from responders (CR or nCR or PR) in the FAS.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

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 30+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

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

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

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

10.5.3.3 Laboratory abnormalities

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

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

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

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

10.5.3.4 Other safety data

ECG

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

[redacted]

Vital signs

Definitions of notably abnormal results have to part of the RAP.

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

10.5.4 Pharmacokinetics

Summary statistics (n, arithmetic mean, median, SD, geometric mean, coefficient of variation CV (%) and geometric CV (%), minimum and maximum) will be presented for plasma concentrations of PAN (and its metabolite BJB432, if feasible) and BTZ at each scheduled time point for each analyte. Graphical presentation will also be provided on mean concentration at each scheduled time point for each analyte. PK parameters will be calculated from individual concentration-time data for each analyte. Summary statistics will be presented for all PK parameters except Tmax. For Tmax, only median, minimum, and maximum values will be presented.

10.5.5 Biomarkers

Not applicable.

10.5.6 Patient-reported outcomes

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.

Calculated scores and changes from baseline will be summarized by visit.

In addition, for each domain and item of FACT/GOG-NTX questionnaires, summaries will be provided for changes from baseline for each response category of the Global Change Question as indicated by the patient and the investigator at C3D1, C7D1, and post-treatment assessment.

[redacted]

10.7 Interim analysis

Not applicable.

10.8 Sample size calculation

Sample size assumptions in this trial are based on the data from the PANORAMA-1 study, which enrolled a similar patient population; i.e. patients with relapsed multiple myeloma or

[redacted]

relapsed-and-refractory myeloma. Considering BTZ was currently widely used in newly diagnosed MM and relapsed/refractory MM in Japan, it is expected that most patients in this study have BTZ containing regimen as a prior line of therapy. Based on the data from the PANORAMA-1 study, for patients previously treated with BTZ , the nCR+CR rate for PAN is expected to be around 25 %. nCR+CR rate of 10 % or less is considered as an insufficient level of activity for the proposed patient population. Based on the normal distribution, approximately 33 patients are required to reject a null hypothesis of nCR+CR rate ≤ 10% vs. a target nCR+CR rate of 25% or more, with a one-sided alpha of 0.05 and at least 80% power.

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 Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB -approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

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

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

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Publication of study protocol and results.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as //clinicaltrials.gov. Interim data will be published periodically. 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 trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

[redacted]

electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

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14 Appendices

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

14.1.1 Medication prohibited during the treatment period

The following medications are prohibited:

- Any investigational medication (other than PAN)
- Chemo-, biologic or immunologic therapy and/or other investigational agents 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.
- Any medication which is known to be a strong CYP3A4 inducer* (e.g. avasimibe, carbamazepine, Phenobarbital, phenytoin, rifabutin, or St. John's wort). Co-administration of rifampin, a strong CYP3A4 inducer is expected to decrease exposure of BTZ by at least 45%. Efficacy may be reduced when Velcade® is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving Velcade®.

*This list of strong CYP3A4 inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; from the University of Washington's Drug Interaction Database; and from Pursche et al (2008). 6. Any use of hematopoietic growth factor receptor agonists (including but not limited to:erythropoietin, romiplostim, or eltrombopag).

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

14.1.2 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 of the medications listed in Table 14-1 and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a PAN clinical study, will be excluded from the study. Patients enrolled in a PAN 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 PAN treatment (e.g., for 72 hours) during administration with these drugs or withheld medications in Table 14-1 for at least 72 hours when PAN 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 PAN especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

[redacted]

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

[redacted]

^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 PAN.

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:

//azcert.org/medical-pros/drug-lists/drug-lists.cfm (Version 3/25/2008).

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, see Table 14-3) has been associated with Torsades de points and QT prolongation but has not been shown to cause Torsades de pointes. Therefore, ondansetron is not per se prohibited to be combined with PAN but caution is to be exercised and close monitoring for signs and symptoms of QT prolongation is recommended.

14.1.3 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

PAN is a substrate of CYP3A4 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 PAN in study [CLBH589B2110].

Multiple ketoconazole doses at 400 mg increased Cmax and AUC of PAN by 1.6- and 1.8-fold, respectively, but with no change in Tmax or half-lives in 14 cancer patients. The less than 2-fold increase in PAN AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as PAN doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg) have been safely administered in patients. Thus, co-administration of PAN with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of PAN treatment related adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and PAN is medically indicated or investigated in a clinical study.

BTZ is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2. Co-administration of ketoconazole, increased the exposure of BTZ by 35% in 12 patients. Therefore, patients should be closely monitored when given BTZ in combination with strong CYPA4 inhibitors (e.g. ketoconazole, ritonavir).

Patients with impaired liver function (as defined by NCI CTEP criteria) are recommended not to receive PAN concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

[redacted]

Table 14-2 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics* • telithromycin • troleandomycin
Antifungals (azoles) • ketoconazole • itraconazole • posaconazole • voriconazole
Antidepressants • nefazodone
HIV protease inhibitors: • indinavir • nelfinavir • ritonavir • saquinavir • lopinavir
Miscellaneous drugs or products • [2]Star fruit and pomegranate product and juice • conivaptan
* azithromycin and regular orange juice are allowed. Although clarithromycin is a known strong CYP3A inhibitor, it is also known to prolong QT intervals which is listed in Table 14-1 and is prohibited to be taken with PAN. 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 complied by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at //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: //medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp.

14.1.4 Medications which are known CYP2D6 substrates to be used with caution

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

Multiple PAN doses increased Cmax and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in Tmax in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with PAN indicated that in vivo CYP2D6 inhibition of PAN is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with PAN.

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a

[redacted]

narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).

Table 14-3 Medications which are known CYP2D6 substrates to be used with caution

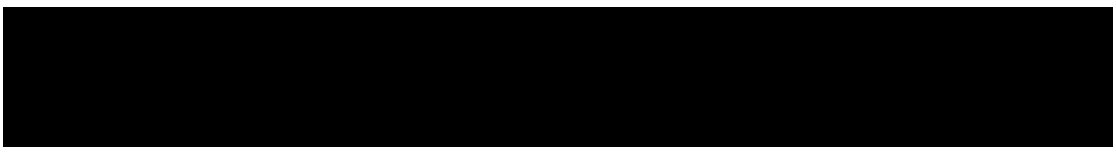
Beta blockers (listed below):	**Antipsychotics (listed below):**
S-metoprolol	aripiprazole
propafenone	haloperidol
timolol	risperidone
Antidepressants (listed below):	thioridazine
amitriptyline	**Antiarrhythmics (listed below):**
clomipramine	mexilletine
desipramine	flecainide
imipramine	**Others (listed below):**
fluoxetine	codeine
paroxetine	dextromethorphan
venlafaxine	tamoxifen
duloxetine	tramadol
Antiemetics (listed below):	
ondansetron^	
^Intravenous dolasetron is a CYP2D6 substrate and contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Please see Table 14-1.	

14.1.5 Medications which are known to be moderate inducers of CYP3A4 are to be used with caution

During the study, the use of moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, talviraline, tipranavir) is discouraged, and investigators should seek alternatives where possible. However, any concomitant use of moderate CYP3A4 inducers must be documented.

