APL-C-001-09 (NCT01102426)

(ADMYRE: Aplidin – Dexamethasone in RElapsed/Refractory MYeloma)

Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone *vs.* Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma

STATISTICAL ANALYSIS PLAN

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
AP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BM	Bone Marrow
BMI	Body Mass Index
BSA	Body Surface Area
C	Cycle/s
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPK-MB	Serum CPK Isoenzymes (Found In Cardiac Muscle)
CR	Complete Response
CRF	Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CT-scan	Computed Tomography Scan
d/D	Day(s)
DB	Data Base
DF	Degrees of Freedom
DI	Dose Intensity
DR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPO	Erythropoietin
FU	Follow-up
G-CSF	Granulocyte Colony Stimulating Factor
h	Hour(s)
Hb	Hemoglobin
HDT	High-dose Therapy
HR	Hazard Ratio
IA	Investigator Assessment
Ig	Immunoglobulin
IDMC	Independent Data Monitoring Committee
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IPCW	Inverse Probability of Censoring Weighting
IR	Independent Review
IRC	Independent Review Committee
ISS	International Staging System
ITT	Intention-to-treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
LDH	Lactate Dehydrogenase
LR	Log-rank Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma

MR	Minor Response
MRI	Magnetic Resonance Imaging
MUGA	Multiple-gated Acquisition Scan
NA	Not Applicable
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NE	Not Evaluable
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
PBSC-T	Peripheral Blood Stem Cell Transplantation
PD	Progressive Disease
PFS	Progression-free Survival
PIs	Proteasome inhibitors
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PS	Performance Status
q4wk	Every Four Weeks
QoL	Quality of Life
RBC	Red Blood Cell
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
SAE(s)	Serious Adverse Event(s)
sCR	Stringent Complete Response
SCT	Stem Cell Transplantation
SD	Stable Disease
sFLC	Serum Free Light Chains
SOC	System Organ Class
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal
UK	Unknown
VGPR	Very Good Partial Response
vs.	versus
WBC	White Blood Cells
WHO	World Health Organization
wk	Week
WPC	Worst per Cycle
WPP	Worst per Patient

Treatment Arm A: Plitidepsin in combination with dexamethasone
Treatment Arm B: Dexamethasone alone

1 STUDY RATIONALE

Clinical development of anticancer treatments usually requires combination of more than one active drug for improving efficacy, with each agent having different targets or mechanisms of action in order to prevent or delay the development of tumor resistance. Ideally, from the preclinical point of view, drugs may have shown either additive or synergistic antitumor activity. It is equally important to avoid agents with overlapping toxicity profiles for the development of successful novel combinations.

Plitidepsin (Aplidin®) is a novel anticancer compound that has shown activity as a single agent in a recently completed phase II study in relapsed/refractory multiple myeloma (MM) patients. In a first stage, this trial explored the objective response to plitidepsin at 5 mg/m^2 as a 3-hour i.v. infusion administered every two weeks (q2wk), with 10% of 21 evaluable patients having a partial response (PR) and, additionally, 14% of patients having clinically meaningful disease stabilization (SD ≥ 3 months), with a median time to progression (TTP) of 2.3 months. Based on preclinical results that showed additive to synergistic effects of dexamethasone/plitidepsin combination, in a second stage of this phase II trial, patients who experienced suboptimal response (stable disease (SD) or progressive disease (PD)) after three to four plitidepsin infusions were allowed to receive oral dexamethasone 20 mg daily on days 1 through 4 q2wk (160 mg total monthly dose) added to plitidepsin. In this cohort of patients, 28% of the 18 evaluable patients had an objective response and TTP was significantly prolonged to 4.2 months. A similar overall safety profile was found, although with a slight increase in muscular events (mostly myalgia and reversible CPK increase) and a mild decrease in grade 3-4 transaminases increase. Of note, as much as two thirds of these patients had previously received bortezomib, thalidomide or lenalidomide and high-dose therapy (HDT) and peripheral blood stem cell transplantation (PBSC-T), whereas all patients had steroids as part of a prior therapy, with a median of four prior lines of systemic treatments. Although the trial design had limitations that precluded comparison between cohorts, both regimens were well tolerated and showed clinical activity in this heavily pretreated population for which limited clinical options were available. The addition of dexamethasone after three to four cycles of plitidepsin did not change dramatically the response (some disease stabilizations were found in patients who were progressing on plitidepsin alone, and one patient who was stable responded after dexamethasone addition), but responses appeared to be more durable and steeped. Therefore, it seems logical to add dexamethasone to plitidepsin upfront in order to optimize any synergistic effect that may occur clinically to achieve a better and longer disease control.

This approach has been extensively used for most active agents in MM. In fact, corticosteroids have long been a central component of the treatment for MM, with the most commonly used regimens being high-dose dexamethasone alone, melphalan and prednisone**,** vincristine, doxorubicin, and dexamethasone (VAD)**,** thalidomide, lenalidomide plus dexamethasone, and bortezomib plus dexamethasone. Moreover, dexamethasone can be used as monotherapy as well, the dose and regimen being typically around 20-40 mg on days 1-4, 9-12, and 17-20 of a 28- to 35-day cycle for a total of 240-480 mg per cycle**,** although adverse reactions may be observed including principally endocrine axis suppression, serious infection derived from clinically relevant immunosuppression, and confusion or mood changes including acute psychosis. In fact,

dose of dexamethasone has recently raised some concerns particularly after the Eastern Cooperative Oncology Group (ECOG) 4A03 study. The ECOG, compared the administration of lower doses of dexamethasone (40 mg d 1, 8, 15, and 22 p.o. q4wk, for a total monthly dose of 160 mg) plus lenalidomide with high-dose dexamethasone at the usual dose (40 mg d 1-4, 9-12, and 17-20 p.o. q4wk, for a total monthly dose of 480 mg) plus the same lenalidomide regimen, and reported a significant improvement in overall survival with a better safety profile for the lower dose arm. A second study with lenalidomide plus dexamethasone in the relapsed/refractory setting showed that patients who had dose reductions of dexamethasone have shown a significantly higher overall response rate, including a higher complete response, progression-free survival (PFS) and improved median overall survival, when compared to those who received dexamethasone at the assigned dose, with adverse events rates comparable between both groups**.** Finally, and based on data from last available publications on dexamethasone and bortezomib combinations**,** dexamethasone administered at reduced doses (20 mg) the same day and the day after bortezomib infusion up to a total dose of 160 mg/cycle, has been associated with a better safety profile while maintaining the same level of activity.

2 STUDY DESIGN

This will be a prospective, multicenter, open-label, two-arm, 2:1 randomized phase III study of plitidepsin in combination with dexamethasone *vs.* dexamethasone alone in patients with relapsed/refractory MM.

The primary study endpoint is progression free survival (PFS).

- Treatment Arm A:
    - Dexamethasone: 40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.
    - Plitidepsin: 5 mg/m^2 intravenously (i.v.) diluted to a total volume of 250 ml in 0.9% saline via a central venous catheter (suggested) or diluted to a total volume of 500 ml in 0.9% saline via a peripheral line. Infusion will be performed through a pump device over three hours (fixed rate) on Day 1 and 15 q4wk.

- Treatment Arm B:
    - Dexamethasone: 40 mg orally on Day 1, 8, 15 and 22 q4wk.

Patients in the control arm (dexamethasone alone, Arm B) who have documented disease progression after a minimum of eight weeks from randomization should be offered to cross over to combination arm (plitidepsin + dexamethasone, Arm A) upon Sponsor agreement.

Patients may be treated with additional cycles of plitidepsin and dexamethasone or dexamethasone alone, as long as no unacceptable toxicity and/or disease progression is documented.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary objective

- To compare the efficacy of plitidepsin in combination with dexamethasone *vs.* dexamethasone alone as measured by progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (MM).

3.2 Secondary objectives

- To evaluate tumor response according to the international myeloma working group (IMWG) criteria.
- To assess duration of response (DR) and overall survival (OS).
- To assess efficacy in patients who undergo crossover from dexamethasone alone to plitidepsin and dexamethasone combination.
- To characterize and compare the safety profile on both arms in this population.
- To characterize the pharmacokinetics (PK) and pharmacokinetic/pharmacodynamic (PK/PD) relationship.

3.3 Endpoints

Primary endpoint:

- PFS, according to independent review committee (IRC) assessment, as per intention-to-treat (ITT) analysis.

Secondary endpoints:

- Objective RR.
- Best overall response including rate of minor response (MR) or better (according to the IMWG criteria).
- Response and progression-free survival to combination treatment in patients who crossed over after progression on dexamethasone alone.
- Time-to-event endpoints: DR and OS.
- Safety as per-protocol will be evaluated in each arm separately. Adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.
- PK/PD parameters.

4 PATIENTS EVALUABILITY CRITERIA

The study population will include patients who have relapsed or refractory MM after all standard available therapy. To be enrolled in this study, the patients must meet all inclusion criteria and no exclusion criteria.

4.1 Analysis sets definitions

"All Randomized Patients" analysis set is defined as all patients who are randomized to either treatment arm, independent of whether they received the study drug.

"All Treated Patients" analysis set is defined as all randomized patients who receive at least part of one dose or infusion of the investigational agents.

"All Evaluable Patients" analysis set is defined as all randomized patients who have completed at least one full cycle of treatment or have received two incomplete cycles followed by at least one response assessment not less than eight weeks (± one week) after treatment onset. Patients withdrawn from the study due to early disease progression or treatment-related toxicity will be considered as "early progression" or "treatment failure", respectively, even though they have not received a full cycle. Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, or refusal to continue on study for any reason or unrelated AEs without any disease assessments after the start of study treatment or those patients with a protocol deviation resulting in an impossibility of drawing conclusions about the efficacy of the study therapy will be considered not evaluable for efficacy and their response will be categorized as "non evaluable".

"All Responder Patients" analysis set is defined as all evaluable patients who have minor response or better as overall best response.

"All Crossover Patients" analysis set is defined as all patients randomized to Arm B who have documented disease progression after their eighth week from randomization and cross over to Arm A.

4.2 Efficacy populations

The "All Randomized Patients" analysis set will be used for the primary endpoint analysis of Progression-free survival (PFS) and the main efficacy analysis, as well as for all OS analyses.

For futility analysis based on objective response rate, the "All Evaluable Patients" analysis set will be used.

The "All Randomized Patients" and "All Evaluable Patients" datasets will be used for the final analysis of RR.

The "All Responder Patients" dataset will be used for the duration of response (DR) calculation.

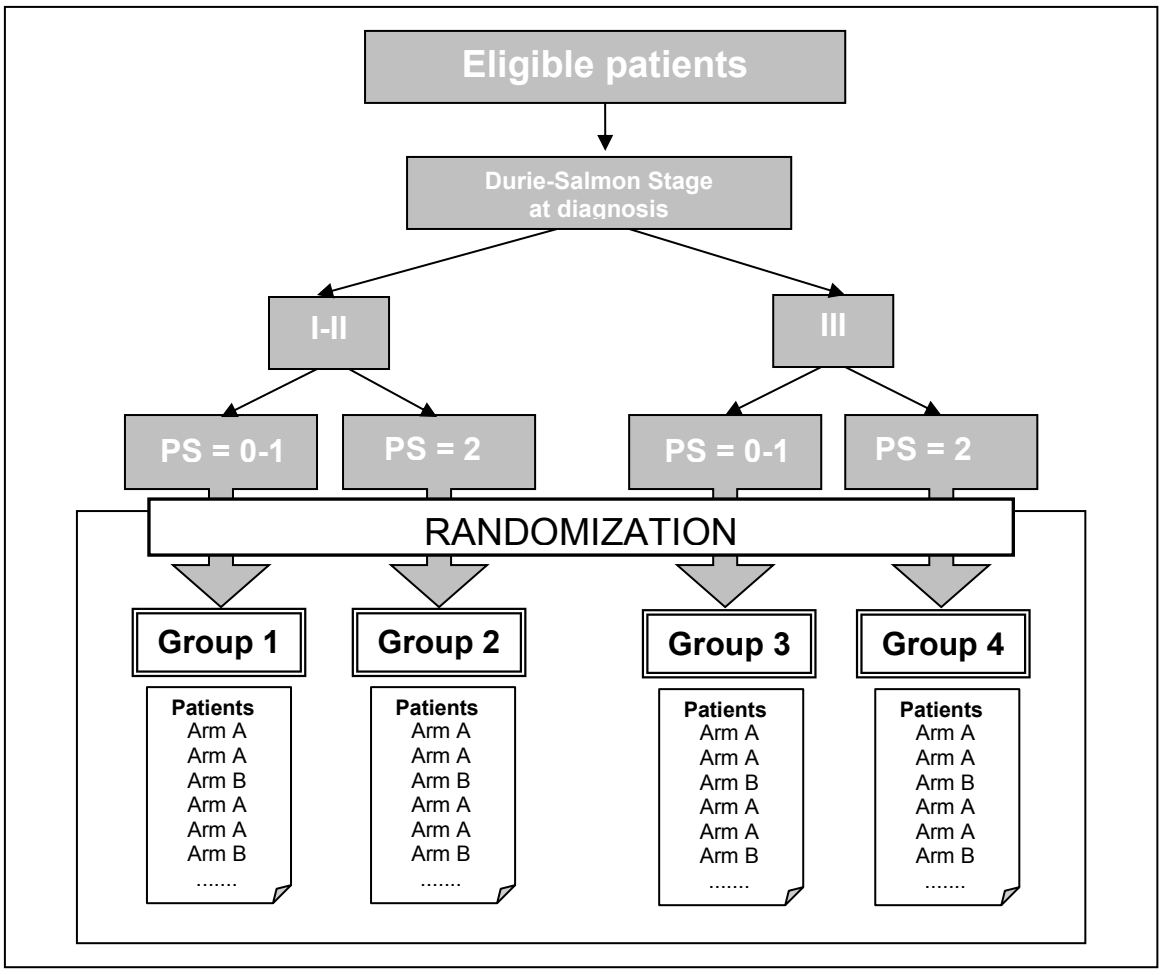
The "All Crossover Patients" dataset will be used for the exploratory intrapatient comparison of response and PFS (before and after crossover).

4.3 Safety population

The safety analysis is based on the "All Treated Patients" analysis set.

5 SAMPLE CONSIDERATIONS

5.1 Randomization



Patients fulfilling all eligibility criteria will be stratified according to the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score (0 and 1 *vs.* 2) and Durie-Salmon stage at diagnosis (I/II *vs.* III) and then randomized using a 2:1 randomization procedure to Arm A (plitidepsin in combination with dexamethasone) or Arm B (dexamethasone alone). Randomization will be used to avoid bias in the assignment of patients to treatment, and to increase the likelihood that known and unknown patient attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups.

Randomization of patients should occur as close in time as possible before administration of the first dose of study drug(s) and must occur within 7 days of the patient receiving the first dose of study treatment. The randomization number and treatment code will be assigned after phoning into the Interactive Voice Response System (IVRS).

On the basis of the patient identification and stratum information, the IVRS will assign a treatment code, which will dictate the treatment assignment for that patient.

Patients will be assigned to each group by strata random list, so that a patient will have a two-thirds chance of getting Arm A (plitidepsin in combination with dexamethasone) and a one-third chance of getting Arm B (dexamethasone alone). The random permuted blocks method will be used; the size of the blocks in the randomization list will be fixed and not accessible to investigators. To select the blocks, a uniform (0, 1) variable with a random seed will be used.

5.2 Sample size

The number of patients randomized in the trial has been calculated based on PFS estimates obtained from the previous phase II study (APL-B-014-03).

1. **Arm A** (plitidepsin plus dexamethasone combination): approximately 167 patients.
2. **Arm B** (dexamethasone single agent): approximately 83 patients.

Approximately 210 progression or death events would be needed in this trial to detect a HR of 0.625 in favor of the combination arm (equivalent to an increase of 60% in PFS, i.e., from 10 to 16 weeks, 12 to 19.2 weeks, 16 to 25.6 weeks) with 90% power and 1-sided 2.5% significance level. As a preliminary hypothesis, it is estimated that up to 250 randomized patients will be needed to achieve the 210 events in 24-30 months. For the calculation of the number of events needed, the target HR to be detected is 0.625, with 90% power and 2.5% unilateral significance level. This is equivalent to a minimum 60% increase in PFS, which has been considered statistically and clinically significant by the Sponsor.
An early futility analysis will be performed with the data collected when 40 patients in Arm A are evaluable for response. A response rate (IMWG criteria) of at least 30% (twelve or more responses by IRC review) will be taken as threshold for continuation of the study. A minimum response rate of 30% has been considered as clinically significant in this setting. This result will ensure that the lower limit of the exact binomial 95% Confidence Interval for the response rate will be greater than 15% (95% CI in case of 12 responses would be 16.6% - 46.5%).