This is not a comprehensive list of medications which may induce 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: //medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp, and “drug interaction database” from University of Washington.

[redacted]



14.4 Appendix 4: Protocol Post-text Supplement - Guidelines for response assessment in Multiple Myeloma

[redacted]

NOVARTIS

Novartis Oncology

Clinical Development
and
Biometrics and Data Management

Study no: CLBH589D1201

Harmonization of Efficacy Analysis of Multiple Myeloma Studies

Protocol Post-text Supplement: Guidelines for response assessment in Multiple Myeloma

Authors: [redacted]

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Release date: 23-Oct-2009

[redacted]

List of abbreviations

Abbreviation	Details
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
BL	Baseline
BM	Bone marrow
CR	complete response
CT	Computed tomography
DAR	Dose administration record
DFS	Disease-free survival
diff	difference
DOR	Duration of response
decr.	Decrease
(e)CRF	(electronic) Case Report Form
[redacted]	[redacted]
[redacted]	[redacted]
incr.	Increase
[redacted]	[redacted]
MM	Multiple myeloma
MR	Minor response
MRI	Magnetic resonance imaging
NC	No change
nCR	Near-complete response
ORR	Overall response rate
OS	Overall survival
PC	Plasma cells
PD	Progressive disease
PEP	Protein electrophoresis
PFS	Progression-free survival
PR	Partial response
RAP	Report and analysis plan
[redacted]	[redacted]
[redacted]	[redacted]
SPD	Sum of the products of the diameters
TNT	Time to next treatment
TTR	Time to response
[redacted]	[redacted]

[redacted]

14.4.1 Introduction and scope

This document provides the working definitions and specifications for consistent and efficient analyses of efficacy for Novartis clinical studies assessing antineoplastic activity in multiple myeloma (MM).

This document is based on the following classification systems:

- Uniform response criteria from the European Group for Blood and Bone Marrow Transplant (EBMT), International Bone Marrow Transplant Registry (IBMTR) and the American Bone Marrow Transplant Registry (ABMTR) (Bladé et al 1998), including modifications as used consecutively by Richardson et al (2003), Richardson et al (2005), Orlowski et al (2007), San Miguel et al (2008), and these response criteria will be referred to as the modified EBMT criteria.

[redacted]

The modified EBMT criteria for multiple myeloma are well established, endorsed by major institutions and health authorities, and widely used in clinical trials.

[redacted]

While making decisions on response criteria for primary, secondary [redacted] efficacy endpoints of a clinical trial on multiple myeloma, the above situation needs to be taken into account.

Other references were used to add recommendations (e.g. SWOG 2009).

The objectives of this document are:

- to ensure that the definitions of responses in a clinical study protocol correctly reflect modified EBMT criteria in the target patient population

[redacted]

- to provide guidance for the response assessment and clinical monitoring to ensure consistency with modified EBMT criteria in the target patient population.

[redacted]

Moreover, this document describes data handling and derivation rules. Respective sections may be used in the report and analysis plan (RAP) to provide further details. As for a usual Novartis template, comments are written in *italic* font. The protocol and RAP authors must take these comments into consideration and provide project or study specific details in the protocol. Specifically, definitions highlighted in **bold *italic*** font must be discussed, defined and then documented in the study protocol. Any deviations to this guideline must be clearly specified in the protocol with justification.

[redacted]

14.4.2 Efficacy Assessments

Efficacy assessments based on modified EBMT [redacted] criteria are discussed in this section. Common assessments and issues associated with both modified EBMT [redacted] criteria are discussed in Section 14.4.2.1. Assessments and issues associated with specific response criteria are discussed in Section 14.4.2.2 (modified EBMT criteria) [redacted]

14.4.2.1 Assessments - General

14.4.2.1.1 Assessment of response

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 and also to the classification system used*
2. *schedule for response assessments should be included in the protocol*
3. *appropriate confirmation response assessments should be indicated in the protocol*
4. *guideline on following-up patients for PD or relapse (relapse is applicable for modified EBMT criteria only) 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 (e)CRF (i.e. not merged from several sources), if possible.

14.4.2.1.2 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 level in serum as well as in urine

1. Protein electrophoresis (PEP): Provides quantitative measurements
2. Immunofixation (IF): Provides qualitative measurements (Present/absent). This is a more sensitive method than PEP.

The following are disease measurability criteria based on serum and urine M-protein measured by PEP:

1. Serum M-protein ≥ 1 g/dL
2. Urine M-protein ≥ 200 mg/24h.

The PEP has to be performed to assess serum and urine M-protein levels at baseline and post baseline. Both serum and urine M-protein should be measured by PEP routinely at post baseline even if the disease is non-measurable based on one or both of the criteria above at baseline.

Absence of serum/urine M-protein should be determined by Immunofixation.

Laboratory to laboratory variability in regard to assessments performed by PEP and IF could potentially be high. So, central laboratory for PEP and IF is recommended, specially for single arm non-randomized studies.

[redacted]

14.4.2.1.3 Assessment of bone marrow for percent plasma cell

Bone marrow should be assessed for percent plasma cell. This assessment can be performed in terms of bone marrow aspirate and/or biopsy. The same method (aspirate versus biopsy) should be used throughout the trial, if possible. In case both aspirate and biopsy were done, the response criteria need to be satisfied by the both assessments.

Bone marrow samples can be drawn from either sternum or iliac crest. Percent plasma cell will be determined by using cytological examination.

In case of inadequate/uninterruptible bone marrow sample, the sampling must be repeated in a timely manner.

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

Bone marrow sample collection process can be uncomfortable to patients. Standard practice is to perform bone marrow assessment only when it is essential. Therefore, recommendation is for performing bone marrow assessments under the following conditions:

1. to confirm some response categories
2. in case of clinical symptoms indicating issues associated with plasma cell in bone marrow

If bone marrow assessment for percent plasma cell was done at post baseline then results from this assessment must be used in determining PD/relapse (relapse is applicable for modified EBMT criteria only). Otherwise, PD/relapse will be determined based on mandatory assessments (See Section 14.4.2.2.3 and Section 14.4.2.3.7) and available (if there is any) non-mandatory assessments only.

14.4.2.1.4 Assessment of soft tissue plasmacytomas

The following steps should be used to assess soft tissue plasmacytomas:

1. Each patient should be clinically examined for soft tissue plasmacytoma in each visit for response assessments.
2. For baseline or new soft tissue plasmacytoma(s) at post-baseline, in case of appearance or clinical suspicion of appearance of a soft tissue plasmacytoma, imaging by using CT or MRI should be performed to confirm and to determine size and location of the soft tissue plasmacytoma (if exists).
3. In case of existing soft tissue plasmacytoma(s) at baseline, size and location of soft tissue plasmacytoma(s) will be monitored and documented on the (e)CRF regularly by imaging according to the requirements of the individual study protocol. In addition, in between two consecutive assessments by CT/MRI, clinical examinations can be performed to monitor existing soft tissue plasmacytoma(s).
4. Size and location of identified soft tissue plasmacytoma(s) should be captured on the (e)CRF.

[redacted]

- The size should be captured in terms of longest perpendicular diameters
- If any of the perpendicular diameters can not 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.
- A value of 0 mm X 0 mm should be entered in case of disappearance of a soft tissue plasmacytoma

The same imaging technique should be used to assess soft tissue plasmacytoma of a patient throughout the course of the trial, if possible.

The size of the soft tissue plasmacytomas is defined as the sum of the products of the cross-diameters (SPD) of each soft tissue plasmacytoma using the longest perpendicular diameters.

A definite increase in the size is defined as a $\geq$ 50% increase (and at least 10 mm^2) of this sum from the nadir.

CT and MRI should be performed with slice thickness $\leq$ 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 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 part of the soft tissue plasmacytoma should contribute to the SPD.

14.4.2.1.5 Assessment of lytic bone lesions

Full body (in 13 different body regions) skeletal survey using conventional X-rays or CT or MRI should be performed on every patient prior to treatment start. Overall interpretation (in terms of presence or absence of lytic bone lesion) of full body skeletal survey will be captured on the (e)CRF.

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

The same imaging technique should be used to assess lytic bone lesions of a patient throughout the course of the trial, if possible.

14.4.2.1.6 Assessment of serum calcium levels

For each response classification, the determination of corrected serum calcium levels is required. The correction will be done according to the following formula (Ladenson et al 1978):

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

[redacted]

14.4.2.1.7 Baseline assessments

The following baseline assessments are mandatory:

- PEP in urine and serum M-protein
- Plasma cell count in bone marrow
- Clinical examinations for soft tissue plasmacytomas. In case of known or detectable soft tissue plasmacytoma at baseline, further measurements are required at baseline by imaging techniques (CT/MRI)
- Full body skeletal survey using imaging techniques X-ray.
- Routine biochemistry including total serum calcium and albumin

For baseline assessments, no confirmation measurement is required.

14.4.2.1.8 Response assessments

Assessments to determine PD are largely dependent on change from 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.

If contradictory results are observed from different tests then all contradicting tests should be repeated unless PD is confirmed.

14.4.2.1.9 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 less than 4 weeks prior to the first intake of study treatment/randomization.

All measurements required for a response assessment should be performed within a predefined time window. It is recommended to align this time window with the treatment cycle length.

Unless PD/relapse (relapse is applicable for modified EBMT criteria only) is observed, response status can not be determined if there is incomplete/missing response assessment within a time window. In this case, “unknown” will be used as response status for this time window.

In case of more than one measurements of any variable in the predefine time window, the latest non-missing measurement of this variable will be used. **Exception:** In case of one measurement qualifying for PD/relapse, this will be used for the response assessment irrespective of subsequent measurements of the same variable.

14.4.2.1.10 Response assessment by time point

The response assessment depends on the data of the respective measurements. In case the current assessment is not the first post-baseline assessment, response assessment also depends on previous response assessment.

For the first post baseline assessment, the rules as provided in Table 14-4 (modified EBMT criteria) [redacted] apply.

The general rule for subsequent assessments is that - except the classification of PD/relapse (relapse is applicable for modified EBMT criteria only) or unknown - only a “better” response

[redacted]

can be assigned for a specific time point. If the assessment does not allow for a better assessment the previous confirmed response class will be retained provided that there are sufficient data to support this. Therefore, at a given time point, there are four possibilities:

1. Maintaining the current response status, OR
2. Obtaining a better response, OR
3. Having PD/relapse (relapse is applicable for modified EBMT criteria only)
4. Unknown

14.4.2.1.11 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/relapse (relapse is applicable for modified EBMT criteria only). In case of PD/relapse, 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.

14.4.2.2 Response assessment - modified EBMT criteria

14.4.2.2.1 Measurable disease

For the modified EBMT criteria, a patient is considered to have measurable disease if at least one of the following two conditions is true at baseline:

1. Serum M-protein ≥ 1 g/dL
2. Urine M-protein ≥ 200 mg/24h

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

14.4.2.2.2 Eligibility

If response assessments for primary and secondary objectives are based on modified EBMT criteria, then only those patients who have measurable disease according to Section 14.4.2.2.1 should be included in the trial.

14.4.2.2.3 Mandatory assessments

All assessments listed in Section 14.4.2.1.7 should be performed at baseline.

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

1. PEP serum M-protein
2. PEP urine M-protein
3. Soft-tissue plasmacytoma
4. Serum calcium and albumin

Note: Both serum and urine M-protein should be measured by PEP routinely at post baseline even if the disease was not measurable based on serum or urine M-protein measured by PEP at baseline.

[redacted]

14.4.2.2.4 Response assessment

Response assessment according to modified EBMT criteria is described in Table 14-4 and presented in flow charts (Figure 14-1 to Figure 14-4).

Table 14-4 Response classification in MM according to modified EBMT criteria

Response category	Definition
Complete response (CR)	• Absence of M-protein in serum and urine by immunofixation, maintained ≥ 6 weeks (presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR), AND • < 5% plasma cells in bone marrow. No confirmation on bone marrow plasma cell (additional assessment) is needed to document CR except patients with non-secretory myeloma where the bone marrow examination must be repeated after an interval of at least 6 weeks, AND • In case of presence of lytic bone lesion(s) at baseline, no increase in size or number of lytic bone lesions (development of a compression fracture does not exclude CR), AND • In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytoma
Near-complete response (nCR)	All criteria of CR apply except that absence of serum and urine M-protein can not be confirmed by immunofixation. Note: This category is not part of the original EBMT criteria (Bladé 1998). It is introduced to enable comparisons to other pivotal clinical trials in MM (e.g. Richardson et al 2003, Richardson et al 2005, Orlowski et al 2007, San Miguel et al 2008).
Partial response (PR)	• reduction in serum M-protein as measured by PEP from baseline either by ≥ 50% or to < 1 g/dL, maintained for ≥ 6 weeks AND • reduction in 24h urine M-protein as measured by PEP from baseline either by ≥ 90% or to < 200 mg, maintained ≥ 6 weeks, AND • ≥ 50% reduction from baseline in the size of soft tissue plasmacytomas (by CT/MRI), AND • no increase in size or number of lytic bone lesions (development of a compression fracture does not exclude PR) • for patients with non-secretory myeloma, in addition to the above, ≥ 50% reduction from baseline in plasma cells in a bone marrow aspirate and/or on biopsy (if both available then “and”, otherwise “or”), maintained for ≥ 6 weeks
Minimal response (MR)	• 25 to <50% reduction from baseline in serum M-protein as measured by PEP and absolute value is still ≥ 1 g/dL, maintained for ≥ 6 weeks, AND • 50 to < 90% reduction from baseline in 24h urine M-protein as measured by PEP and absolute value is still ≥ 200 mg/24h, maintained for ≥ 6 weeks, AND • 25 to < 50% reduction from baseline in the size of soft tissue plasmacytomas (by CT/MRI) AND • no increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude MR) • For patients with non-secretory myeloma, in addition to the above, 25 to <50% reduction from baseline in plasma cells in a bone marrow aspirate and/or on biopsy, maintained for ≥ 6 weeks
No change (NC)	• not meeting the criteria of either CR, nCR, PR, MR or PD/relapse

[redacted]