However, the efficacy and safety information from all randomized patients in both arms at that time will be used by the independent data monitoring committee (IDMC) to provide the Sponsor with a recommendation for further study conduct.

The final PFS analysis will be performed when at least 210 progression or death events are observed.

An interim analysis of OS will be performed concomitantly with the final PFS analysis. In addition, a final analysis of OS will be performed when 80% of death events (approximately 200 death events) have occurred or 24 months after the inclusion of the last patient, whichever occurs first. At the interim OS analyses, the significance level determined by the O'Brien-Fleming (1) boundary with overall 2.5% 1-sided significance level will be used.

6 STATISTICAL METHODOLOGY FOR EFFICACY

6.1 Planned analyses and definitions

Protocol-specified analyses are foreseen at the time of the futility evaluation (approximately 40 patients in Arm A), final PFS analysis (main endpoint, approximately 210 progression or death events) and follow-up evaluation of OS at 24 months after the inclusion of the last patient or 80% of death events (approximately 200 death events), whichever occurs first. Accrual will be on-hold while data for the futility analysis is being assessed, when 40 patients in Arm A fully evaluable for response have been accrued.

6.1.1 Early futility analyses

An early futility analysis will be performed when information from the first 40 patients in Arm A are evaluable for response. A response rate (IMWG criteria) of at least 30% (12 or more responses by IRC review) will be taken as threshold for continuation of the study. A minimum response rate of 30% has been considered as clinically significant in this setting. This result will ensure that the lower limit of the exact binomial 95% Confidence Interval for the response rate will be greater than 15% (95% CI in case of 12 responses would be 16.6% - 46.5%).

However, the efficacy and safety information from all randomized patients in both arms at that time will be used by the IDMC to provide the sponsor with a recommendation for the further study conduct. No claim for superiority in efficacy will be formulated in this interim analysis and no alpha-spending for the analysis of PFS is foreseen.

6.1.2 Final analyses

Primary endpoint.

Efficacy will be assessed by comparing the PFS in each treatment arm.

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of documented progressive disease (PD) by IMWG criteria or death (regardless of the cause of death). If the patient receives further antitumor therapy before PD, PFS will be censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient is lost to follow-up for the assessment of progression, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS will be censored at the date of last valid tumor assessment before the missing evaluations.

An external review committee blinded to treatment arm will assign the objective response and a progression or censoring date for each patient based on laboratory data, radiologic and bone marrow assessments when required and evaluation of all relevant clinical information; then, this information will be merged with the date of death from the death report forms and with further antitumor therapy data for the calculation of PFS. Patients with missing IRC evaluations will have their PFS censored at randomization date.

The primary study analysis will be based on externally assessed PFS data in the "All Randomized Patients" population, defined as all patients randomized to either treatment arm.

By design, disease response will be assessed every four weeks symmetrically across treatment arms irrespectively of treatment delays or omissions. Disease assessments (e.g., serum or urine M-spike, sFLC) and evaluation of extent of disease will be done within two weeks before randomization and every four weeks thereafter in the absence of PD while on treatment. If disease progression has not occurred at treatment termination, then disease assessments should continue every four weeks until evidence of disease progression or other antitumor therapy, whichever occurs first, and then will be followed every three months for survival until death, or until the date of study termination, whichever occurs first.

Study termination date is defined as the date in which 80% of death events occurred, 24 months after the accrual of the last randomized patient, or IDMC recommendation (whichever occurs first).

PFS and objective tumor response will be assessed according to IMWG criteria. Centralized laboratory reports and copies of computed tomography scans (CT-scans), magnetic resonance imaging (MRI) (in case of soft tissue plasmacytoma) and any other documented means to evaluate tumor response or progression should be available for IRC review.

For patients within the "All Crossover Patients" dataset, the PFS is defined as the time from the day of the last disease assessment, before the first administration of the combination, to the date of documented progressive disease (PD) by IMWG criteria or death (regardless of the cause of death). The same censoring rules described above for PFS calculation will be considered.

Secondary endpoints.

Objective response is defined as having minor response (MR) or better as best overall response based on the IMWG criteria (See Appendix 5 of the clinical protocol). The ***objective response rate (RR)*** is calculated as the number of objective responders divided by the number of patients in the "All Evaluable Patients" and "All Randomized Patients" analysis sets.

For patients within the "All Crossover Patients" dataset, the reference value for the calculation of response after crossover will be the protein value determined immediately before the administration of the combination of plitidepsin plus dexamethasone after crossover.

The ***duration of objective response*** (DR) will be analyzed in all patients for whom at least a MR has been observed. Duration of response will be calculated from the date of first documentation of response (not the confirmation) to the date of disease progression or death with the same censoring rules as PFS.

Overall survival (OS) is defined as the time from the date of randomization to the date of death or last contact.

Symmetry of evaluations.

Assessments must be done consistently in both treatment arms to ensure a symmetrical assessment of tumor response and progression. Every effort should be made to ensure that

these assessments are done on the required date, although a window of ±2 days will be allowed.

Sensitivity analyses of PFS.

The impact of potential asymmetry of assessments or missing tumor evaluations on the PFS analysis will be assessed by three imputation analyses as follows:

In the key primary analysis of PFS, a patient's event date is taken as the first date of documented disease progression based on IMWG criteria. This may potentially delay the time to actual disease progression, especially when there is a missing assessment prior to the documented disease progression.

In the first sensitivity analysis, the midpoint of the last two assessment dates on or prior to the documented disease progression will be used to impute the actual date of the disease progression. For those patients who have disease progression in the first assessment, the midpoint of randomization date and the documented disease progression will be used. For those patients who die, the midpoint between last disease assessment without PD and the date of death will be used. For patients without documented disease progression, the PFS will be censored following the same rules than in the main analysis.

In the second sensitivity analysis, the following imputation method will be used to make sure the disease assessments fall exactly ix4 weeks after randomization.

Recorded Time Window (weeks from randomization)	Imputed Time (weeks from randomization)
[0 ; 6 [	4
[6 ; 10 [	8
[10 ; 14[	12
…	…
[i x 4 – 2 ; i x 4 + 2[	i x 4

In the third sensitivity analysis, disease progression will be assumed for the first missing scheduled assessment following the last evaluation without progression.

A sensitivity analysis of PFS in the "All Evaluable Patients" population according to IRC and investigator assessment will be performed in order to present the results in the population described in the protocol.

Due to the variability of the protein used for the disease assessment, a sensitivity analysis of PFS requiring the confirmation of the disease progression by IRC assessment will be performed. Patients who die within the timeframe expected for the confirmation of PD, will be considered as PD confirmed by death. Those patients without confirmation of PD with a second disease assessment due to crossover, further antitumor therapy, lost to follow-up or other reasons, will be censored. The same censoring rules described above for PFS calculation will be considered.

6.2 Efficacy analysis methods

6.2.1 Primary endpoint

For the evaluation of the main primary endpoint (PFS), the ”All Randomized Patients” population, the data from the Independent Review Committee (IRC), and the unstratified log-rank test will be used to compare both treatment arms. The final PFS analysis will be performed when at least 210 progression or death events are observed.

Cox regression will be used to calculate the risk reduction in PFS

6.2.2 Supportive PFS analyses

A stratified log-rank test for the main endpoint (PFS by IRC) will be performed as supportive analysis.

A Cox regression stratifying by randomization factors and using only treatment as covariate will be used to calculate the risk reduction in PFS.

PFS by investigator assessment in the ‘All Randomized Patients’ population will be analyzed according to the Kaplan-Meier method. The corresponding unstratified and stratified log-rank tests will be used to evaluate the differences between. Besides, Cox regressions will be performed to calculate the risk reduction in PFS, stratifying by randomization factors and using only treatment as covariate.

The reasons for censoring, and the concordance between the IRC and investigator evaluation of PFS will be shown using counts and percentages.

6.2.3 Secondary analyses

Overall survival:

Although the study is powered for the evaluation of the main endpoint PFS, two analyses of OS will be performed to ascertain if a trend in OS is observed in favor of the experimental arm. A first analysis of OS will be performed concomitantly with the final PFS analysis. In addition, a second analysis of OS will be performed when 80% death events (approximately 200 death events) have occurred or 24 months after the inclusion of the last patient, whichever occurs first. At the interim OS analysis the significance level determined by the O’Brien-Fleming boundary with overall 2.5% 1-sided significance level will be used.

OS analyses will be performed according to the Kaplan-Meier method and the unstratified and stratified log rank tests will be used in order to ascertain if clinically significant OS effect in favor of the experimental arm is observed.

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of crossover in a first sensitivity analysis excluding the patients who crossed over and a second analysis censoring survival at the time of crossover. Estimates of the unbiased effect in survival will be studied by means of, rank preserving structural failure time (RPSFT)

models for correcting for treatment changes (2), by the inverse probability of censoring weighting (IPCW) method (6) and by means of the two-stage method proposed by Latimer *et al.* (7) in order to try to control any bias caused by treatment crossover.

The following time-dependent covariates will be included in the IPCW analysis: ECOG, Body Surface Area (BSA), m-protein value (serum/urine), number of adverse events grade≥3, bone marrow plasma cells, creatinine, LDH, hemoglobin and corrected serum calcium. Also, baseline covariates such us gender, age, MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed *vs.* relapsed/refractory), refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, presence of plasmacytomas, presence of lytic lesions, number of plasmacytomas, sum of the dimensions of plamacytomas, will be included.

The reasons for censoring of OS will be shown using counts and percentages.

An analysis will be carried out in the subpopulation of patients without crossover or subsequent therapy in order to investigate the isolated effect of study treatments in survival in this subpopulation. It will be also carried out in the subpopulation of patients without crossover or subsequent therapy and with event in the primary analysis of PFS by IRC.

Response rate:

Binomial estimates with exact 95% CIs will be calculated for the analysis of response rate. Randomized patients not evaluable for response will be excluded from the denominator exclusively for the futility analysis, but will be included in all the final efficacy analyses. A supportive analysis will be also done in the "All Evaluable Patients" population.

The magnitude of response, in patients with secretory MM, will be described by waterfall plots showing the best M-spike reduction from baseline.

A supportive analysis of response rate will be performed taking into account PR or better as best overall response based on the IMWG criteria.

Duration of response:

Duration of objective response will be analyzed according to the Kaplan-Meier method and compared between treatment groups using the log-rank test.

DR requiring confirmation of PD for determination of PFS will be analyzed according to the Kaplan-Meier method and compared between treatment groups using the log-rank test.

DR for patients who have PR or better as best overall response based on the IMWG criteria will be calculated as a supportive analysis.

Time to response:

Time to response will be analyzed according to the Kaplan-Meier method and compared between treatment groups using the log-rank test.

Time to response for patients who have PR or better as best overall response based on the IMWG criteria will be also calculated as a supportive analysis.

Analysis of crossover:

Descriptive frequency tables with the number of patients who switch from Arm B to Arm A after disease progression will be calculated.

Exploratory intrapatient comparison of response and PFS (before and after crossover) will be performed for patients who switch from Arm B to Arm A after disease progression.

The patients within the "All Crossover Patients" dataset will be listed with the cycle when the crossover occurs, and the response and PFS before and after crossover.

A comparison of the baseline characteristics in patients with Crossover *vs.* No crossover will be done to rule out that patients with crossover can have a better prognosis than patients without crossover. For two-stage method a logistic stepwise regression and the comparison of PFS between patients with crossover versus patients with no crossover is performed to check the assumption of no 'unmeasured confounders'. Post-progression survival data is adjusted by a Weibull parametric accelerated failure time model.

A listing of patients with crossover will be provided in order to confirm if PD was seen before crossover and if this PD was confirmed.

Statistics of the time (in months) from study initiation to crossover will also be included.

Analysis of prognostic factors, subgroup analysis and multivariate analyses:

Univariate evaluation of the influence of different prognostic factors on the main efficacy endpoints will be performed by using the following covariates: Gender, age, baseline ECOG, Body Surface Area (BSA), MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed *vs.* relapsed/refractory) refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, bone marrow plasma cells, bone lytic lesions (Y/N), plasmacytomas at baseline (Y/N), number of lesions at baseline, sum of the dimensions of plamacytomas, creatinine (≥2 mg/dl *vs.* < 2 mg/dl), LDH, hemoglobin and corrected serum calcium (>11.5 mg/100ml *vs.* ≤11.5 mg/100ml).

Exploratory subgroup analyses will be performed by means of logistic regression, Kaplan-Meier analysis and Cox regression. The different subgroup analyses will be summarized by means of Forest plots.

Cox proportional hazard models for PFS and OS and logistic regression models for RR will include the prognostic factors specified for the univariate analysis. More relevant and explanatory covariates from the univariate analysis will be included in the multivariate analyses (p-value < 0.10). Prognostic factors with more than 10% missing values will be excluded in the multivariate analyses.

The analyses above mentioned will be also performed for the sensitivity analysis of PFS with confirmation of PD by IRC.

In addition, and in order to check if there are differences in the main efficacy endpoint between different continents/geographical areas, multivariate analyses of PFS by IRC, adding region as a covariate, will be performed. The variable "region" will be created with four categories (Europe, Asia, Oceania, and USA) and then three Cox regressions will be performed.

1) PFS by IRC with arm, region and interaction term.
2) PFS by IRC with arm and region as main effects.
3) Full model selected in the multivariate analysis of PFS by IRC, including region as variable.

Symmetry of evaluations.

Wilcoxon test will be used to compare time to disease assessments between treatment arms. Moreover, Kaplan-Meier curves of the time from randomization to first and second disease assessment will be plotted.

An analysis of the median time window between the first documentation of PD and PD confirmation in a second assessment will be done to rule out that confirmation of PD could have been advanced or delayed in any of the treatment groups.

Sensitivity analyses of PFS.

For the three sensitivity analyses using imputation methods for the date of progression, similar unstratified log-rank test as for the key primary PFS analysis will be performed, based on the imputed data sets.

Interval censoring methods will be used for the comparison of PFS in both arms by IRC and investigator assessment. An iterative algorithm developed by Turnbull(3) will be used to compute a non-parametric maximum likelihood estimate of the cumulative distribution function for the data. After that, the log-rank score of permutational test will be calculated and the normalized test statistic and associated p-value will be presented to test the difference between the two treatment groups.

7 STATISTICAL METHODOLOGY FOR SAFETY

Patients are evaluable for general safety if they received any study treatment. Safety will be evaluated in each arm separately according to the actual treatment received.

7.1 Toxicity and adverse events

All the adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The toxicity evaluation will be coded with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 4.

As far as all the toxicities are concerned, the NCI-CTC grade will be used wherever an NCI-CTC grading exists. Otherwise, the severity will be noted. As a convention, the term «Grade» will always be used. Toxicities will be described according to the worst NCI-CTC grade or, for toxicities which do not form the subject of NCI-CTC classification, according to the worst severity.

Summary of overall adverse events will be done by body system and preferred term, by severity (worst toxicity grade), by relationship to the study drug/s, and by AE outcome. Tables will be sorted by body system/preferred term and by the highest incidence.

A frequency table will be made for the AEs leading to cycle delay, dose reduction, skipped dose, or withdrawal of study medication. Adverse events with outcome of death will also be presented by relationship to the study drugs.

7.2 Clinical laboratory evaluation

Laboratory results will be classified according to the NCI-CTC version 4.

For hematology values: absolute neutrophil count, lymphocyte count, WBC count, platelet count and hemoglobin worst grade per patient and per cycle will be displayed.

Overall cross tabulation will be presented for the worst grade during treatment versus the baseline toxicity grading of anemia, lymphopenia, leukopenia, neutropenia and thrombocytopenia.

The worst grade per patient during treatment and per cycle will be also calculated for the biochemical tests: ALT, AST, Total bilirubin, AP, CPK, creatinine, calcium, potassium, sodium, glucose and albumin.

Time and duration of AST and ALT increases in cycles with grade 3-4 abnormality will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment versus the baseline toxicity grading of AST and ALT increase.

If appropriate, the laboratory abnormalities before and after crossover in patients who switch arm after progression will be compared descriptively.

7.3 Vital signs, physical examination, left ventricular ejection fraction (LVEF) and electrocardiogram findings

Tabulation will be made summarizing the performance status, body weight, LVEF and electrocardiogram abnormalities at baseline and during the treatment for each patient.

7.4 Deaths and other Serious Adverse Events

Deaths and other Serious Adverse Events will be tabulated.