Response category	Definition
Relapse from CR	● reappearance/presence of serum or urine M-protein on immunofixation or PEP confirmed by ≥ one further investigation and excluding oligoclonal immune reconstitution, OR ● ≥ 5% plasma cells in a bone marrow aspirate or on bone biopsy, OR ● development of new soft tissue plasmacytoma(s),or reappearance of soft tissue plasmacytomas, OR ● development of new lytic bone lesions or increase in the size of lytic bone lesions (development of a compression fracture does not exclude continued response and hence does not indicate PD), OR ● development of hypercalcemia (corrected serum calcium >11.5 mg/dL, see Section 14.4.2.1.6) not attributable to any other cause. In case of preexisting hypercalcemia at baseline, this criterion applies only in case the corrected serum calcium level was ≤11.5 mg/dL during the course of the study. This criterion does qualify for relapse even if no previous calcium assessment. There is no given time frame for the confirmation measurement of serum or urine M-protein. A repetition and confirmation at any time qualifies for relapse.
Progressive disease (PD)*	● 25% increase from nadir in the serum M-protein as measured by PEP which must also be an absolute increase from nadir of at least 0.5 g/dL and absolute value of serum M-protein ≥ 1.0 g/dL, and confirmed by at least one repeated investigation, OR ● 25% increase from nadir in the 24h urine M-protein as measured by PEP which must also be an absolute increase from nadir of at least 200 mg/24h and confirmed by at least one repeated investigation, OR ● 25% increase from nadir in plasma cells in a bone marrow aspirate or on biopsy which must also be an absolute increase from nadir of at least 10%, OR ● increase from baseline in size of existing lytic bone lesions, OR ● development of new lytic bone lesion (development of a compression fracture does not exclude continued response and does not indicate PD), OR ● definite increase (Section 14.4.2.1.4) from nadir in size of existing soft tissue plasmacytomas, OR ● development of new soft tissue plasmacytomas, OR ● development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will only be assessed due to the hypercalcemia criterion in case the corrected serum calcium level was ≤ 11.5 mg/dL post-baseline and increased thereafter beyond 11.5.g mg/dL. There is no given time frame for the confirmation measurement of serum or urine PEP. A repetition and confirmation at any time qualifies for PD.
* only for patients not being in CR 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.	

14.4.2.2.5 Time frame of response assessments

Instructions in Section 14.4.2.1.9 should be followed.

In addition, confirmation assessments for a response should be performed at least 6 weeks after the initial diagnosis of response.

Confirmation assessments for PD (only required for PEP measurements) should be performed as soon as possible.

[redacted]

14.4.2.2.6 Confirmation of response

To qualify for a CR, nCR, PR or MR, a confirmation measurement needs to be repeated, after at least 6 weeks. Declaring PD, if based on PEP measurements, also requires confirmation. Confirmation of PD (if based on PEP measurements) should be performed as soon as possible.

The following rules apply:

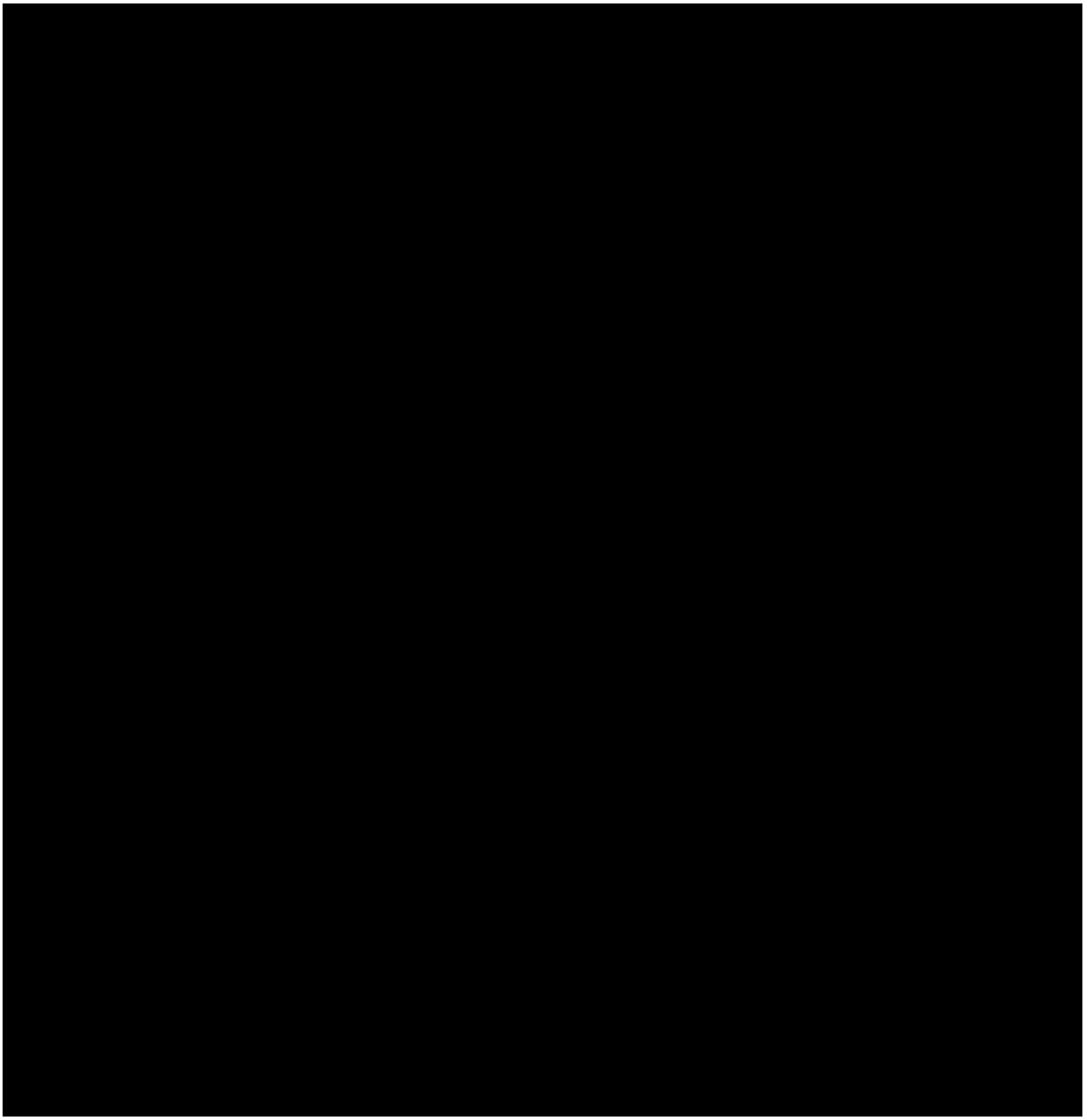
- For confirmation of a CR, the following assessments are mandatory, after 6 weeks:
  - Immunofixation in serum and urine
  - Percent plasma cell in bone marrow (only in patients with non-secretory myeloma)
- For confirmation of nCR, PR or MR, the following assessments are mandatory, after 6 weeks:
  - Serum and urine M-protein measured by PEP
  - Percent plasma cell in bone marrow (only in patients with non-secretory myeloma)
- For confirmation of relapse, the following assessments are mandatory, as soon as possible:
  - Only if relapse is indicated by serum M-protein: Serum M-protein assessed by immunofixation
  - Only if relapse is indicated by urine M-protein: Urine M-protein assessed by immunofixation
- For confirmation of PD, the following assessments are mandatory, as soon as possible:
  - Only if PD is indicated by serum M-protein: Serum M-protein measured by PEP
  - Only if PD is indicated by urine M-protein: Urine M-protein measured by PEP

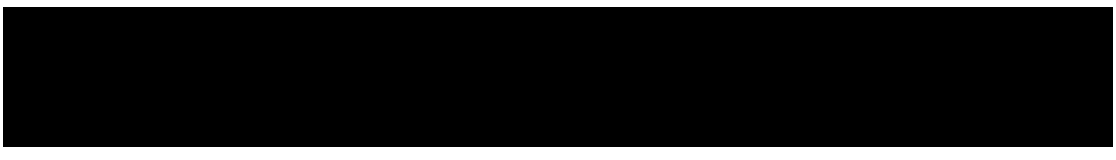
There is no need to repeat CT/MRI for plasmacytoma(s), X-ray/CT/MRI for lytic bone lesion(s) and assessment of corrected serum calcium for confirmation purpose.

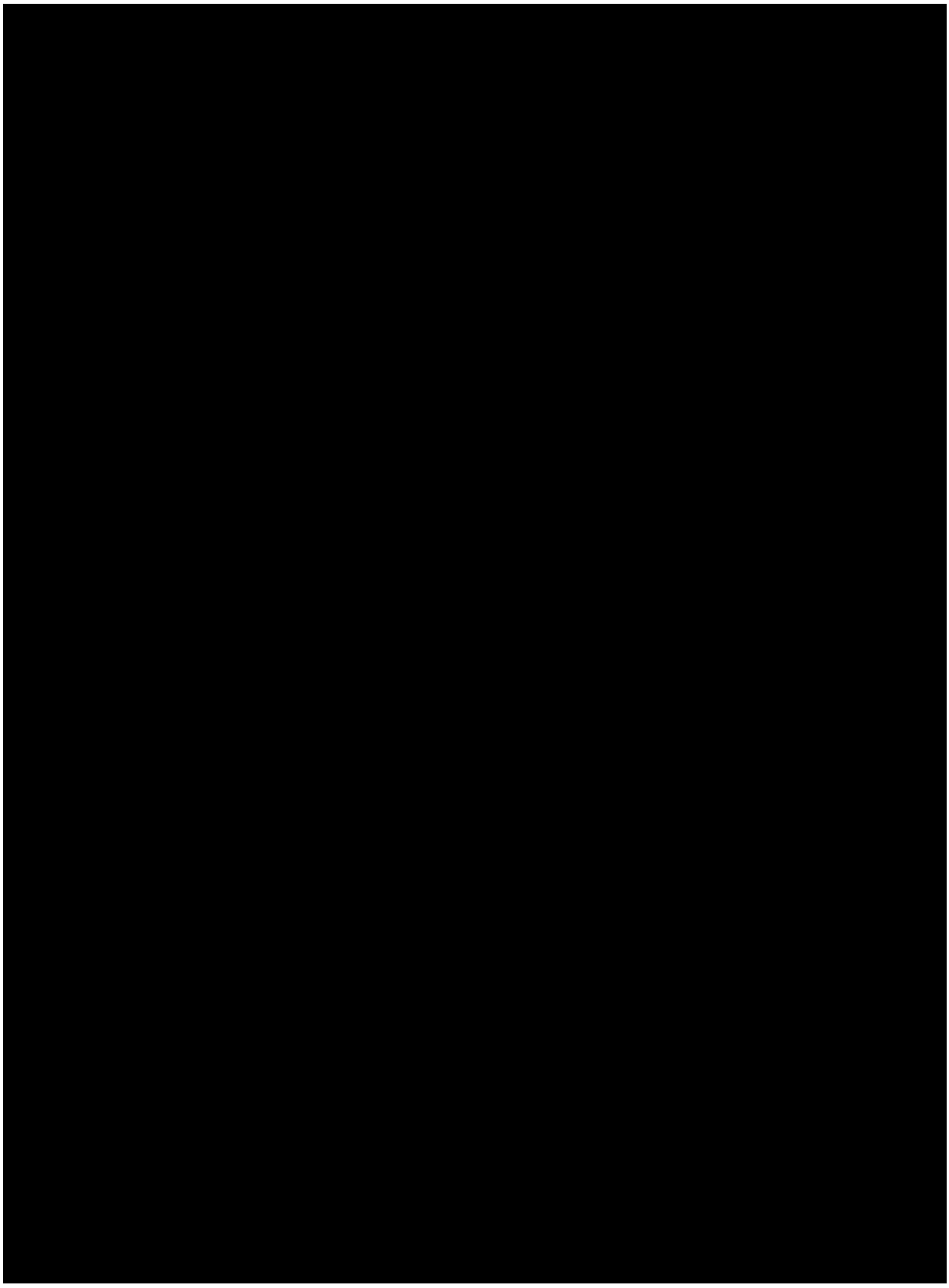
If the confirmation assessments indicate a worse response category compared to the unconfirmed response category, then this worse response category will be considered as confirmed. If the confirmation assessments indicate a better response category compare to the unconfirmed response category, then the unconfirmed response category will be considered as confirmed. In this case, subsequent response assessments should be performed 6 weeks after the confirmatory assessment for the purpose of confirmation of the observed better response.

[redacted]

[redacted]







[redacted]

14.4.3 Capturing response classification

Response classification can be obtained/determined from two different sources:

1. Response classification provided by investigators
2. Response classification derived from data collected in the (e)CRF

Source of response classification to use in the protocol defined efficacy analyses should be pre-specified. In general, response classification provided by investigators will be used in the main analyses associated with protocol objectives.

In case of assessing response by [redacted] modified EBMT [redacted] criteria, the investigator should assess response only in terms of the primary classification system.

The best overall response can be determined and captured in (e)CRF by investigators.

14.4.4 Data sources

The data sources refers to disease-specific (e)CRF standard modules. It is not appropriate to deviate from these specifications

Table 14-7 Data sources

Data	CRF module	Specification	Relevant for [redacted]	Relevant for Modified EBMT
Response	Laboratory standard module	Value for serum calcium and serum albumin	[redacted]	Yes
	Adverse events	Hyperviscosity*	[redacted]	No
	Bone marrow standard module	Aspirate or biopsy can be used. Relevant variable is the count of plasma cells	[redacted]	Yes
	Flow cytometry	Determination of aberrant plasma phenotypes in bone marrow	[redacted]	No
	Plasmacytoma module	Capturing size and localization as well as examination technique	[redacted]	Yes
	Bone lesion module	Capturing lesion size and location as well as imaging technique	[redacted]	Yes
	PEP	Serum and urine M-protein assessment	[redacted]	Yes
	Immunofixation	Serum and urine M-protein assessment	[redacted]	Yes
	FLC module	Immunoassay of serum for determination of FLC	[redacted]	No

[redacted]

Data	CRF module	Specification	Relevant for [redacted]	Relevant for Modified EBMT
	PCR module	ASO-PCR module for bone marrow PC	[redacted]	No
	MM investigator's response assessment	Capturing response categories as defined in Section 14.4.5.1 (separate module for modified EBMT [redacted])	[redacted]	Yes
Time frames	various	See list of variables in the response assessment part of this table. For each of these assessments the date needs to be captured. For definition of baseline use time of first use of study treatment (DAR standard module).	[redacted]	Yes

DAR - Dose administration record [redacted]

14.4.5 Derivation rules

14.4.5.1 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 treatment/randomization until PD/relapse or end of study, whatever comes first.