8 OTHER ANALYSES

Non-continuous variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, minimum and maximum.

8.1 Baseline and demographic data

Baseline data such as demographics, multiple myeloma history, prior therapy, prior relevant history, signs and symptoms, electrocardiogram, LVEF, protein measurements, laboratory values and concomitant medication (ATC-WHO coded) will be described following standard tables detailed in Appendix I. When two or more assessments have been done for the same parameter, the last assessment before the first drug administration will be taken into account for the analysis.

8.2 Treatment administration

Total cumulative dose, time on treatment, dose intensity and relative dose intensity, cycle delay, and dose reductions will be described following standard tables detailed in Appendix I.

Total cumulative dose by drug, expressed in mg/m² for plitidepsin, or in mg of dexamethasone, is the sum of all the product doses from the first cycle until last cycle including the dose received in last cycle.

Patients will be considered to be on-treatment for the duration of their treatment and 30 days following the last treatment dose. Those patients in the control arm (Arm B) who crossed over to the combination arm (Arm A) after disease progression will be considered on-treatment for the duration of their whole treatment (dexamethasone alone + dexamethasone in combination with plitidepsin) and during the first 30 days following the last treatment dose. If the patient starts any new antitumor therapy outside this clinical trial or dies within 30 days of last treatment dose, the date of administration of this new therapy or the date of death will be considered the date of treatment discontinuation.

However, as a convention, for dose intensity calculation purposes, the duration of the last cycle is considered to be 28 days. If the patient starts any new antitumor therapy outside this clinical trial or dies within 28 days of last cycle initiation this will be taken into account for the calculation of the duration of the last cycle.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle (2.5mg/m^2/wk for plitidepsin, 40mg/wk for dexamethasone).

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity.

The item «Infusion delayed/ omitted: yes/no» in the case report form (CRF) will be used to calculate the delay (on day 1 infusion) or skipped infusions (on day 15 infusion). For cycles considered as delayed by the investigator, the delay will be calculated as:

Delay: Date of current drug administration – Date of previous drug administration – 28.

The first infusion of the first cycle will be excluded from all cycle delay and cycle modification calculations.

8.3 Subsequent therapy

A table summarizing the subsequent therapies received after treatment discontinuation will be shown.

Time to first subsequent therapy or death will be analyzed as a measure of the time from randomization to treatment failure that leads to the need of a further treatment regimen (regardless the method of PD detection or the components of the PD).

8.4 Protocol deviations

Analysis of inclusion/exclusion criteria deviations, retreatment restrictions, used concomitant medication and clinically relevant discontinuations will be done as described in Appendix I.

8.5 Pharmacokinetic analyses

Methods for pharmacokinetics will be described in a separate document.

8.6 Imputation of incomplete dates

The dates of certain historical or current clinical activities are key component for statistical analysis. Incomplete date appears when day, month or year is/are missing, and it could be imputed so that variables like time to and duration of certain event can be calculated. If none of day, month and year is available, then the date is missing, no imputation is necessary.

Before randomization

If day of a date is unknown then the imputed day will be 15, if the month is also unknown then the imputed date will be July 1st. This assumption will be valid if the imputed date is earlier than the randomization date; otherwise the imputed date will be the first day of the randomization month if only the day is missing, or the 15th day of the month prior to the randomization date (i.e. 15/Month of randomization date - 1/Year) if day and month are missing.

After end of treatment

To ensure the most conservative approach for the main time-to-event variables (i.e. PFS and OS) that can be affected by missing values the following rules will be implemented: if the day of a date is unknown then the imputed day will be 1. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be the last drug administration date plus 1 day.

8.7 Subgroup analyses

Analysis of efficacy profile by age in order to characterize a potential benefit of the drug in elderly population is planned. Exploratory efficacy subgroup analyses according to genetic risk, the refractory status to prior therapies such as bortezomib, lenalidomide/thalidomide, last prior therapy, IMiD therapy and PIs are planned. No other specific subgroup analysis is planned for efficacy. However, the influence of the study strata and other prognostic factors on the efficacy endpoints will be studied in the multivariate analysis.

No formal statistical allowance will be made for multiple subgroup investigations, but any apparent subgroup interactions will be interpreted appropriately in a cautious way.

Analysis of safety profile by age, gender and body mass index (BMI) will be provided as specified in section 12.7.

Handling of multicenter data

No randomization or stratification by center will be performed as the sample size by center is expected to be low. Further "by center" analyses may be performed upon request if appropriate.

Handling of multiple comparisons

Single comparison of PFS between arm A and B will be made for the primary endpoint. No adjustment, except for the sequential OS analyses described in section 5.1, will be made for multiple comparisons in secondary analyses.

8.8 Methods for handling missing data

Missing values will be tabulated with their frequency but they will not be included in the calculation of percentages.

8.9 Interim and group sequential analyses

See details of the interim analyses and stopping rules in sections 5.1 and 6.1.

8.10 Data analysis for the Independent Data Monitoring Committee

These analyses will be specified in the independent data monitoring committee charter, in a separate document.

8.11 Identification of fixed or random effects models

Not applicable

8.12 Analyses of the effects of plitidepsin on the QTc interval

A substudy will be conducted to assess the potential effects of plitidepsin on the QTc interval of patients with relapsed/refractory multiple myeloma enrolled in clinical trial APL-C-001-09. These analyses will be specified in a separate document.

8.13 Analyses of performance status as an index of quality of life

Since patient reported outcome questionnaires have not been collected in this study, indirect measures of improvement like time to first performance status deterioration will be analyzed according to the Kaplan-Meier method.

9 STATISTICAL SOFTWARE

EAST v5.2 has been used to calculate sample size. SAS v9 (4) will be used for all statistical analysis outputs. Stata v14 or greater will be used for the analysis of crossover by RPSFT method.

APPENDIX I

All tables will be created at the time of each analysis planned in the protocol if applicable, and at study end.

10 Study Patients

10.1 Patient disposition

Main characteristics concerning inclusion in the study, patient crossover from arm B to arm A, withdrawal from the study and protocol deviations will be displayed in this section.

Table 10.1.1 Number of patients included, treated and evaluable for the main endpoint.

	Arm A		Arm B		Total	
	N	%	N	%	N	%
All Randomized Patients						
Eligible patients*						
All Treated Patients						
All Evaluable Patients						
All Crossover Patients	NA	NA				

(*)Patients meeting all inclusion criteria and not meeting any exclusion criteria.

Listing 10.1.2 Patients randomly assigned to one treatment arm and treated in the other one by mistake

Patient id.	Assigned arm by randomization	Treatment received
…		

Listing 10.1.2a Patients assigned to the wrong stratum by mistake

Patient id.	Assigned stratum by randomization	Actual stratification values
…		

Listing 10.1.2b Comparison of Durie-Salmon at IVRS and baseline value

Patient id.	Durie-Salmon value at IVRS	Actual Durie-Salmon value
…		

Listing 10.1.2c Comparison of ECOG PS at IVRS and baseline value

Patient id.	PS ECOG value at screening	PS ECOG value at IVRS	Last ECOG before start of study treatment
…			

Table 10.1.3 Patients accrual by institution

			Arm A	Arm B	Total
No. included	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			
No. treated	Country 1	Institution 1			
		…			
		Total			
	…	Institution 1			
		…			
		Total			
	Total	Institution 1			
		…			
		Total			

Table 10.1.4 Study dates

	Arm A	Arm B	Total
Date of first randomization			
Date of first dose of the first patient			
Date of last randomization			
Date of first dose of the last patient			
Date of last dose			
Date of last follow-up*			

(*) Last follow-up or exam or procedure before clinical cut-off or study closure

Table 10.1.5 Last cycle in Arm A before crossover

Last cycle before crossover	Crossover patients	
	N	%
Cycle 1	X	XX.X
Cycle 2		
…		
Total		

10.2 Reasons for treatment discontinuation

Table 10.2.1 Study discontinuation

Reason	Arm A		Arm B		Total	
	N	%	N	%	N	%
End of study (study stopped)						
Patient refusal						
Never treated*						
Death (due to toxicity)**						
Death (non-treatment-related)***						
Investigator decision						
Other ****						
Lost to follow-up						
Total						

(*) See Listing 10.2.3 (**) Cause of death = Toxicity (study drug related) (***) Cause of death = Malignant disease or Other (****) See Listing 10.2.2

Listing 10.2.2 Study discontinuation due to other reason

Arm	Patient id.	Specify
…		

Listing 10.2.3 Patients randomized but not treated

Arm	Patient id.	Off-study reason
…		

Table 10.2.4 Treatment discontinuation

Reason	Arm A		Arm B		Total	
	N	%	N	%	N	%
Progressive disease						
Toxicity						
Patient refusal						
Investigator decision						
Death (due to toxicity)*						
Death (non-treatment-related)**						
Other ***						
Total						

(*) Cause of death = Toxicity (study drug related) (**) Cause of death = Malignant disease or Other (***) Specify (see listing 10.2.6)

Table 10.2.5 Reasons for treatment discontinuation by cycles received

Reason	Arm A				Arm B				Total			
	Last cycle				Last cycle				Last cycle			
	1	2	…****	Total	1	2	…	Total	1	2	…	Total
Progressive disease												
Toxicity												
Patient refusal												
Investigator decision												
Death (due to toxicity)*												
Death (non-treatment-related)**												
Other ***												
Total												

(*) Cause of death = Toxicity (study drug related) (**) Cause of death = Malignant disease or Other (***) Specify (see listing 10.2.6) (****) Cycles > % will be grouped as 6-10, 10-20 and >20.

When reason for discontinuation is toxicity or study treatment-related death, identify patients and describe them in depth here.

Listing 10.2.6 Reasons for treatment discontinuation other than progressive disease.

Arm	Patient id.	Reason	Last cycle	Comments
…				

Listing 10.2.7 Treatment discontinuation due to AEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences
…									

Action taken: study drug withdrawal

10.3 Protocol deviations

Listing 10.3.1 Protocol deviations

Arm	Patient id.	Deviation type	Description
…			

11 Efficacy Evaluation

11.1 Demographic and other baseline characteristics

11.1.1 Patient characteristics at baseline

Table 11.1.1.1 Baseline characteristics: Gender

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Male	X	XX.X	X	XX.X	X	XX.X
Female						
Total						

Table 11.1.1.2 Baseline characteristics: Age at treatment registration

		N	Median	Min	Max
Age (years)	Arm A				
	Arm B				
	Total				

Table 11.1.1.3 Baseline characteristics: Age grouped

	Arm A		Arm B		Total	
	N	%	N	%	N	%
18-64	X	XX.X	X	XX.X	X	XX.X
65-74						
75-84						
≥85						
Total						

Table 11.1.1.4 Baseline characteristics comparison by treatment arm

Variable**	Value	N	Arm A	Arm B	p-value*
Sex	F	XXX	XX (XX.X%)	XX (XX.X%)	X.XXXX
	M	XXX	XX (XX.X%)	XX (XX.X%)	
Age	Median(range)	XXX	XX.X (XX-XX)	XX.X (XX-XX)	X.XXXX
…					

(*)Fisher's exact test (categorical variables); Mann-Whitney-Wilcoxon (continuous variables)
(**)Sex, age, region, PS (ECOG), BSA, Durie Salmon stage, International Staging System, Secretory/Non-secretory, MM type, time from diagnosis, time from last PD, number of prior lines, status to prior therapy, status to prior bortezomib therapy, status to prior thalidomide/lenalidomide therapy, status to prior IMiD therapy, status to prior PIs therapy, stem cell transplantation, plasma cells, hemoglobin, creatinine, calcium, genetic risk, lytic lesions and plasmacytomas.

11.1.2 Disease at diagnosis, time from diagnosis and current disease

Table 11.1.2.1 Time from diagnosis to randomization

		N	Median	Min	Max
Time from diagnosis to randomization (months)	Arm A				
	Arm B				
	Total				

Table 11.1.2.2 Time from last PD/relapse

		N	Median	Min	Max
Time from last PD* to first infusion (weeks)	Arm A				
	Arm B				
	Total				

(*)PD date will be taken from MM History form. If the day or the month or the full date is missing, further information will be taken from Prior anticancer therapy form. After that, if the date is still incomplete, imputation rules described in section 8.6 will be used.

Table 11.1.2.3 Multiple Myeloma type at diagnosis

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Secretory	X	XX.X	X	XX.X	X	XX.X
G						
A						
M						
Light chain						
Other						
Non-secretory						
Total						

Table 11.1.2.4 Durie-Salmon stage at diagnosis.

	Arm A		Arm B		Total	
	N	%	N	%	N	%
I-A	X	XX.X	X	XX.X	X	XX.X
I-B						
II-A						
...						
Total						

Table 11.1.2.5 International Staging System stage at diagnosis.

	Arm A		Arm B		Total	
	N	%	N	%	N	%
I	X	XX.X	X	XX.X	X	XX.X
II						
III						
Total						

Listing 11.1.2.6 Cytogenetic, karyotype and FISH at first diagnosis.

Arm	*Patient id.*	*Cytogenetic at first diagnosis*	*Karyotype at first diagnosis*	*FISH at first diagnosis*
...				

Table 11.1.2.7 Genetic risks at diagnosis.

Genetic Risks*	Arm A		Arm B		Total	
	N	%	N	%	N	%
High risk	X	XX.X	X	XX.X	X	XX.X
Intermediate risk						
Good prognostic						
Total						

(*)Patients will be classified in “high risk”, “intermediate risk” or “good prognosis” according to their genetic results (cytogenetic or FISH) at by clinical review. Further details in section 11.3.7.

Table 11.1.2.8 Baseline characteristics: MM protein measurements (Serum*)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Total Ig G (mg/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Total Ig A (mg/dL)												
Total Ig M (mg/dL)												

* Based on central lab assessments.

Table 11.1.2.9 Baseline characteristics: MM protein measurements (Serum)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
M-spike(SPE)(g/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Kappa (mg/L)												
Lambda (mg/L)												
sFLC ratio												

* Based on central lab assessments.

Listing 11.1.2.10 Baseline characteristics: MM protein type

Arm	Patient id.	Serum / Urine	Type
…			

* Based on central lab assessments.

Table 11.1.2.11 Baseline characteristics: MM protein measurements (24h Urine analysis)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Protein -24h urine (mg/24 h)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Urine M-spike (UPE) (Bence Jones) (g/24 hrs)												
Urine M-protein (Bence Jones) (mg/L)												
Kappa (mg/L)												
Lambda (mg/L)												

* Based on central lab assessments.

Table 11.1.2.12 Baseline characteristics: Immunofixation urine

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Positive	X	XX.X	X	XX.X	X	XX.X
Negative						
Total						

* Based on central lab assessments.

Table 11.1.2.13 Baseline characteristics: Non-secretory myeloma

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
Total						

* Based on central lab assessments.

Table 11.1.2.14 Baseline characteristics: Percentage of bone marrow plasma cells

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Plasma cells in smears (%)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Plasma cells in biopsy (%)												

Listing 11.1.2.15 Baseline characteristics: Bone marrow assessment

Arm	Patient id.	Date	Method*	%Plasma cells in smears	%Plasma cells in biopsy	Cytogenetic	Karyotype	FISH
…								

(*)Aspiration/Biopsy

Table 11.1.2.16 Genetic risks at baseline.

Genetic Risks*	Arm A		Arm B		Total	
	N	%	N	%	N	%
High risk	X	XX.X	X	XX.X	X	XX.X
Intermediate risk						
Good prognostic						
Total						

(*)Patients will be classified in "high risk", "intermediate risk" or "good prognosis" according to their genetic results (cytogenetic or FISH) at by clinical review. Further details in section 11.3.7.

11.1.3 Skeletal sites involved at baseline

Listing 11.1.3.1 Baseline characteristics: Skeletal/soft tissue evaluation

Arm	Patient id.	Date of assessment	No lesion / NA	Type	Anatomic localization	Method	Measurements for soft tissue lesions (mm)	Diffuse osteoporosis
…							XXX x XXX	

Table 11.1.3.2 Baseline characteristics: Skeletal sites involved at baseline

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
Plasmacytoma						
Bone (Lytic lesion)						
No						
Total						

Table 11.1.3.3 Baseline characteristics: Number of lesions

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Plasmacytoma	X	XX.X	X	XX.X	X	XX.X
1						
2						
…						
Bone (Lytic lesion)						
1						
2						
…						
Total						

Table 11.1.3.4 Baseline characteristics: Sum of plasmacytomas dimensions

		N	Median	Min	Max
Sum of plamacytomas product of diameters	Arm A				
	Arm B				
	Total				

11.1.4 Prior anticancer therapy

Listing 11.1.4.1 Patients with prior radiotherapy

Arm	Patient id.	Site (Anatomic)	Total dose (Gy)	First dose	Last dose
…					

Table 11.1.4.2 Number of patients with prior radiotherapy

Prior radiotherapy	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
Total						

Table 11.1.4.3 Number of lines of prior systemic therapy

No. lines	Arm A		Arm B		Total	
	N	%	N	%	N	%
1	X	XX.X	X	XX.X	X	XX.X
2						
...						
Total						
Median (Range)						

Table 11.1.4.4 Prior anticancer agents

Antineoplastic and Immunomodulating agents (ATC-class.)	Arm A		Arm B		Total	
	N	%	N	%	N	%
Antineoplastic Agents (L01)	X	XX.X	X	XX.X	X	XX.X
….						
….						

Table 11.1.4.5 Status regarding response to prior therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						

(*)Relapsed myeloma: at least one prior regimen, and not meeting criteria for relapsed and refractory myeloma.
(**) Relapsed/refractory myeloma: non responder or relapse of disease while on salvage therapy, or progression within 60 days of most recent therapy.

Table 11.1.4.6 Status regarding response to bortezomib therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior bortezomib regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last bortezomib therapy.
(***)Refractory myeloma: non responder to last bortezomib therapy.

Table 11.1.4.7 Status regarding response to lenalidomide therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior lenalidomide regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last lenalidomide therapy.
(***)Refractory myeloma: non responder to last lenalidomide therapy.

Table 11.1.4.8 Status regarding response to thalidomide therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior thalidomide regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last thalidomide therapy.
(***)Refractory myeloma: non responder to last thalidomide therapy.

Table 11.1.4.9 Status regarding response to bortezomib, lenalidomide/thalidomide therapy

(*)	Arm A		Arm B		Total	
	N	%	N	%	N	%
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies *	X	XX.X	X	XX.X	X	XX.X
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib **						
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide ***						
Other than the above						

(*) Resistant or refractory myeloma: non responder or relapse of disease while on salvage therapy, or progression within 60 days of therapy.

Table 11.1.4.10 Status regarding response to last therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last therapy.
(***)Refractory myeloma: non responder to last therapy.

Table 11.1.4.11 Status regarding response to IMiD therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior IMiD regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of IMiD therapy.
(***)Refractory myeloma: non responder to IMiD therapy.

Table 11.1.4.12 Status regarding response to PIs therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Relapsed*	X	XX.X	X	XX.X	X	XX.X
Relapsed/Refractory**						
Refractory***						

(*)Relapsed myeloma: at least one prior PIs regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of PIs therapy.
(***)Refractory myeloma: non responder to PIs therapy.

Table 11.1.4.13 TTP to last prior anticancer therapy

		N	Median	Min	Max
Time to progression. Last anticancer therapy (months)	Arm A				
	Arm B				
	Total				

*In case of non-PD to last therapy, TTP will be calculated until the date of informed consent.

Table 11.1.4.14 Response to last therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
sCR	X	XX.X	X	XX.X	X	XX.X
CR						
VGPR						
PR						
MR						
SD						
PD						

Listing 11.1.4.15 Patients who have been previously treated with Bortezomib, Lenalidomide or Thalidomide.

Arm	Patient id.	Regimen #	Agents (Literal)	Agents (ATC4)	Start date	End date	Best Response	Progression date	TTP (months)
…									

Table 11.1.4.16 Prior stem cell transplantation

	Arm A		Arm B		Total	
	N	%	N	%	N	%
0	X	XX.X	X	XX.X	X	XX.X
1						
≥2						
Total						
Type	N	%	N	%	N	%
Autologous	X	XX.X	X	XX.X	X	XX.X
Allogeneic						

11.1.5 Prior history

Listing 11.1.5.1 Prior history

Arm	Patient id.	Description	Onset Date	Resolved Date	Ongoing
…					

11.1.6 Physical examination, vital signs, electrocardiogram and other tests

For the physical examination, vital signs, electrocardiogram and other tests, the last examination available before treatment will be described in the following tables.

Table 11.1.6.1 Baseline characteristics: Physical exam

Physical examination	Arm A		Arm B		Total	
	N	%	N	%	N	%
Normal	X	XX.X	X	XX.X	X	XX.X
Abnormal*						
Total						

(*)See tables of signs and symptoms and prior history for details

Table 11.1.6.2 Baseline characteristics: Physical exam and vital signs.

Arm	Parameter	N	Median	Min	Max
Arm A	Weight (kg.)				
	Height (cm.)				
	BSA (m^2)				
	Heart rate (beats/min)				
	Systolic blood pressure (mmHg)				
	Diastolic blood pressure (mmHg)				
	Temperature (ºC)				
Arm B	Weight (kg.)				
	Height (cm.)				
	BSA (m^2)				
	Heart rate (beats/min)				
	Systolic blood pressure (mmHg)				
	Diastolic blood pressure (mmHg)				
	Temperature (ºC)				
Total	Weight (kg.)				
	Height (cm.)				
	BSA (m^2)				
	Heart rate (beats/min)				
	Systolic blood pressure (mmHg)				
	Diastolic blood pressure (mmHg)				
	Temperature (ºC)				

Table 11.1.6.3 Baseline characteristics: ECOG Performance Status

PS	Arm A		Arm B		Total	
	N	%	N	%	N	%
0	X	XX.X	X	XX.X	X	XX.X
1						
2						
Total						

Table 11.1.6.4 Baseline characteristics: Electrocardiogram

ECG	Arm A		Arm B		Total	
	N	%	N	%	N	%
Normal	X	XX.X	X	XX.X	X	XX.X
Abnormal*						
Total						

(*)See tables of signs and symptoms or prior history for details

Listing 11.1.6.5 Baseline characteristics: Left Ventricular Ejection Fraction (LVEF)

Arm	Patient id.	Not done	Date	LVEF (%)	Interpretation	Institutional normal range (%)	Method
…							

Table 11.1.6.6 Baseline characteristics Median and range of LVEF

Arm		N	Median	Range
Arm A	MUGA			
	ECHO			
	Both			
Arm B	MUGA			
	ECHO			
	Both			
Total	MUGA			
	ECHO			
	Both			

Table 11.1.6.7 Baseline characteristics: Adequate contraception

Adequate birth control	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
NA*						
Total						

(*) Specify reasons

Table 11.1.6.8 Baseline characteristics: Pregnancy test

Pregnancy test	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
NA*						
Total						

(*) Specify reasons

11.1.7 Hematological values at baseline

Table 11.1.7.1 Hematological abnormalities at baseline

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Leukopenia																
Anemia																
Thrombocytopenia																
Neutropenia																
Lymphopenia																

(*)Any grade

Table 11.1.7.2 Hematology values at baseline

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
WBC (10^9/L)			
Hemoglobin (g/dL)			
Hematocrit (%)			
Platelets (10^9/L)			
Neutrophils (10^9/L)			
Lymphocytes (10^9/L)			
Plasma cells (10^9/L)			

Listing 11.1.7.3 Hematological tests not assessed at baseline

Arm	Patient id.	Lab. test
…		

Listing 11.1.7.4 Hematological abnormalities at baseline. Grade ≥ 2

Arm	Patient id	Parameter	Value	Grade
…				

11.1.8 Biochemical values at baseline

Table 11.1.8.1 Biochemical abnormalities at baseline

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
AST increase																
ALT increase																
Total bilirubin increase																
AP increase																
Creatinine increase																
CPK increase																

(*)Any grade

Table 11.1.8.2 Biochemical values at baseline

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
AST (xULN)			
ALT (xULN)			
Total bilirubin (xULN)			
Direct bilirubin (xULN)			
AP (xULN)			
Creatinine (xULN)			
Cr. Clearance (Calculated) (ml/min)			
Cr. Clearance* (Measured) (ml/min)			
CPK (xULN)			
CPK MB (IU/L)			
Cardiac Troponin I (ng/ml)			
Total proteins (g/dL)			
Albumin (g/dL)			
Uric acid (mg/dL)			
LDH (xULN)			
Beta-2-microglobulin (mg/L)			

(*)If available

Listing 11.1.8.3 Biochemical tests not assessed at baseline

Arm	Patient id.	Lab. test
…	…	

*CPKMB to be assessed as missing only if CPK>ULN

Listing 11.1.8.4 Biochemical abnormalities at baseline. Grade ≥ 2

Arm	Patient id	Parameter	Value	Grade
…				

11.1.9 Other metabolic values at baseline

Table 11.1.9.1 Other metabolic abnormalities at baseline

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Hyperglycemia																
Hypoglycemia																
….																
Hypoalbuminemia																

(*)Any grade

Table 11.1.9.2 Other metabolic values at baseline

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
Sodium (mmol/L)			
Potassium (mmol/L)			
Calcium (mmol/L)			
Magnesium (mmol/L)			
Glucose (mmol/L)			

Listing 11.1.9.3 Metabolic tests not assessed at baseline

Arm	Patient id.	Lab. test
…	…	

Listing 11.1.9.4 Metabolic abnormalities at baseline. Grade ≥ 2

Arm	Patient id	Parameter	Value	Grade
…				

11.1.10 Signs and symptoms at baseline

Table 11.1.10.1 Patients with signs and symptoms at baseline

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. signs and symptoms per patient						
0 1 2 ≥ 3						
Median (Range)						

Table 11.1.10.2 Signs and symptoms at baseline

SOC	Preferred Term	Arm A								Arm B							
		N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
		N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Gastrointestinal disorders	Constipation																
	Diarrhea NOS																
	…																
General disorders and administration site conditions	Fatigue																
	…																

(*)Any grade

Listing 11.1.10.3 Signs and Symptoms at baseline

Arm	Patient id.	Sign/symptom	Grade	Onset date	Relationship	Treated*
…						

(*)See details in Listing 11.2.11.3

11.1.11 Concomitant therapy and procedures at baseline

Concomitant medication at baseline according to the ATC classification.

Table 11.1.11.1 Agents of concomitant therapy started at baseline

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Arm A		Arm B		Total	
			N	%	N	%	N	%
			X	XX.X	X	XX.X	X	XX.X

Table 11.1.11.2 Summary of concomitant medication at baseline

	Arm A		Arm B		Total	
No. of systems at BL (ATC1 level)	N	%	N	%	N	%
0 1 2 ≥ 3 Median (range)						
No. of indications at BL (ATC2 level) 0 1 2 ≥ 3 Median (range)						
No. of agents at BL (ATC4 level) 0 1 2 ≥ 3 Median (range)						

Listing 11.1.11.3 Concomitant therapy/procedures at baseline

Arm	Patient id.	Type	Drug name / Procedure	ATC Code	Route	Total daily dose	Start date	Reason for use	Indication for therapeutic reason
…									

Listing 11.1.11.4 Therapy with antiarrythmics and drugs known to prolong QT at baseline.

Arm	Patient id.	Start date	ATC Code	Type	Reason for use
…					

Taken from concomitant therapy dataset.

Listing 11.1.11.5 Therapy with EPO or G-CSF at baseline.

Arm	Patient id.	Start date	ATC Code	Type	Reason for use
…					

Taken from concomitant therapy dataset. ATC codes L03AA and B03XA

11.2 Measurements of treatment compliance

Not applicable.

11.3 Efficacy analysis

11.3.1 Primary analysis

Table 11.3.1.1 PFS (Independent Review assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.1.1)

11.3.2 Supportive PFS analyses

In the 'time-to-event variables', the unstratified and stratified log-rank test will be used to evaluate the differences between treatment arms and the median values of time-dependent parameters. Their fixed-time estimations will be analyzed according to the Kaplan-Meier method. Median follow-up assessments will be calculated using the Kaplan-Meier method reversing the censoring values (5). Whenever it is not specified, the unstratified test is used.

Table 11.3.2.1 PFS (Investigator Assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.2.1)

Table 11.3.2.2 PFS (Independent Review assessment and "All Randomized Patients" population). Stratified.

	Arm A	Arm B
Stratum 1		
N		
Events		
Censored		
Median PFS		
PFS at 6 months		
Stratum 2		
N		
….		
….		
Log-Rank* / p-value** / HR (95% CI) :		

(*)Stratified log-rank test statistic. (**) p-value from stratified log-rank test

Table 11.3.2.3 PFS (Investigator Assessment and "All Randomized Patients" population). Stratified comparison.

	Arm A	Arm B
Stratum 1		
N		
Events		
Censored		
Median PFS		
PFS at 6 months		
Stratum 2		
N		
Events		
….		
….		
Log-Rank* / p-value** / HR (95% CI) :		

(*)Stratified log-rank test statistic. (**) p-value from stratified log-rank test

Table 11.3.2.4 PFS – Concordance between Independent Review assessment and Investigator assessment ("All Randomized Patients" population)

	Arm A (N=XX)		Arm B (N=YY)		Total (N=ZZ)	
	N	%	N	%	N	%
Event by investigator						
Agreement on event						
Same date						
Later date						
Earlier date						
Censored by investigator						
Agreement on censoring						
Same date						
Different date						
Agreement on status						
Agreement on status and date						

XX, YY, ZZ = Patients evaluable for both Independent review assessment and investigator assessment

Table 11.3.2.5 PFS – Reason of censoring ("All Randomized Patients" population)

Reason of censoring	Independent review assessment				Investigator assessment			
	Arm A		Arm B		Arm A		Arm B	
	N	%	N	%	N	%	N	%
Lost to follow-up								
Subsequent therapy								
>1 missing assessment								
Still on treatment								
…								

11.3.3 Sensitivity analyses of PFS

Table 11.3.3.1 PFS (midpoint imputation method of PD dates) (Independent Review assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.1) .
See imputation methods in section 6.1.

Table 11.3.3.2 PFS (weeks from randomization imputation method of PD dates) (Independent Review assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.2) .
See imputation methods in section 6.1.

Table 11.3.3.3 PFS (missing assessment imputation method of PD dates) (Independent Review assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.3).
See imputation methods in section 6.1.

Two tables and figures 11.3.3.4 and 11.3.3.5 will be performed describing the PFS outcome by Independent Review and Investigator assessment, respectively, using interval censoring methods.

Table 11.3.3.6 PFS (Independent Review assessment and "All Evaluable Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.6)

Table 11.3.3.7 PFS (Investigator Assessment and "All Evaluable Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.7)

Table 11.3.3.8 PFS with confirmation of PD (Independent Review assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.8)

Table 11.3.3.9 PFS with confirmation of PD (Investigator Assessment and "All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.3.9)

Table 11.3.3.10 Time to PD confirmation (Independent Review Assessment and "All Randomized Patients" population)

	Arm A		Arm B		p-value
	Median	95% CI	Median	95% CI	
Time to PD confirmation (days)					

Table 11.3.3.11 Time to PD confirmation (Investigator Assessment and "All Randomized Patients" population)

	Arm A		Arm B		p-value
	Median	95% CI	Median	95% CI	
Time to PD confirmation (days)					

11.3.4 Secondary analyses

11.3.4.1 OS analyses

Table 11.3.4.1.1 OS ("All Randomized Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.1).

Table 11.3.4.1.2 OS stratified comparison ("All Randomized Patients" population)

	Arm A	Arm B
Stratum 1		
N		
Events		
Censored		
Median OS		
OS at 12 months		
OS at 24 months		
Stratum 2		
N		
Events		
….		
….		
Log-Rank* / p-value** / HR (95% CI) :		

(*)Stratified log-rank test statistic. (**) p-value from stratified log-rank test

Table 11.3.4.1.3 OS ("All Randomized Patients" population excluding crossover patients)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.3).

Table 11.3.4.1.4 OS ("All Randomized Patients" population censoring crossover patients at cross-over date)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.4).

Table 11.3.4.1.5 OS ("All Randomized Patients" population and IPCW method)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.5).

Table 11.3.4.1.6 OS ("All Randomized Patients" population and RPSFT method)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.6).

A forest plot (Figure 11.3.4.1.7) with the summary of hazard ratios for PFS and OS in the different analysis populations will be shown to check the consistency across the different measurements.

Table 11.3.4.1.8 OS – Reason of censoring ("All Randomized Patients" population)

Reason of censoring	Arm A		Arm B	
	N	%	N	%
Alive				
Lost to follow-up				
Withdrawal of consent				

Table 11.3.4.1.9 OS (Subpopulation without crossover or subsequent therapy)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.9).

Table 11.3.4.1.10 OS (Subpopulation of patients with event in the primary analysis and without crossover or subsequent therapy)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.10).