If the first complete post-baseline response assessment indicates, for example, PR or better (For EBMT nCR and CR, [redacted]) and no confirmation response assessment available then NC for EBMT criteria [redacted] will be considered as best overall response. For the case of MR in EBMT, similar approach will be considered to determined the best overall response.

Best overall response will be assigned according to the classification system in the following ascending order (Table 14-8).

[redacted]

Table 14-8 Best overall response by classification system

Best overall response category	Classification		Modified EBMT rank		Comment
CR			Yes	1	-
nCR		-	Yes	2	-
PR			Yes	3	-
MR			Yes	4	
NC		-	Yes	5	
Unknown			Yes	6	
PD			Yes	7	.

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 who had valid disease assessment at baseline.

14.4.5.2 Calculation of time-to-event variables

In case more than one response classification systems are used, the underlying response classification system to derive each of the time-to-event endpoints should be clearly specified in the protocol.

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 treatment will be used as end date (duration = 1 day), i.e. time to event variables will never be negative.

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".

Note: The term "relapse" used in the following sections is applicable for the modified EBMT criteria only.

14.4.5.2.1 Overall survival

Overall survival (OS) is defined as the time from date of randomization/start of 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.

14.4.5.2.2 Progression-free survival

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

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

14.4.5.2.3 Duration of response

>> If the following variable is analyzed, it should be stated that this analysis might introduce a bias as it includes only responders. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response. The analysis of duration of responses should only be used as a descriptive analysis. If they are used as inferential comparison between treatments, clear justification must be given in the protocol. It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed 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/relapse or death due to multiple myeloma.

In case a patient does not have PD/relapse 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.

14.4.5.2.4 Time to response

Time to response (TTR) is defined as the time between date of randomization/start of 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/relapse 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/relapse will be censored at their last adequate response assessment date which is different from “unknown” or “not done”.

[redacted]

14.4.5.2.5 Time to relapse

Time to relapse is usable for modified EBMT criteria and is defined as the time between date of first documented CR to the date of first documented relapse.

In case a patient does not have relapse, time to relapse will be censored at the date of the last adequate assessment.

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

[redacted]

14.4.5.3 Incomplete assessment dates

All investigation dates (e.g. X-ray, bone marrow aspirate) must be completed with day, month and year. If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date.

[redacted]

If all measurement dates have no day recorded, the 1st day of the month is used for PD/relapse and last day of the month will be used for other response categories.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.4.5.4 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.4.5.5 Event and censoring date, sensitivity analyses

This section outlines the possible event and censoring dates for PD/relapse (Table 14-9), 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 14-9 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/relapse at scheduled assessment date or before next scheduled assessment	(1) Date of PD/relapse (2) Date of next scheduled assessment	Event Event
C1	PD/relapse or death after **exactly one** missing assessment	(1) Date of PD/relapse (or death) (2) Date of next scheduled assessment[1]	Event Event
C2	PD/relapse 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/relapse (or death)	Censor Event Event
D	No PD/relapse	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease PD/relapse' without documented PD/relapse, i.e. clinical PD/relapse based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical PD/relapse was determined)	Ignored Event
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Deaths due to reason other than multiple myeloma	(1) Date of last adequate assessment	Censor (only TTP and TNT)
[1] PD/relapse			

>> The primary analysis and the sensitivity analyses must be specified in the Study Protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

[redacted]

Situations C (C1 and C2): PD/relapse 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/relapse 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/relapse' without documented PD/relapse: By default, option (1) is used for situation E as patients without documented PD/relapse should be followed for PD/relapse after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If PD/relapse 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 14-9 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 [redacted] modified EBMT 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.

[redacted]

14.4.6 Medical review of investigator's response assessment

In case the investigator assesses response in the (e)CRF, this assessments 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 PD, the respective patients' response needs to qualify the criteria for this category as defined in this document.

[redacted]

14.4.7 References (available upon request)

Bladé J, Samson D, Reece D, et al (1998) Criteria for evaluating disease response and PD in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Brit J Haem 102:111-1123

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San Miguel JF, Schlag R, Khuageva NK (2008) Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma. N Engl J Med 359:906-917

Orlowski RZ, Nagler A, Sonneveld P et al (2007) Randomized Phase III Study of Pegylated Liposomal Doxorubicin Plus Bortezomib Compared With Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression. JCO 25(25):3892-3901

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[redacted]

SWOG - Southwest Oncology Group (2009) Response assessment myeloma. Chapter 11C. Revision 2009, 13p

[redacted]

14.4.8 Appendices

On the flow charts, start the assessment at the upper box of the respective chart and follow the arrows downwards in a stepwise manner. A diamond represents a decision with a “Yes” or “No” outcome. The response assessment stops at a colored box which provides the response category. A circle indicates that a flow chart continues at another page as indicated in legend.

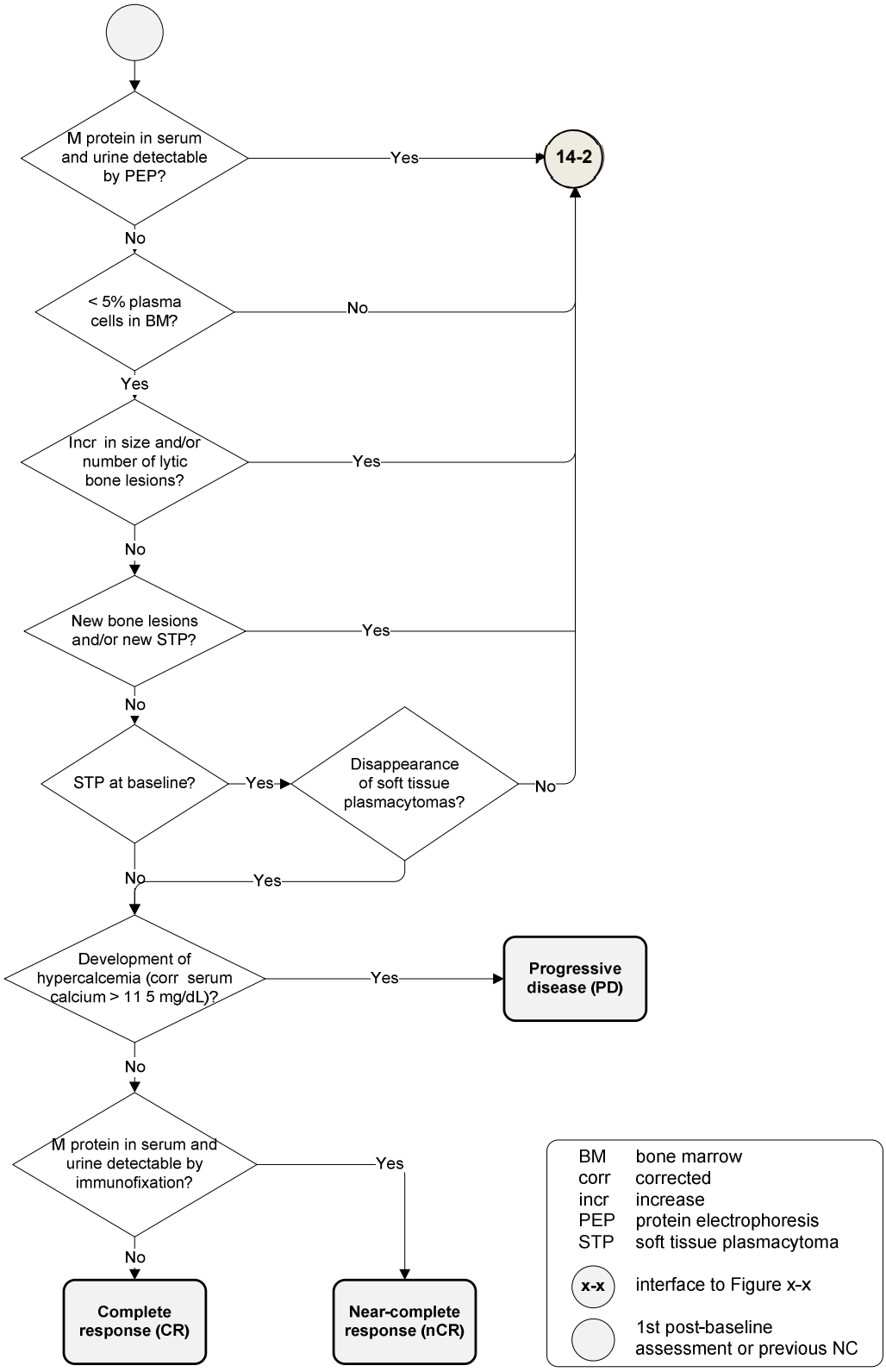
Appendix A Modified EBMT - Flowchart of response assessment