Table 11.3.4.1.11 OS ("All Randomized Patients" population and Two-stage method)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.11).

A forest plot (Figure 11.3.4.1.12) with the summary of hazard ratios for OS in the different analysis populations will be shown to check the consistency across the different measurements.

Supportive analyses needed to adjust OS by crossover by the two-stage method

Table 11.3.4.1.13 Logistic regression (Crossover patients *vs* no crossover patients)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits

* Logistic regression
See list of covariates in section 6.2.3

Table 11.3.4.1.14 PFS (Crossover patients *vs* no crossover patients)

	Crossover	No crossover	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.14).

Table 11.3.4.1.15 Post progression survival (Weibull adjustment)

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept								
Treatment arm	-							
Treatment arm	Crossover							
Scale								
Weibull Shape								

11.3.4.2 Response rate by independent review committee

Table 11.3.4.2.1 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population)

Response	Arm A		Arm B	
	N	%	N	%
sCR				

CR				
VGPR				
PR				
MR				
SD				
PD				
Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.4.2.2 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial exact estimator and 95% confidence interval

Table 11.3.4.2.3 Response rate comparison by IMWG (Independent Review assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR+MR					
SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.2.4 Response rate by IMWG (Independent Review assessment and "All Evaluable Patients" population)

Response	Arm A		Arm B	
	N	%	N	%
sCR				
CR				
VGPR				
PR				
MR				
SD				
PD				

Table 11.3.4.2.5 Response rate estimates by IMWG (Independent Review assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial exact estimator and 95% confidence interval

Table 11.3.4.2.6 Response rate comparison by IMWG (Independent Review assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR+MR					
SD+PD					

Table 11.3.4.2.7 Response rate by IMWG at early futility analysis (Independent Review assessment and "All Evaluable Patients" population)

Response	Arm A		Arm B	
	N	%	N	%
sCR				
CR				
VGPR				
PR				
MR				
SD				
PD				

Table 11.3.4.2.8 Response rate estimates without MR by IMWG (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.2.9 Response rate comparison without MR by IMWG (Independent Review assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.2.10 Response rate estimates without MR by IMWG (Independent Review assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.2.11 Response rate comparison without MR by IMWG (Independent Review assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD					

Table 11.3.4.2.12 Median Time to Response (Independent Review assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR, PR or MR

Table 11.3.4.2.13 Median Time to Response without MR (Independent Review assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR or PR

11.3.4.3 Response rate by investigator assessment

Table 11.3.4.3.1 Response rate by IMWG (Investigator assessment and "All Randomized Patients" population)

Response	Arm A		Arm B	
	N	%	N	%
sCR				
CR				
VGPR				
PR				
MR				
SD				
PD				
Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.4.3.2 Response rate estimates by IMWG (Investigator assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.3 Response rate comparison by IMWG (Investigator assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR+MR					
SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.3.4 Response rate by IMWG (Investigator assessment and "All Evaluable Patients" population)

Response	Arm A		Arm B	
	N	%	N	%
sCR				
CR				
VGPR				
PR				
MR				
SD				
PD				

Table 11.3.4.3.5 Response rate estimates by IMWG (Investigator assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.6 Response rate comparison by IMWG (Investigator assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR+MR					
SD+PD					

Table 11.3.4.3.7 Response rate estimates without MR by IMWG (Investigator assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.8 Response rate comparison without MR by IMWG (Investigator assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.3.9 Response rate estimates without MR by IMWG (Investigator assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.10 Response rate comparison without MR by IMWG (Investigator assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD					

Table 11.3.4.3.11 Median Time to Response (Investigator assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR, PR or MR

Table 11.3.4.3.12 Median Time to Response without MR (Investigator assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR or PR

11.3.4.4 Duration of response

Table 11.3.4.4.1 DR (Independent Review assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.1)

Table 11.3.4.4.2 DR (Investigator assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.2)

Table 11.3.4.4.3 DR without MR (Independent Review assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.3)

Table 11.3.4.4.4 DR without MR (Investigator assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.4)

Table 11.3.4.4.5 DR with PD confirmation (Independent Review assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.5)

Table 11.3.4.4.6 DR with PD confirmation (Investigator assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.6)

11.3.4.5 Analysis of crossover

Table 11.3.4.5.1 RR to combination treatment in patients who crossed over from Arm B to Arm A ("All Crossover Patients" population)

		After crossover (N,%)							
		sCR	CR	VGPR	PR	MR	SD	PD	NE
Before crossover	sCR								
	CR								
	VGPR								
	PR								
	MR								
	SD								
	PD								
	NE								

Table 11.3.4.5.2 Intrapatient PFS comparison of patients who crossed over from Arm B to Arm A ("All Crossover Patients" population)

PFS	Before crossover	After crossover
Median		
PFS at 6 months		

Table 11.3.4.5.3 PFS comparison of patients ("All Randomized Patients" population)

PFS	Arm A	Arm B	
		Before crossover	After crossover
Median			
PFS at 6 months			

Listing 11.3.4.5.4 Best response and PFS before and after crossover.

Patient id.	Cycle of crossover	Best response		PFS	
		Before crossover	After crossover	Before crossover	After crossover
…					

Listing 11.3.4.5.5 Best response and PFS before in crossover patients.

Patient id.	Independent review assessment				Investigator assessment			
	Best response	PFS	PFS event	PD confirmation	Best response	PFS	PFS event	PD confirmation
…								

Table 11.3.4.5.6 Time to crossover

	N	Median	Min	Max
Time to crossover (months)				

Table 11.3.4.5.7 Baseline characteristics comparison patients without crossover vs crossover

Variable**	Value	N	Without Crossover	Crossover	p-value*
Sex	F	XXX	XX (XX.X%)	XX (XX.X%)	X.XXXX
	M	XXX	XX (XX.X%)	XX (XX.X%)	
Age	Median(range)	XXX	XX.X (XX-XX)	XX.X (XX-XX)	X.XXXX
…					

(*)Fisher's exact test (categorical variables); Mann-Whitney-Wilcoxon (continuous variables)
(**)Sex, age, PS (ECOG), BSA, Durie Salmon stage, International Staging System, Secretory/Non-secretory, MM type, time from diagnosis, time from last PD, number of prior lines, status to prior therapy, status to prior bortezomib therapy, status to prior thalidomide/lenalidomide therapy, status to prior IMiD therapy, status to prior PIs therapy, stem cell transplantation, plasma cells, hemoglobin, creatinine, calcium, genetic risk, lytic lesions and plasmacytomas.

11.3.4.6 Follow-up

Table 11.3.4.6.1 Median FU for PFS

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Follow-up				

Table 11.3.4.6.2 Median FU for OS

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Follow-up				

11.3.4.7 Symmetry of evaluations

Table 11.3.4.7.1 Time to MM assessments

MM assessment	Treatment group	n	Median (days)	Wilcoxon p-value
1	Arm A			
	Arm B			
2	Arm A			
	Arm B			
…	Arm A			
	Arm B			

This table will be complemented with a boxplot showing the time to first, second, third and further MM assessments by treatment arm (Figure 11.3.4.7.1).

Table 11.3.4.7.2 Time to first assessment

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median to first assessment			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.7.2)

Table 11.3.4.7.3 Time to second assessment

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median second assessment			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.7.3)

11.3.4.8 Univariate analyses

Table 11.3.4.8.1 Univariate analysis of PFS (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.1)

Table 11.3.4.8.2 Univariate analysis of PFS (Investigator Assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.2)

Table 11.3.4.8.3 Univariate analysis of OS (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.3)

Table 11.3.4.8.4 Univariate analysis of OS (Investigator Assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.4)

Table 11.3.4.8.5 Univariate analysis of RR (Independent Review assessment and "All Randomized Patients" population)

	Arm A				Arm B				
Prognostic factors**	N	RR	Proportion (%)	95% CI	N	RR	Proportion (%)	95% CI	p-value*
Gender									
Age									
…									

(*) Logistic regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of ORR confidence intervals will be also shown (Figure 11.3.4.8.5)

Table 11.3.4.8.6 Univariate analysis of RR (Investigator Assessment and "All Randomized Patients" population)

	Arm A				Arm B				
Prognostic factors**	N	RR	Proportion (%)	95% CI	N	RR	Proportion (%)	95% CI	p-value*
Gender									
Age									
…									

(*) Logistic regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of ORR confidence intervals will be also shown (Figure 11.3.4.8.6)

Table 11.3.4.8.7 Univariate analysis of PFS with PD confirmation (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.7)

11.3.4.9 Multivariate analyses

Table 11.3.4.9.1 Multivariate analysis of PFS (Independent Review assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

Table 11.3.4.9.2 Multivariate analysis of PFS (Investigator assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

Table 11.3.4.9.3 Multivariate analysis of RR (Independent Review assessment and "All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits

* Logistic regression
See list of covariates in section 6.2.3

Table 11.3.4.9.4 Multivariate analysis of RR (Investigator assessment and "All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits

* Logistic regression
See list of covariates in section 6.2.3

Table 11.3.4.9.5 Multivariate analysis of OS ("All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

Table 11.3.4.9.6 Multivariate analysis of PFS by region (Independent Review assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

Table 11.3.4.9.7 Multivariate analysis of PFS with PD confirmation (Independent Review assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

11.3.4.10 Best Protein reduction

Table 11.3.4.10.1 Best M-spike reduction from baseline

M-spike reduction from baseline	Arm A				Arm B			
	N	Median	Min	Max	N	Median	Min	Max
Serum (g/dL)								
Urine (mg/24hrs)								

Waterfall plot (Figure 11.3.4.9.1) will be also shown for all patients with at least one post-baseline M-spike evaluation. Applicable only for patients with secretory multiple myeloma. Central lab evaluation.

11.3.5 Characteristics of responders

A summary of the main characteristics of patients showing clinical benefit, defined as patients with MR or better as best response or SD longer than 6 months assessed by Independent Review or by Investigators will be shown.

Listing 11.3.5.1 Characteristics of patients with clinical benefit.

Arm	Patient id.	Gender PS Age	Primary MM type	Relapsed / Refractory	ISS	No. of prior lines	Cycles received	Best response IMWG (IA)	Best response IMWG (IR)	PFS (IA)	DR (IA)	PFS (IR)	DR (IR)	OS
…														

IR- Independent review IA- Investigator assessment

11.3.6 Efficacy analysis by age

If there is a group of patients with scarce percentage of patients (i.e. 5%), it will be joined to the nearest group of age. Age ≥ 85 to Age 75-84, age 75-84 to age 65-74 and age 65-74 to age 18-64.

Table 11.3.6.1 PFS (Independent Review assessment and "All Randomized Patients" population) by age

Age		Arm A	Arm B	Parameter	p-value
Age 18-64	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age 65-74	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age 75-84	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age ≥85	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.6.1a/b/c/d)

Table 11.3.6.2 PFS (Investigator Assessment and "All Randomized Patients" population) by age

Age		Arm A	Arm B	Parameter	p-value
Age 18-64	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age 65-74	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age 75-84	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Age ≥85	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.6.2a/b/c/d)

Table 11.3.6.3 OS ("All Randomized Patients" population) by age

Age		Arm A	Arm B	Parameter	p-value
Age 18-64	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Age 65-74	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Age 75-84	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Age ≥85	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.6.3a/b/c/d).

Table 11.3.6.4 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by age

Age	Response	Arm A		Arm B	
		N	%	N	%
Age 18-64	sCR CR VGPR PR MR SD PD Unknown*				
Age 65-74	sCR CR VGPR PR MR SD PD Unknown*				
Age 75-84	sCR CR VGPR PR MR SD PD Unknown*				
Age ≥85	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.6.5 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by age

Age		Arm A			Arm B		
		Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Age 18-64	Response rate						
Age 65-74	Response rate						
Age 75-84	Response rate						
Age ≥85	Response rate						

Binomial exact estimator and 95% confidence interval

11.3.7 Efficacy analysis based on genetic risks

Patients will be classified in “high risk”, “intermediate risk” or “good prognosis” according to their genetic results (cytogenetic or FISH) at diagnosis or study entry.

Patients with translocations such as t(4;14), t(14;16), t(14;20), del 17, del 13 or single alterations such as +1q or +1p will be classified as “high risk”; patients with translocations such as t(11;14), t(6;14) or other will be classified “intermediate risk”; and finally, those patients with single alterations of trisomies 3, 5, 6, 9, 11, 15, 19 or 21 will be classified as “good prognosis”. This classification will be done by clinical review.

Results from independent review assessment are shown in the following tables.). In case of a high difference between independent review and investigator assessments, RR and PFS tables in this section will be duplicated to show the results according to the investigator assessment and they will be differentiate with “b” (i.e. 11.3.7.1 will be 11.3.7.1b).

Table 11.3.7.1 PFS (Independent Review assessment and “All Randomized Patients” population) by genetic risks

Cytogenetic profile		Arm A	Arm B	Parameter	p-value
High risk	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Intermediate risk	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Good prognosis	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.7.1a/b/c)

Table 11.3.7.2 OS ("All Randomized Patients" population) by genetic risks

Cytogenetic profile		Arm A	Arm B	Parameter	p-value
High risk	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Intermediate risk	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Good prognosis	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.7.2a/b/c).

Table 11.3.7.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by genetic risks

Cytogenetic profile	Response	Arm A		Arm B	
		N	%	N	%
High risk	sCR CR VGPR PR MR SD PD Unknown*				
Intermediate risk	sCR CR VGPR PR MR SD PD Unknown*				
Good prognosis	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.7.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by genetic risks

Cytogenetic profile	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
High risk						
Intermediate risk						
Good prognosis						

Binomial exact estimator and 95% confidence interval

11.3.8 Efficacy analysis in patients resistant or refractory to last lenalidomide/thalidomide or last bortezomib therapy

Patients will be classified in four groups according to their response to prior lenalidomide/thalidomide or bortezomib therapies.

-Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies
-Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib
-Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide
-Other than the above

Results from independent review assessment are shown in the following tables.). In case of a high difference between independent review and investigator assessments, RR and PFS tables in this section will be duplicated to show the results according to the investigator assessment and they will be differentiate with "b" (i.e. 11.3.8.1 will be 11.3.8.1b).

Table 11.3.8.1 PFS (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies		Arm A	Arm B	Parameter	p-value
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Other than the above	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.8.1a/b/c/d)

Table 11.3.8.2 OS ("All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies		Arm A	Arm B	Parameter	p-value
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Other than the above	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.8.2a/b/c/d).

Table 11.3.8.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies	Response	Arm A		Arm B	
		N	%	N	%
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	sCR CR VGPR PR MR SD PD Unknown*				
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	sCR CR VGPR PR MR SD PD Unknown*				
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	sCR CR VGPR PR MR SD PD Unknown*				
Other than the above	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.8.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies						
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib						
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide						
Other than the above						

Binomial exact estimator and 95% confidence interval

11.3.9 Efficacy analysis in patients refractory to last prior therapy

Patients will be classified as refractory to last prior therapy or other.

Results from independent review assessment are shown in the following tables.). In case of a high difference between independent review and investigator assessments, RR and PFS tables in this section will be duplicated to show the results according to the investigator assessment and they will be differentiate with "b" (i.e. 11.3.9.1 will be 11.3.9.1b).

Table 11.3.9.1 PFS (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to last prior therapy	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Other	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.9.2 OS ("All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to last prior therapy	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Other	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.9.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy	Response	Arm A		Arm B	
		N	%	N	%
Refractory to last prior therapy	sCR CR VGPR PR MR SD PD Unknown*				
Other	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.9.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Refractory to last prior therapy						
Other						

Binomial exact estimator and 95% confidence interval

11.3.10 Efficacy analysis in patients exposed to IMiD therapies

Patients who were exposed to IMiD therapies (pomalidomide, thalidomide or lenalidomide) will be classified as responders or refractory

Results from independent review assessment are shown in the following tables.). In case of a high difference between independent review and investigator assessments, RR and PFS tables in this section will be duplicated to show the results according to the investigator assessment and they will be differentiate with "b" (i.e. 11.3.10.1 will be 11.3.10.1b).

Table 11.3.10.1 PFS (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to IMiD therapy	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Responders	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.10.2 OS ("All Randomized Patients" population) in patients exposed to IMiD

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to IMiD therapy	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Responders	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.10.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy	Response	Arm A		Arm B	
		N	%	N	%
Refractory to IMiD therapy	sCR CR VGPR PR MR SD PD Unknown*				
Responders	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.10.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Refractory to IMiD therapy						
Responders						

Binomial exact estimator and 95% confidence interval

11.3.11 Efficacy analysis in patients exposed to PIs therapies

Patients who were exposed to PIs therapies (bortezomib or carfilzomib) will be classified as responders or refractory

Results from independent review assessment are shown in the following tables.). In case of a high difference between independent review and investigator assessments, RR and PFS tables in this section will be duplicated to show the results according to the investigator assessment and they will be differentiate with "b" (i.e. 11.3.11.1 will be 11.3.11.1b).

Table 11.3.11.1 PFS (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to PIs therapy	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	
Responders	N				
	Events				
	Censored				
	Median PFS			Log-Rank: HR (95% CI) :	LR: HR:
	PFS at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.11.2 OS ("All Randomized Patients" population) in patients exposed to PIs

Prior therapy		Arm A	Arm B	Parameter	p-value
Refractory to PIs therapy	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	
Responders	N				
	Events				
	Censored				
	Median OS			Log-Rank: HR (95% CI) :	LR: HR:
	OS at 12 months			Diff:	
	OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.11.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy	Response	Arm A		Arm B	
		N	%	N	%
Refractory to PIs therapy	sCR CR VGPR PR MR SD PD Unknown*				
Responders	sCR CR VGPR PR MR SD PD Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.11.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Refractory to PIs therapy						
Responders						

Binomial exact estimator and 95% confidence interval

12 Safety Analysis

Safety analysis will be carried out on the "All Treated Patients" population.

12.1 Extent of exposure

12.1.1 Treatment administration

Table 12.1.1.1 Number of cycles administered and dose intensity

	Arm A		Arm B	
No. of cycles administered per patient	N	%	N	%
1 2 3 …				
Median (range)				
Time on treatment (weeks) Median Range				
Plitidepsin cumulative dose (mg/m²) Median Range			NA	
Plitidepsin dose intensity (mg/m²/wk) Median Range			NA	
Plitidepsin relative dose intensity (%) Median Range			NA	
Dexamethasone cumulative dose (mg) Median Range				
Dexamethasone dose intensity (mg/wk) Median Range				
Dexamethasone relative dose intensity (%) Median Range				

NA: Not applicable. Cycles after crossover will be excluded.

Table 12.1.1.2 Number of cycles administered and dose intensity after crossover

	After crossover	
No. of cycles administered per patient	N	%
1 2 3 …		
Median (range)		
Time on treatment (weeks) Median Range		
Plitidepsin cumulative dose (mg/m²) Median Range		
Plitidepsin dose intensity (mg/m²/wk) Median Range		
Plitidepsin relative dose intensity (%) Median Range		
Dexamethasone cumulative dose (mg) Median Range		
Dexamethasone dose intensity (mg/wk) Median Range		
Dexamethasone relative dose intensity (%) Median Range		

12.1.2 Cycle delays

12.1.2.1 Number of patients and cycles with dosing delay, any relationship

Listing 12.1.2.1.1 Delays

Arm	Patient id.	Cycle	Day	Agent	Previous cycle	Previous cycle start date	Delayed cycle start date	Dose Delay calculated. (days)	Reason for dose delay	Dose Delay Spec.
…										

Results after crossover will be highlighted

Table 12.1.2.1.2 Number of patients and cycles with dosing delay, any relationship

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. of patients treated						
No. of patients with any dose delay						
No. of cycles administered						
No. of cycles susceptible to be delayed*						
No. of cycles with dosing delay**						
No. of patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed						

(*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to be delayed
Cycles after crossover will be excluded

Table 12.1.2.1.3 Number of patients and cycles with dosing delay according to the relationship

	Arm A				Arm B			
	Treatment-related**		Non-treatment-related		Treatment-related**		Non-treatment-related	
	N	%	N	%	N	%	N	%
No. of patients with 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed								
No. of cycles with dosing delay*								

(*) Denominator= Number of cycles susceptible to be delayed. (**)Hematological reason, non-hematological reason or both
Cycles after crossover will be excluded

Table 12.1.2.1.4 Length of dosing delay.

		Arm A						Arm B					
		Treatment-related**		Non-treatment-related		Total		Treatment-related**		Non-treatment-related		Total	
Length of delay	Median (range)												
Length of delay		N	%	N	%	N	%	N	%	N	%	N	%
<= 7 days													
>7 days and <=14 days													
> 14 days													

(*) Denominator= Number of cycles susceptible to be delayed. (**)Hematological reason, Non-hematological reason or both
Cycles after crossover will be excluded

12.1.2.2 Number of delays according to cycle number

Table 12.1.2.2.1 Number and reasons of delays according to cycle number

		No. of patients		No. of delays		Treatment-related*		Treatment-related						Non-treatment-related*	
								Hematological reason		Non-hematological reason		Both			
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Arm A	Cycle 2														
	…														
	Cycle n^{th}														
Arm B	Cycle 2														
	…														
	Cycle n^{th}														

(*) Denominator= Number of cycles susceptible to be delayed.
Cycles after crossover will be excluded

Table 12.1.2.2.2 Dose reduction in cycles delayed

		Reduction			
		Yes		No	
		N	%	N	%
Arm A	Cycle 2 … Cycle n^{th} Total				
Arm B	Cycle 2 … Cycle n^{th} Total				

Cycles after crossover will be excluded

The distribution of delays according to the cycle administered will be studied by means of counts and percentages. The reasons for cycle delay will be detailed, specifying how many were due to treatment or not.

Listing 12.1.2.2.3 Cycle delays due to AEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences
…									

AEs with action = 'Dose delayed' or 'Reduced and delayed'. Results after crossover will be highlighted

12.1.3 Dose omissions

Listing 12.1.3.1.1 Dose omissions

Arm	Patient id.	Cycle	Day	Agent omitted	Cycle start date	Reason for dose omission	Dose omission Spec.
…							

Results after crossover will be highlighted

Table 12.1.3.1.2 Number of patients and cycles with dose omitted, any relationship

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. of patients treated	X	XX.X	X	XX.X	X	XX.X
No. of patients with any dose omitted						
No. of patients with:						
No plitidepsin omissions			NA			
1 cycle with plitidepsin dose omitted						
2 cycles with plitidepsin dose omitted						
≥ 3 cycles with plitidepsin dose omitted						
No. of patients with:						
No dexamethasone omission						
1 cycle with dexamethasone dose omitted						
2 cycles with dexamethasone dose omitted						
≥ 3 cycles with dexamethasone dose omitted						
No. of cycles administered						
No. of cycles susceptible to have any dose omitted*						
No. of cycles with plitidepsin dosing omitted**			NA			
No. of cycles with dexamethasone dosing omitted**						
No. of cycles with plitidepsin dosing omitted (treatment-related)			NA			
No. of cycles with dexamethasone dosing omitted (treatment-related)						

(*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to have a dose omission
NA: Not applicable. Cycles after crossover will be excluded

Table 12.1.3.1.3 Number of cycles with treatment-related dose omission by patient

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. of patients with:	X	XX.X	X	XX.X	X	XX.X
No omission						
1 cycle with treatment-related plitidepsin dose omitted			NA			
2 cycles with treatment-related plitidepsin dose omitted						
≥ 3 cycles with treatment-related plitidepsin dose omitted						
No. of patients with:						
No omission						
1 cycle with treatment-related dexamethasone dose omitted						
2 cycles with treatment-related dexamethasone dose omitted						
≥ 3 cycles with treatment-related dexamethasone dose omitted						

Denominator= Number of patients that were on treatment on day 14 of cycle 1.
NA: Not applicable. Cycles after crossover will be excluded

Table 12.1.3.1.4 Reasons for dose omissions

Reasons for omissions	Arm A		Arm B		Total	
	N	%	N	%	N	%
Plitidepsin						
Treatment-related	X	XX.X	NA		X	XX.X
Hematological						
Non-hematological						
Both						
Non–treatment-related						
Dexamethasone						
Treatment-related	X	XX.X	X	XX.X	X	XX.X
Hematological						
Non-hematological						
Both						
Non-treatment-related						

NA: Not applicable. Cycles after crossover will be excluded

Listing 12.1.3.2 Dose omissions due to AEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences
…									

AEs with action = 'Dose skipped" on day 8, 15 or 22. Results after crossover will be highlighted

12.1.4 Dose reductions

All dose reductions should be considered and described, specifying the reason for reduction (hematological toxicity, non-hematological toxicity or other causes).

Listing 12.1.4.1.1 Dose reductions

Arm	Patient id.	Cycle	Day	Agent reduced	Cycle start date	Previous dose	Reduced dose	Reason for dose reduction	Dose reduction Spec.
…									

Results after crossover will be highlighted

Table 12.1.4.2 Number of patients and cycles with dose reduction, any relationship

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. of patients treated	X	XX.X	X	XX.X	X	XX.X
No. of patients with any dose reduced						
No. of patients with:			NA			
No plitidepsin reduction						
1 cycle with plitidepsin dose reduced						
2 cycles with plitidepsin dose reduced						
No. of patients with:						
No dexamethasone reduction						
1 cycle with dexamethasone dose reduced						
2 cycles with dexamethasone dose reduced						
No. of cycles administered						
No. of cycles susceptible to have any dose reduced*						
No. of cycles with plitidepsin dose reduced **			NA			
No. of cycles with dexamethasone dose reduced**						
No. of cycles with plitidepsin dose reduced (Treatment-related)			NA			
No. of cycles with dexamethasone dose reduced (Treatment-related)						

(*) All cycles excluding first cycle of those patients who have only received the first infusion. (**) Denominator= Number of cycles susceptible to have a dose omission
NA: Not applicable. Cycles after crossover will be excluded

Table 12.1.4.3 Number of patients and cycles with dose reduction according to the relationship

Reasons for reductions	Arm A		Arm B		Total	
	N	%	N	%	N	%
Plitidepsin						
No. of cycles with dose reductions*			NA			
Treatment-related	X	XX.X			X	XX.X
Hematological						
Non-hematological						
Both						
Non-treatment-related						
Dexamethasone						
No. of cycles with dose reductions*						
Treatment-related	X	XX.X	X	XX.X	X	XX.X
Hematological						
Non-hematological						
Both						
Non–treatment-related						

(*) Denominator= Number of cycles susceptible to have a dose omission. (**)Hematological reason, non-hematological reason or both.
NA: Not applicable. Cycles after crossover will be excluded

Listing 12.1.4.4 Dose reductions due to AEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences
…									

AEs with action = 'Dose reduced/adjusted' or 'Reduced and delayed'. Results after crossover will be highlighted

12.1.5 Infusions temporarily interrupted

A listing of the patients who had infusions temporarily interrupted with the corresponding reasons will be provided.

Listing 12.1.5.1 Interrupted Infusions listing.

Arm	Patient id.	Cycle	Infusion	Interrupted	Reason
…				Yes	

Results after crossover will be highlighted

12.1.6 Prophylactic medication administration

A listing of the patients who have not received Ondansetron, Diphenhydramine and Ranitidine or equivalents in the Arm A with the corresponding reasons will be reported.

Listing 12.1.6.1 Patients and cycles without prophylactic medication administration

Arm	Patient id.	Cycle	Infusion	Prophylactic medication not taken*	Reason
	…				

(*) Ondansetron, diphenhydramine or ranitidine.

12.2 Adverse Events (AEs)

12.2.1 Adverse events

As far as all the toxicities are concerned, the NCI-CTC grade will be used wherever an NCI-CTC grading exists. Otherwise, the severity will be noted. As a convention, the term «Grade» will always be used. Toxicities will be described according to the worst NCI-CTC grade or, for toxicities which do not form the subject of NCI-CTC classification, according to the worst severity.

In this section the adverse events will be described and different tables will be created for events related to treatment (stated as related to at least one of the two trial medications or unknown relationship). In case of a high frequency of adverse events attributable only to one of the investigational drugs, all tables in this section will be duplicated to show adverse events related to plitidepsin or dexamethasone (i.e. table 12.2.2.2, additional tables 12.2.2.2p and 12.2.2.2d).

Type of toxicity and worst grade or severity by cycle and by patient will be summarized according to the Preferred Term coded with MedDRA. Tables will be organized per category of events using System Organ Class of MedDRA.

12.2.2 Display of adverse events

Table 12.2.2.1 Summary of adverse events.

Category	Arm A	Arm B
	N (%)	N (%)
Patients with at least one AE regardless relationship		
Any treatment-related AE		
Any grade 3/4 AE		
Any grade 3/4 treatment-related AE		
Any SAE in DB		
Any treatment-related SAE		
Any grade 3/4 SAE		
Any grade 3/4 treatment-related SAE		
AEs leading to death		
AEs treatment-related leading to death		
AEs leading to dose delay		
AEs leading to dose reduction		
AEs leading to treatment discontinuation		
AEs treatment-related leading to treatment discontinuation		

Events with onset date after crossover will be excluded

Table 12.2.2.2 Evolution of myeloma-related AEs at baseline

	Arm A		Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Fatigue	Grade 0								
		Grade 1								
		……								
	Bone Pain	Grade 0								
		Grade 1								
		……								
	Myopathy	Grade 0								
		Grade 1								
		……								
	……									
	Arm B									
	Fatigue	Grade 0								
		Grade 1								
		……								
	Bone Pain	Grade 0								
		Grade 1								
		……								
	Myopathy	Grade 0								
		Grade 1								
		……								

Events with onset date after crossover will be excluded

Table 12.2.2.3 Treatment-related adverse events. Worst grade by patient

SOC	Preferred Term	Arm A							Arm B						
		Grade 1		…	Grade 4		All*		Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.2.2.4 Treatment-related adverse events. Worst grade by cycle

SOC	Preferred Term	Arm A							Arm B						
		Grade 1		…	Grade 4		All*		Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

* Any grade. Events with onset date after crossover will be excluded

Table 12.2.2.5 Treatment-related adverse events in "All Crossover Patients" population. Worst grade by patient

SOC	Preferred Term	Before crossover							After crossover*						
		Grade 1		…	Grade 4		All**		Grade 1		…	Grade 4		All**	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

(*)All events with onset date ≥ administration date after crossover (**) Any grade

Table 12.2.2.6 Adverse Events regardless of relationship. Worst grade by patient

SOC	Preferred Term	Arm A							Arm B						
		Grade 1		…	Grade 4		All*		Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.2.2.7 Adverse Events regardless of relationship. Worst grade by cycle

SOC	Preferred Term	Arm A							Arm B						
		Grade 1		…	Grade 4		All*		Grade 1		…	Grade 4		All*	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.2.2.8 Adverse Events regardless of relationship in "All Crossover Patients" population. Worst grade by patient

SOC	Preferred Term	Before crossover							After crossover*						
		Grade 1		…	Grade 4		All**		Grade 1		…	Grade 4		All**	
		N	%	…	N	%	N	%	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS														
	Diarrhea NOS														
	…														
Cardiac disorders	Arrhythmia NOS														
	…														

(*)All events with onset date ≥ administration date after crossover (**) Any grade.

Listing 12.2.2.9 Treatment-related grade 3-4 adverse events. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

Events with onset date after crossover will be excluded

Listing 12.2.2.10 Treatment-related grade 3-4 adverse events. Worst grade by cycle

Arm	Patient id.	Cycle	SOC Name	Preferred term	Grade
…					

Events with onset date after crossover will be excluded

Listing 12.2.2.11 Adverse Events grade 3-4 regardless of relationship. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

Events with onset date after crossover will be excluded

Listing 12.2.2.12 Adverse Events grade 3-4 regardless of relationship. Worst grade by cycle

Arm	Patient id.	Cycle	SOC Name	Preferred term	Grade
…					

Events with onset date after crossover will be excluded

Listing 12.2.2.13 Treatment-related grade 3-4 adverse events in "All Crossover Patients" population. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

Listing 12.2.2.14 Adverse Events grade 3-4 regardless of relationship in "All Crossover Patients" population. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

At the time of the analysis, if appropriate, grouping of similar or clinically related items will be made.

12.3 Serious Adverse Events and deaths.

12.3.1 Serious Adverse Events

Listing 12.3.1.1 SAEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolved date	Action	Serious Criteria
…											

SAEs narratives of pharmacovigilance DB will be provided by the pharmacovigilance department.

12.3.2 Deaths

Table 12.3.2.1 Cause of death

Reason*	Arm A		Arm B	
	N	%	N	%
Malignant disease				
Treatment-related adverse event				
Other				
Total				

(*) Denominator=Number of patients who died

Listing 12.3.2.2 Deaths

Arm	Patient id.	Death date	Cause	Comments	Autopsy	Autopsy report available	Number of cycles administered	Last infusion date	Time on treatment*	Time from Last dose**
…										

(*)Time on treatment: defined as last infusion date plus 30 days, or date of death or subsequent therapy (whichever comes first) minus first infusion date. (**)Time from last dose defined as death date minus last infusion date.