Table 14-10 Overview: Flowcharts for response assessment according to EBMT

Flow chart	Description	Section in core document
Figure 14-1	Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria	14.4.2.2.4
Figure 14-2	Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria (link from Figure 14-1)	14.4.2.2.4
Figure 14-3	Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria (link from Figure 14-1 and Figure 14-2)	14.4.2.2.4
Figure 14-4	Flowchart for relapse in patients with MM after CR according to modified EBMT criteria	14.4.2.2.4

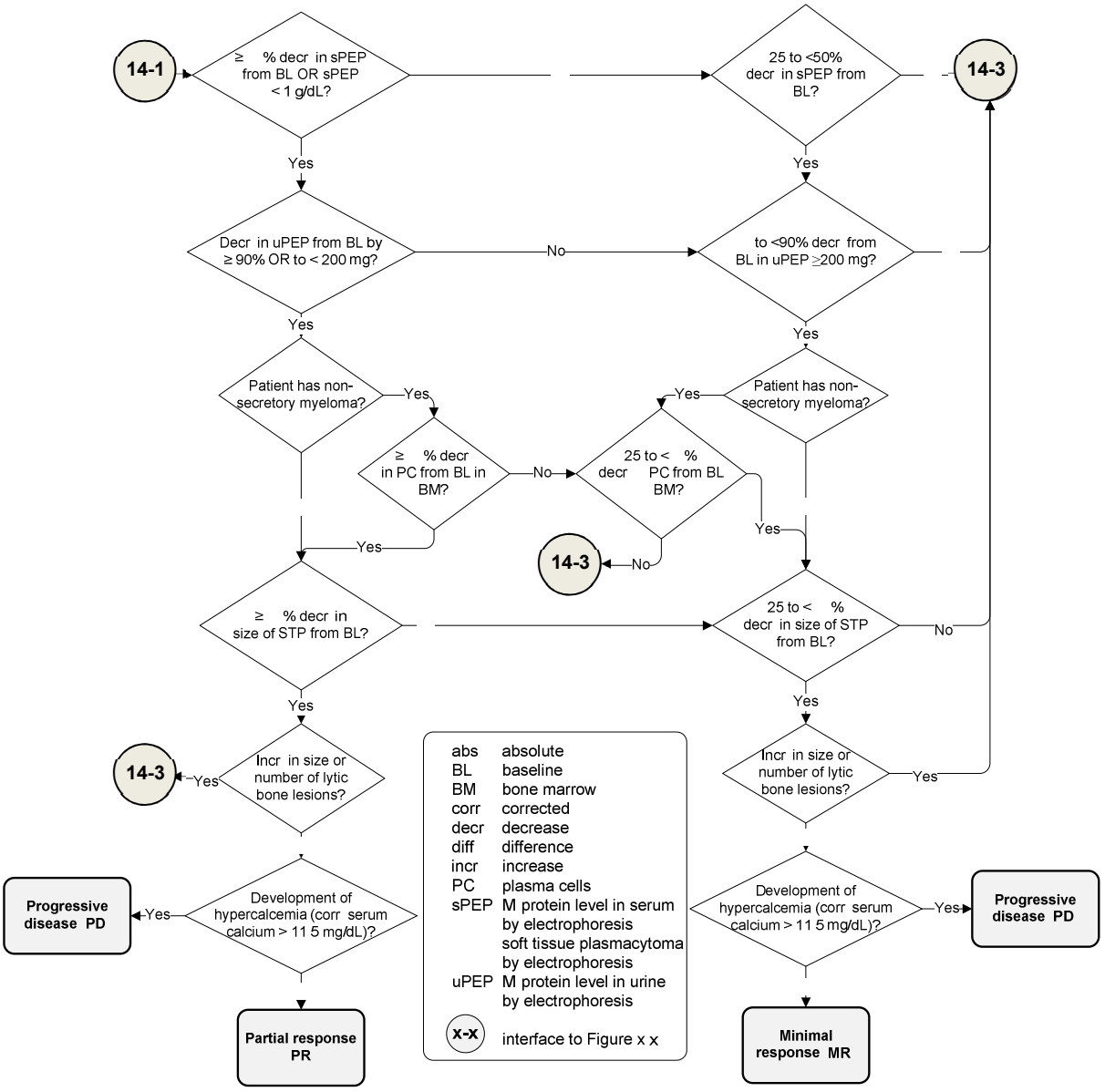
[redacted]