Listing 12.3.2.3 Deaths due to AEs

Arm	Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Action
…									

* AEs with Seriousness=Death

12.4 Clinical laboratory evaluation

12.4.1 Hematological abnormalities

Hematological toxicities classified according to the NCI-CTC will be calculated for all cycles. The worst grade reached by each patient during treatment will be also calculated.

If serious toxicities happen, special follow-up, with descriptives and graphs (boxplots, line plots) will be made to find out the pattern of thrombocytopenia and neutropenia within and between the different cycles.

Table 12.4.1.1 Hematological abnormalities during treatment, worst grade per patient

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Leukopenia																
Anemia																
Thrombocytopenia																
Neutropenia																
Lymphopenia																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.1.2 Hematological abnormalities during treatment, worst grade per cycle

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Leukopenia																
Anemia																
Thrombocytopenia																
Neutropenia																
Lymphopenia																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.1.3 Hematological abnormalities in during treatment in the "All Crossover Patients" population, worst grade per patient

	Arm B, before crossover								Arm B, after crossover to Arm A							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Leukopenia																
Anemia																
Thrombocytopenia																
Neutropenia																
Lymphopenia																

(*) Any grade

Listing 12.4.1.4 Grade 3-4 hematological abnormalities during treatment. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Events with onset date after crossover will be excluded

Listing 12.4.1.5 Grade 3-4 hematological abnormalities during treatment. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

Events with onset date after crossover will be excluded

Listing 12.4.1.6 Hematological tests not assessed at any treatment visit per patient

Arm	Patient id.	Lab. test
…		

Listing 12.4.1.7 Hematological tests not assessed by patient and cycle

Arm	Patient id.	Cycle	Lab. test
…			

Table 12.4.1.8 Platelets and RBC transfusions during the study

		Platelets (Units)		Red Blood Cells (Units)	
		Arm A	Arm B	Arm A	Arm B
		N(%)	N(%)	N(%)	N(%)
Platelets (Units)	0 transfusions				
	1 transfusion				
	…				
	Median (range)				
Red Blood Cells (Units)	0 transfusions				
	1 transfusion				
	…				
	Median (range)				

Events with onset date after crossover will be excluded

These tables will be complemented with plots for the median nadir of neutrophils (Figure 12.4.1.9), platelets count (Figure 12.4.1.10) and hemoglobin values (Figure 12.4.1.11) by cycle along the treatment. Furthermore, if appropriate, graphs of the intercycle time course of neutropenia and thrombocytopenia will be provided. Eventually, graphs comparing the time course during the first and second cycle will be created.

Listing 12.4.1.12 Grade 3-4 hematological abnormalities during treatment in the "All Crossover Patients" population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.1.13 Grade 3-4 hematological abnormalities during treatment in the "All Crossover Patients" population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

12.4.2 Biochemical abnormalities

Grades of liver toxicity and intercycle pattern of creatinine, CPK, bilirubin, transaminases increase and alkaline phosphatase increase during a cycle will be calculated, as it is explained in the corresponding section for hematological toxicities.

Table 12.4.2.1 Biochemical abnormalities during treatment, worst grade per patient

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
AST increase																
ALT increase																
Total bilirubin increase																
AP increase																
Creatinine increase																
CPK increase																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.2.2 Biochemical abnormalities during treatment, worst grade per cycle

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
AST increase																
ALT increase																
Total bilirubin increase																
AP increase																
Creatinine increase																
CPK increase																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.2.3 Biochemical abnormalities during treatment in the "All Crossover Patients" population, worst grade per patient

	Arm B, before crossover								Arm B, after crossover to Arm A							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
AST increase																
ALT increase																
Total bilirubin increase																
AP increase																
Creatinine increase																
CPK increase																

(*) Any grade

Listing 12.4.2.4 Grade 3-4 biochemical abnormalities during treatment. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Events with onset date after crossover will be excluded

Listing 12.4.2.5 Grade 3-4 biochemical abnormalities during treatment. Worst grade per cycle

Arm	Patient id.	Cycle	Test	Grade
…				

Events with onset date after crossover will be excluded

Listing 12.4.2.6 Biochemical tests not assessed at any treatment visit by patient

Arm	Patient id.	Lab. test
…		

Listing 12.4.2.7 Biochemical tests not assessed by patient and cycle

Arm	Patient id.	Cycle	Lab. test
…			

These tables will be complemented with plots for the median peak of ALT (Figure12.4.2.8), AST (Figure12.4.2.9) and CPK values (Figure12.4.2.10) by cycle along the treatment. If appropriate, graphs of the intercycle time course of ALT, AST and CPK will be provided.

Listing 12.4.2.11 Grade 3-4 biochemical abnormalities during treatment in the "All Crossover Patients" population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.2.12 Grade 3-4 biochemical abnormalities during treatment in the "All Crossover Patients" population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

12.4.3 Other metabolic parameters

Table 12.4.3.1 Metabolic abnormalities during treatment, worst grade per patient

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Hyperglycemia																
Hypoglycemia																
Hypoalbuminemia																
….																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.3.2 Metabolic abnormalities during treatment, worst grade per cycle

	Arm A								Arm B							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Hyperglycemia																
Hypoglycemia																
Hypoalbuminemia																
….																

(*) Any grade. Events with onset date after crossover will be excluded

Table 12.4.3.3 Metabolic abnormalities during treatment in the "All Crossover Patients" population, worst grade per patient

	Arm B, before crossover								Arm B, after crossover to Arm A							
	N	Grade 1		…	Grade 4		All*		N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%		N	%	…	N	%	N	%
Hyperglycemia																
Hypoglycemia																
Hypoalbuminemia																
….																

(*) Any grade

Listing 12.4.3.4 Grade 3-4 metabolic abnormalities during treatment. Worst grade by patient

Arm	Patient id.	Test	Grade
…			

Events with onset date after crossover will be excluded

Listing 12.4.3.5 Grade 3-4 metabolic abnormalities during treatment. Worst grade by cycle

Arm	Patient id.	Cycle	Test	Grade
…				

Events with onset date after crossover will be excluded

Listing 12.4.3.6 Metabolic tests not assessed at any treatment visit by patient

Arm	Patient id.	Lab. test
…		

Listing 12.4.3.7 Metabolic tests not assessed by patient and cycle

Arm	Patient id.	Cycle	Lab. test
…			

Listing 12.4.3.8 Grade 3-4 metabolic abnormalities during treatment in the "All Crossover Patients" population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.3.9 Grade 3-4 metabolic abnormalities during treatment in the "All Crossover Patients" population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

12.4.4 Laboratory values over time

In this section, grades 3-4 hematological and liver enzyme abnormalities will be displayed according to the cycle in which they occurred.

Table 12.4.4.1 Evolution of hematological abnormalities from baseline by treatment arm, worst case per patient.

	Arm A		Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								
	Arm B									
	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	…	Grade 0								
		Grade 1								
		……								

Events with onset date after crossover will be excluded

Table 12.4.4.2 Evolution of transaminase abnormalities from BL by treatment arm, worst case per patient.

	Arm A		Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	Arm B									
	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								

Events with onset date after crossover will be excluded

Table 12.4.4.3 Grade 3-4 laboratory abnormalities in the first cycle and in all other cycles

Laboratory abnormalities	Arm A						Arm B					
	Cycle 1			Cycle>1			Cycle 1			Cycle>1		
	No. cycles evaluated	No. cycles grade 3-4	%	No. cycles evaluated	No. cycles grade 3-4	%	No. cycles evaluated	No. cycles grade 3-4	%	No. cycles evaluated	No. cycles grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												
ALT												
CPK												

Events with onset date after crossover will be excluded

Table 12.4.4.4 ALT time-course pattern

Laboratory abnormalities	Onset day grade 3-4	Days in grade 3-4	Day of recovery to 2.5 x ULN			Days to recovery		
			<=28	29-35	>35	<=28	29-35	>35
Arm A								
ALT								
Arm B								
ALT								

Events with onset date after crossover will be excluded

Table 12.4.4.5 AST time-course pattern

Laboratory abnormalities	Onset day grade 3-4	Days in grade 3-4	Day of recovery to 2.5 x ULN			Days to recovery		
			<=28	29-35	>35	<=28	29-35	>35
Arm A								
AST								
Arm B								
AST								

Events with onset date after crossover will be excluded

12.5 Vital signs, physical findings, LVEF, ECG and other tests related to safety

12.5.1 Vital signs and physical findings

Table 12.5.1.1 ECOG performance status during the study

	Cycle/PS*						
	0	1	2	3	..	..	..
Arm/Patient id.							
…					.	.	.
…					.	.	.

(*) Worst ECOG PS of the cycle determinations. Results after crossover will be highlighted.

Table 12.5.1.2 Weight by patient per cycle

	Cycle/Weight						
	0 (kg)	1* (%)	2* (%)	3* (%)	..	..	..
Arm/Patient id.							
…					.	.	.

(*) % of changes respect to baseline Results after crossover will be highlighted.

12.5.2 LVEF, ECG and other related tests

Listing 12.5.2.1 LVEF evolution during the study.

Arm	Patient id.	LVEF(%)		
		Baseline*	Minimum*	End of treatment*
All	Median(Range)			

(*) LVEF (%) value and method

Listing 12.5.2.2 Electrocardiogram results. Evolution during the study.

Arm	Patient id.	Cycle	ECG result
…			

Results after crossover will be highlighted.

Listing 12.5.2.3 Median change in LVEF.

Arm	Cycles	LVEF
	Baseline	XX
	Minimum	YY
	End of treatment	ZZ

Listing 12.5.2.4 Troponin values. Evolution during the study.

Arm	Patient id.	Cycle	Infusion	Value	ULN
…					

Results after crossover will be highlighted.

12.6 Concomitant therapy / procedures according to the ATC classification.

Table 12.6.1 Concomitant medication during treatment (ATC1, ATC2 and ATC4 levels)

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Arm A		Arm B		Total	
			N	%	N	%	N	%
			X	XX.X	X	XX.X	X	XX.X

Table 12.6.2 Summary of concomitant medication during treatment

	Arm A		Arm B		Total	
	N	%	N	%	N	%
No. of systems at BL (ATC1 level) 0 1 2 ≥ 3 Median (range)						
No. of indications at BL (ATC2 level) 0 1 2 ≥ 3 Median (range)						
No. of agents at BL (ATC4 level) 0 1 2 ≥ 3 Median (range)						

Listing 12.6.3 Patients on antiarrhythmics and/or known QT prolongation inducers treatment.

Arm	Patient id.	Type	Agent	Route	Dose	Unit	Start date	Stop date	Reason	Indication
…										

Listing 12.6.4 Patients with EPO or G-CSF.

Arm	Patient id.	Type	Agent	Route	Dose	Unit	Start date	Stop date	Reason	Indication
…										

Listing 12.6.5 Patients with any transfusion during treatment

Arm	Patient	Cycle	Date	Specify (Nº units required)	Reason
…					

Taken from concomitant therapy dataset.

Table 12.6.6 G-CSF, transfusions or EPO during treatment

	Arm A		Arm B		Total	
	N	%	N	%	N	%
G-CSF Platelets transfusions RBC transfusions EPO						

Table 12.6.7 Subsequent therapy

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Type Chemotherapy …						
Subsequent chemotherapy agents (ATC) … …						

Table 12.6.8 Time to subsequent therapy or death

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Time to subsequent therapy or death			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 12.6.8)

12.7 Safety analysis in special subgroups

Table 12.7.1 Worst grade 3-4 by patient in special subgroups (Gender)

Events	Arm A						Arm B					
	Male			Female			Male			Female		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												
ALT												
CPK												
Nausea												
Vomiting												
Fatigue												
Other*												

(*)Any treatment-related toxicity present in >=5% of patients in any group

Table 12.7.2 Worst grade 3-4 by patient in special subgroups (Age)

Events	Arm A						Arm B					
	<65 years old			…**			<65 years old			…**		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												
ALT												
CPK												
Nausea												
Vomiting												
Fatigue												
Other*												

(*)Any treatment-related toxicity present in >=5% of patients in any group
(**) Age 65-74, Age 75-84, Age ≥85. If there is a group of age with less than 5% of patients, it could be join with the previous/next group of age.

Table 12.7.3 Worst grade 3-4 by patient in special subgroups (BMI)

Events	Arm A						Arm B					
	<30			≥30			<30			≥30		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												
ALT												
CPK												
Nausea												
Vomiting												
Fatigue												
Other*												

(*)Any treatment-related toxicity present in >=5% of patients in any group

12.8 Time to PS (ECOG) deterioration as index of QoL

Table 12.8.1 Time to PS (ECOG) deterioration

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Time to first PS (ECOG) deterioration			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 12.8.1)
Time to PS value 2 or worse in patients with PS 0 or 1 at baseline will be assessed

APPENDIX II

13 DB Listings

CRF Listings.

-Listing 13.1.1: Cover
-Listing 13.1.2: Study registration
-Listing 13.1.3: Demography
-Listing 13.1.4: Pregnancy test
-Listing 13.1.5: Prior history
-Listing 13.1.6: Multiple myeloma history
-Listing 13.1.7: Prior radiotherapy
-Listing 13.1.8: Prior anticancer therapy
-Listing 13.1.9: Prophylactic medication
-Listing 13.1.10: Drug administration
-Listing 13.1.11: Hematology laboratory values
-Listing 13.1.12: Biochemical laboratory values
-Listing 13.1.13: Coagulation laboratory values
-Listing 13.1.14: Physical examination
-Listing 13.1.15: Performance status
-Listing 13.1.16: Vital signs
-Listing 13.1.17: Electrocardiogram
-Listing 13.1.18: LVEF
-Listing 13.1.19: MM protein measurements
-Listing 13.1.20: Bone marrow assessment
-Listing 13.1.21: Tumor evaluation
-Listing 13.1.22: Adverse events (including signs and symptoms)
-Listing 13.1.23: Concomitant therapy/procedures
-Listing 13.1.24: Overall response assessment by cycle
-Listing 13.1.25: Best overall response
-Listing 13.1.26: End of treatment
-Listing 13.1.27: Follow up
-Listing 13.1.28: Death report form
-Listing 13.1.29: Off study
-Listing 13.1.30: Signature report
-Listing 13.1.31: Investigator comments

External review listings

-Listing 13.1.32: MM protein measurement review
-Listing 13.1.33: Bone marrow assessment review
-Listing 13.1.34: Tumor evaluation review
-Listing 13.1.35: External response review

14 References

1. O'Brien P, Fleming T. A multiple testing procedure for clinical trials. Biometrics 1979; 35, 549-556.
2. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Statist Theory Meth. 1991;20(8):2609-31.
3. Turnbull B. The empirical distribution function with arbitrary grouped, censored and truncated data. J R Stat Soc Ser B 1976; 38:290–295
4. SAS OnlineDoc, V9.
5. Parmar M. Machin D. Survival analysis. A practical approach. Wiley, Chichester, 1995.
6. Robins JM, Finkelstein DM: Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 56:779-788, 2000.
7. Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations. Med Decis Making 2014;34(3):387-402.

15 Revision History

From Statistical Analysis Plan v5.0 to v6.0:

This amendment of the Statistical Analysis Plan (SAP) is intended to incorporate an additional overall survival sensitivity analysis in order to better characterize the impact of crossover in arm B. The addition of this new analysis was consulted and agreed with the EMA Product Team Members in a clarification meeting that took place on 12th of June of 2017.

The nature of these analyses is supportive for the secondary analyses of overall survival already described in previous versions of the SAP.

Rational of changes:

In order to improve the characterisation of the actual impact of crossover in those patients who switched from DXM (Arm B) to plitidepsin plus DXM (Arm A), an analysis based on the two-stage method proposed by Latimer *et al.* (7) is performed.
Briefly, the two-stage estimation is a method that provides a good fit to the treatment change mechanics often observed in oncology. Usually, switching is only permitted after disease progression, but this is likely to occur shortly afterwards. In that case, disease progression can be used as a secondary baseline for patients in the control group. Fitting a Weibull model would be expected to produce a reasonable estimate of the effect resulting from switching to the experimental treatment, provided that 1) the model fits the data, 2) "no unmeasured confounders" are present at the secondary baseline, and 3) switching occurs soon after the secondary baseline. The resulting acceleration factor associated with treatment change could then be used to "shrink" survival times in switching patients to derive a counterfactual survival dataset upon which standard survival analysis could be undertaken.