Figure 14-1 Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria



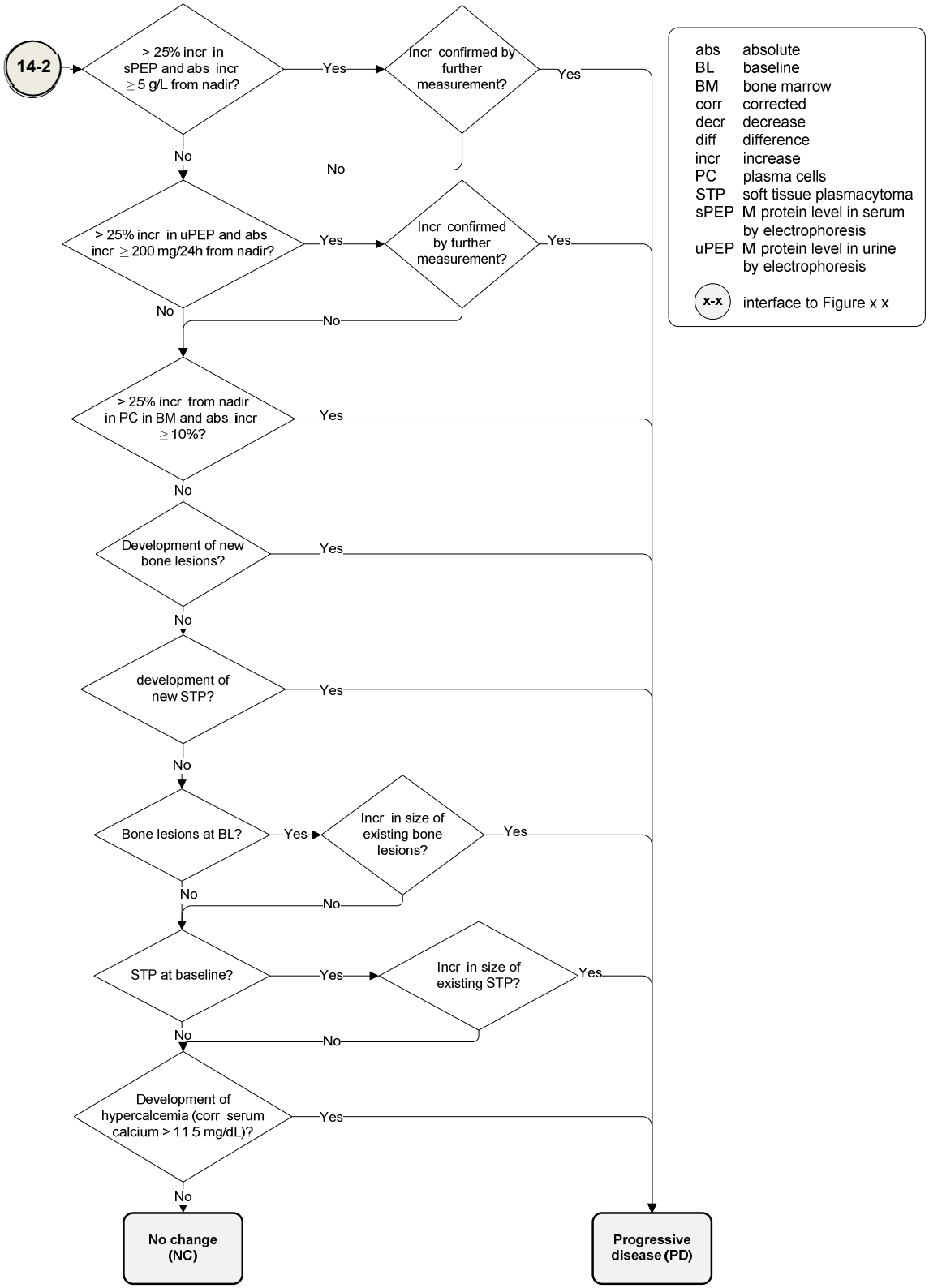
[redacted]

Figure 14-2 Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria



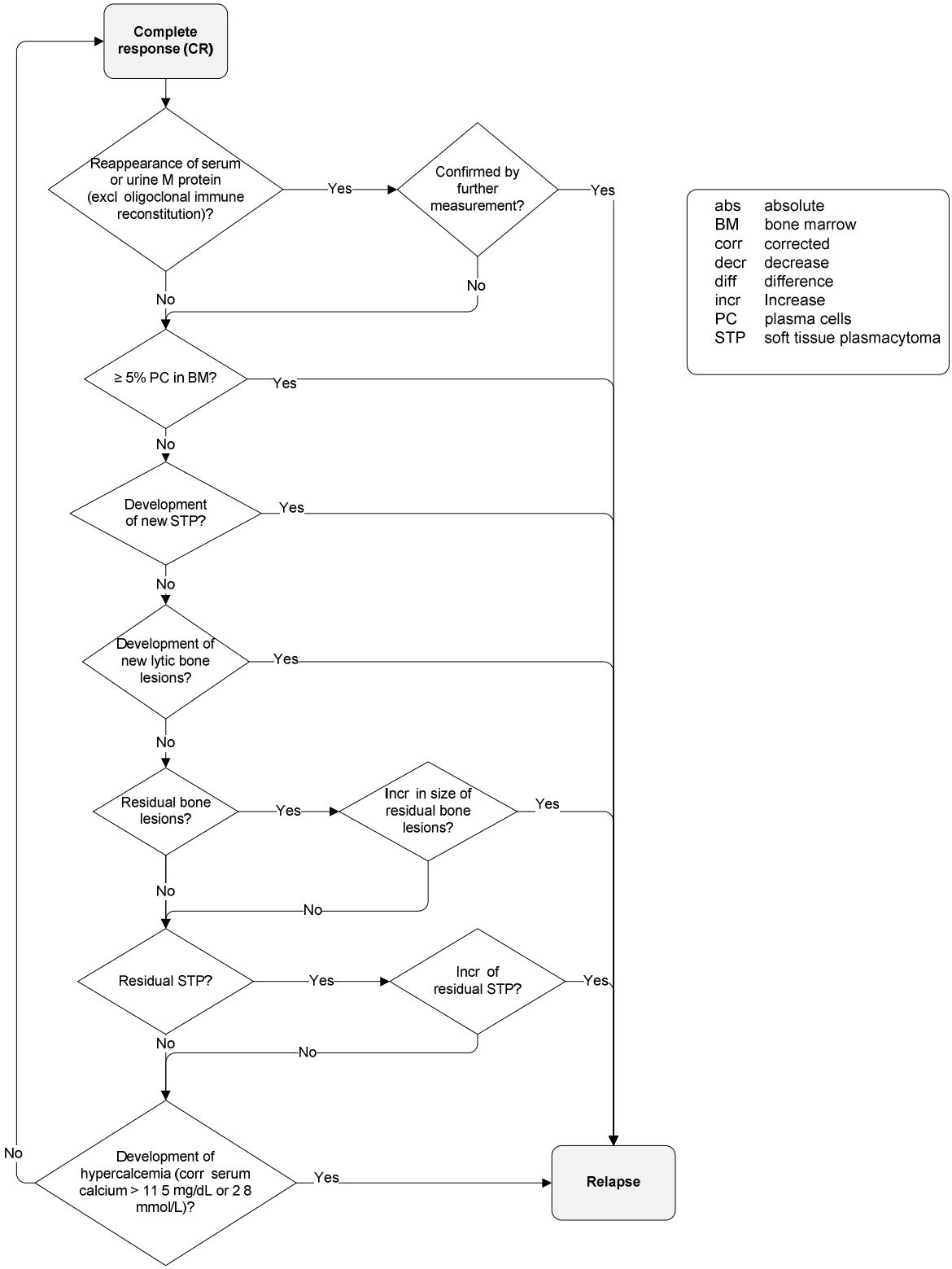
[redacted]

Figure 14-3 Flowchart for response in patients with MM at 1st post-baseline assessment or previous NC according to modified EBMT criteria



[redacted]

Figure 14-4 Flowchart for relapse in patients with MM after CR according to modified EBMT criteria



[redacted]