CHANGES:

Included changes are highlighted in *Italic Bold.*

PAGE 16-17: Section 6.2.3 Secondary analyses – Overall survival

Original text:

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of crossover in a first sensitivity analysis excluding the patients who crossed over and a second analysis censoring survival at the time of crossover. Estimates of the unbiased effect in survival will be studied by means of, rank preserving structural failure time (RPSFT)

models for correcting for treatment changes (2) and by the inverse probability of censoring weighting (IPCW) method (6).

The following time-dependent covariates will be included in the IPCW analysis: ECOG, Body Surface Area (BSA), m-protein value (serum/urine), number of adverse events grade≥3, bone marrow plasma cells, creatinine, LDH, hemoglobin and corrected serum calcium. Also, baseline covariates such us gender, age, MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed *vs.* relapsed/refractory), refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, presence of plasmacytomas, presence of lytic lesions, number of plasmacytomas, sum of the dimensions of plamacytomas, will be included.

Changes to:

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of crossover in a first sensitivity analysis excluding the patients who crossed over and a second analysis censoring survival at the time of crossover. Estimates of the unbiased effect in survival will be studied by means of~~,~~ rank preserving structural failure time (RPSFT) models for correcting for treatment changes (2), ~~***and***~~ by the inverse probability of censoring weighting (IPCW) method (6) ***and by means of the two-stage method proposed by Latimer et al. (7) in order to try to control any bias caused by treatment crossover***.

The following time-dependent covariates will be included in the IPCW analysis: ECOG, Body Surface Area (BSA), m-protein value (serum/urine), number of adverse events grade≥3, bone marrow plasma cells, creatinine, LDH, hemoglobin and corrected serum calcium. Also, baseline covariates such us gender, age, MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed *vs.* relapsed/refractory), refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, presence of plasmacytomas, presence of lytic lesions, number of plasmacytomas, sum of the dimensions of plamacytomas, will be included.

PAGE 49, section 11.3.4.1 OS analyses

ADDED

Table 11.3.4.1.11 OS ("All Randomized Patients" population and Two-stage method)

	Arm A	Arm B	Parameter	p-value
N				
Events				

Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.11).

A forest plot (Figure 11.3.4.1.12) with the summary of hazard ratios for OS in the different analysis populations will be shown to check the consistency across the different measurements.

Supportive analyses needed to adjust OS by crossover by the two-stage method

Table 11.3.4.1.13 Logistic regression (Crossover patients *vs* no crossover patients)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits

* Logistic regression
See list of covariates in section 6.2.3

Table 11.3.4.1.14 PFS (Crossover patients *vs* no crossover patients)

	Crossover	No crossover	Parameter	p-value
N				
Events				
Censored				
Median PFS			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.14).

Table 11.3.4.1.15 Post progression survival (Weibull adjustment)

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept								
Treatment arm	-							
Treatment arm	Crossover							
Scale								
Weibull Shape								

PAGE 103, section 14 References

ADDED

1. Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations. Med Decis Making 2014;34(3):387-402.

From Statistical Analysis Plan v4.0 to v5.0:

This amendment of the Statistical Analysis Plan (SAP) is intended to incorporate some additional analysis and clarifications requested during the pre-submission meetings on (22Apr2016), (27Jun2016) and (30Jun2016), by the EMA Product Team Members, and the CHMP Rapporteur and CHMP Co-Rapporteur appointed for the evaluation of the Marketing Authorization Application of plitidepsin in multiple myeloma in relation with the clinical part of the dossier.

The nature of these analyses is supportive for the main and secondary analyses already described in previous versions of the SAP.

Rational of changes:

A comparison of the baseline characteristics in patients with Crossover *vs.* No crossover has been requested to rule out that patients with crossover can have a better prognosis than patients without crossover. Analysis will be added in section 11.

A description of patients with crossover will be provided in order to confirm if PD prior to crossover was seen. Supplementary statistics of the time (in months) from study initiation to crossover will also be included.

After discussion with the agencies personnel who will be involved in the assessment of the centralized procedure for Aplidin, the sensitivity analysis of PFS taking into account the confirmation of PD has been pointed out as a key sensitivity analysis to put in context the results of Admyre. Thus, not only the univariate analysis of PFS with confirmation of PD by IA, IRC but also subgroup analysis, and analysis of other secondary endpoints like DR using this second algorithm for determination of PD will be added to the set of sensitivity analyses.

In line with the discussion on the management of patients with or without confirmation of PD, a measure of the time from randomization to treatment failure that leads to the need of a further treatment regimen (regardless the method of PD detection or the components of the PD) could by the Time to first subsequent therapy or death. This will be included as supportive analysis.

An analysis of the median time window between the first PD and its confirmation in a second assessment has been requested to rule out that confirmation of PD could have been advanced or delayed in any of the treatment groups.

Multivariate analyses of PFS by IRC (adding region as a covariate) have been added to check if there are differences in the main efficacy endpoint between different continents/geographical areas.

Since the clinical benefit in terms of objective response is measured in different studies and along the different response criteria versions with and without taking into account the MR, a sensitivity analysis of response and its duration will be performed taking into account response equal PR or better. In addition, time to response with and without MR will be added.

The SAP includes different secondary analyses of OS taking into account a potential effect of crossover. It has been hypothesized that patients without crossover or subsequent therapies could have a worse prognosis. Analyses will be carried out to investigate the isolated effect of study treatments in survival in the population of patient without subsequent therapy.

Supportive analysis to describe potential effects of the study drugs in QoL has been requested. Since patient reported outcome questionnaires have not been collected in this study, an indirect measure like time to first performance status deterioration have been added.

CHANGES:

Included changes are highlighted in *Italic Bold.*

PAGE 5: ABBREVIATIONS AND GLOSSARY

ADDED

CHMP	*Committee for Medicinal Products for Human Use*
…	
EMA	*European Medicines Agency*
…	
QoL	*Quality of Life*

PAGE 17: Section 6.2.3 Secondary analyses – Overall survival

ADDED

An analysis will be carried out in the subpopulation of patients without crossover or subsequent therapy in order to investigate the isolated effect of study treatments in survival in this subpopulation. It will be also carried out in the subpopulation of patients without crossover or subsequent therapy and with event in the primary analysis of PFS by IRC.

PAGE 17: Section 6.2.3 Secondary analyses – Response rate

ADDED

A supportive analysis of response rate will be performed taking into account PR or better as best overall response based on the IMWG criteria.

PAGE 17: Section 6.2.3 Secondary analyses – Duration of response

ADDED

DR requiring confirmation of PD for determination of PFS will be analyzed according to the Kaplan-Meier method and compared between treatment groups using the log-rank test.

DR for patients who have PR or better as best overall response based on the IMWG criteria will be calculated as a supportive analysis.

PAGE 17: Section 6.2.3 Secondary analyses – Time to response

ADDED

Time to response

Time to response will be analyzed according to the Kaplan-Meier method and compared between treatment groups using the log-rank test.

Time to response for patients who have PR or better as best overall response based on the IMWG criteria will be also calculated as a supportive analysis.

PAGE 17: Section 6.2.3 Secondary analyses – Analysis of crossover

ADDED

A comparison of the baseline characteristics in patients with Crossover vs No crossover will be done to rule out that patients with crossover can have a better prognosis than patients without crossover.

A listing of patients with crossover will be provided in order to confirm if PD was seen before crossover and if this PD was confirmed.

Statistics of the time (in months) from study initiation to crossover will also be included.

PAGE 18: Section 6.2.3 Secondary analyses – Symmetry evaluations

ADDED

An analysis of the median time window between the first documentation of PD and PD confirmation in a second assessment will be done to rule out that confirmation of PD could have been advanced or delayed in any of the treatment groups.

PAGE 18: Section 6.2.3 Secondary analyses – Analysis of prognostic factors, subgroup analysis and multivariate analyses

ADDED

….

The analyses above will be also performed for the sensitivity analysis of PFS with confirmation of PD by IRC and IA.

In addition, and in order to check if there are differences in the main efficacy endpoint between different continents/geographical areas, multivariate analyses of PFS by IRC, adding region as a covariate, will be performed. The variable "region" will be created with four categories (Europe, Asia, Oceania, and USA) and then three Cox regressions will be performed.

1) PFS by IRC with arm, region and interaction term.

2) PFS by IRC with arm and region as main effects.

3) Full model selected in the multivariate analysis of PFS by IRC, including region as variable.

PAGE 21: Section 8.3 Subsequent therapy

ADDED

Time to first subsequent therapy or death will be analyzed as a measure of the time from randomization to treatment failure that leads to the need of a further treatment regimen (regardless the method of PD detection or the components of the PD).

PAGE 23: Section 8.13 Analyses of performance status as a index of quality of life

ADDED

8.13 Analyses of performance status as a index of quality of life

Since patient reported outcome questionnaires have not been collected in this study, indirect measures of improvement like time to first performance status deterioration will be analyzed according to the Kaplan-Meier method

PAGE 28: Section 11.1.1 Patient characteristics at baseline

ADDED

Table 11.1.1.4 Baseline characteristics comparison by treatment arm

*Variable***	*Value*	*N*	*Arm A*	*Arm B*	*p-value**
Sex	*F*	*XXX*	*XX (XX.X%)*	*XX (XX.X%)*	*X.XXXX*
	M	*XXX*	*XX (XX.X%)*	*XX (XX.X%)*	
Age	*Median(range)*	*XXX*	*XX.X (XX-XX)*	*XX.X (XX-XX)*	*X.XXXX*
…					

(*)Fisher's exact test (categorical variables); Mann-Whitney-Wilcoxon (continuous variables)
(**)Sex, age, region, PS (ECOG), BSA, Durie Salmon stage, International Staging System, Secretory/Non-secretory, MM type, time from diagnosis, time from last PD, number of prior lines, status to prior therapy, status to prior bortezomib therapy, status to prior thalidomide/lenalidomide therapy, status to prior IMiD therapy, status to prior PIs therapy, stem cell transplantation, plasma cells, hemoglobin, creatinine, calcium, genetic risk, lytic lesions and plasmacytomas.

PAGE 46, section 11.3.3 Sensitivity analyses of PFS

ADDED

Table 11.3.3.10 Time to PD confirmation (Independent Review Assessment and "All Randomized Patients" population)

	Arm A		*Arm B*		*p-value*
	Median	*95% CI*	*Median*	*95% CI*	
Time to PD confirmation (days)					

Table 11.3.3.11 Time to PD confirmation (Investigator Assessment and "All Randomized Patients" population)

	Arm A		*Arm B*		*p-value*
	Median	*95% CI*	*Median*	*95% CI*	
Time to PD confirmation (days)					

PAGE 49, section 11.3.4.1 OS analyses

ADDED

Table 11.3.4.1.9 OS (Subpopulation without crossover or subsequent therapy)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.9).

Table 11.3.4.1.10 OS (Subpopulation of patients with event in the primary analysis and without crossover or subsequent therapy)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median OS			Log-Rank: HR (95% CI) :	LR: HR:
OS at 12 months			Diff:	
OS at 24 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.10).

PAGE 51, section 11.3.4.2 Response rate by independent review committee

ADDED

Table 11.3.4.2.8 Response rate estimates without MR by IMWG (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.2.9 Response rate comparison without MR by IMWG (Independent Review assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.2.10 Response rate estimates without MR by IMWG (Independent Review assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.2.11 Response rate comparison without MR by IMWG (Independent Review assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD					

Table 11.3.4.2.12 Median Time to Response (Independent Review assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR, PR or MR

Table 11.3.4.2.13 Median Time to Response without MR (Independent Review assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR or PR

PAGE 53, section 11.3.4.3 Response rate by investigator assessment

ADDED

Table 11.3.4.3.7 Response rate estimates without MR by IMWG (Investigator assessment and "All Randomized Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.8 Response rate comparison without MR by IMWG (Investigator assessment and "All Randomized Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD+UK*					

(*) Including NE and insufficient data available.

Table 11.3.4.3.9 Response rate estimates without MR by IMWG (Investigator assessment and "All Evaluable Patients" population)

	Arm A			Arm B		
	Proportion	Lower 95% limit	Upper 95% limit	Proportion	Lower 95% limit	Upper 95% limit
Response rate						

Binomial estimates and 95% exact confidence interval

Table 11.3.4.3.10 Response rate comparison without MR by IMWG (Investigator assessment and "All Evaluable Patients" population)

Response rate	Arm A		Arm B		Fisher exact test (p-value)
	N	%	N	%	
sCR+CR+VGPR+PR					
MR+SD+PD					

Table 11.3.4.3.11 Median Time to Response (Investigator assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR, PR or MR

Table 11.3.4.3.12 Median Time to Response without MR (Investigator assessment)

	Arm A		Arm B	
	Median	95% CI	Median	95% CI
Time to response*				

(*)sCR, CR, VGPR or PR

PAGE 54, section 11.3.4.4 Duration of response

ADDED

Table 11.3.4.4.3 DR without MR (Independent Review assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.3)

Table 11.3.4.4.4 DR without MR (Investigator assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.4)

Table 11.3.4.4.5 DR with PD confirmation (Independent Review assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.5)

Table 11.3.4.4.6 DR with PD confirmation (Investigator assessment and "All Responder Patients" population)

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median DR			Log-Rank: HR (95% CI) :	LR: HR:
DR at 6 months			Diff:	

Kaplan-Meier plot will be also shown (Figure 11.3.4.4.6)

PAGE 56, section 11.3.4.5 Analysis of crossover

ADDED

Listing 11.3.4.5.4 Best response and PFS before in crossover patients.

Patient id.	Independent review assessment				Investigator assessment			
	Best response	PFS	PFS event	PD confirmation	Best response	PFS	PFS event	PD confirmation
…								

Table 11.3.4.5.5 Time to crossover

	N	Median	Min	Max
Time to crossover (months)				

Table 11.3.4.5.6 Baseline characteristics comparison patients without crossover vs crossover

Variable**	Value	N	Without Crossover	Crossover	p-value*
Sex	F	XXX	XX (XX.X%)	XX (XX.X%)	X.XXXX
	M	XXX	XX (XX.X%)	XX (XX.X%)	
Age	Median(range)	XXX	XX.X (XX-XX)	XX.X (XX-XX)	X.XXXX
…					

(*)Fisher's exact test (categorical variables); Mann-Whitney-Wilcoxon (continuous variables)
(**)Sex, age, PS (ECOG), BSA, Durie Salmon stage, International Staging System, Secretory/Non-secretory, MM type, time from diagnosis, time from last PD, number of prior lines, status to prior therapy, status to prior bortezomib therapy, status to prior thalidomide/lenalidomide therapy, status to prior IMiD therapy, status to prior PIs therapy, stem cell transplantation, plasma cells, hemoglobin, creatinine, calcium, genetic risk, lytic lesions and plasmacytomas.

PAGE 59, section 11.3.4.8 Univariate analyses

ADDED

Table 11.4.3.8.7 Univariate analysis of PFS with PD confirmation (Independent Review assessment and "All Randomized Patients" population)

	Arm A			Arm B			
Prognostic factors**	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Median (months)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p-value*
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.7)

PAGE 61, section 11.3.4.9 Multivariate analyses

ADDED

Table 11.3.4.9.6 Multivariate analysis of PFS by region (Independent Review assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

Table 11.3.4.9.7 Multivariate analysis of PFS with PD confirmation (Independent Review assessment and "All Randomized Patients" population)

Analysis of Maximum Likelihood Estimates*								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits

* Cox regression
See list of covariates in section 6.2.3

PAGE 102, section 12.6 Concomitant therapy / procedures according to the ATC classification

ADDED

Table 12.6.8 Time to subsequent therapy or death

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Time to subsequent therapy or death			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 12.6.8)

PAGE 104 Section 12.8 Time to PS (ECOG) deterioration as index of QoL

ADDED

12.8 Time to PS (ECOG) deterioration as index of QoL

Table 12.8.1 Time to PS (ECOG) deterioration

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Time to first PS (ECOG) deterioration			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 12.8.1)
Time to PS value 2 or worse in patients with PS 0 or 1 at baseline will be assessed.

From Statistical Analysis Plan v3.0 to v4.0:

Rational of changes:

According to EMA guideline "E7 Geriatric Studies", the sponsor has decided to update the SAP to fulfil these requirements. Geriatric patients can respond differently from younger patients to drug therapy, therefore supportive and exploratory age subgroup analyses have been included in this amendment.

In order to characterize the efficacy of Aplidin plus dexamethasone in elderly population, subgroups analyses by age have been added in the efficacy and safety sections.

In addition, other sentitivity analyses for the main endpoint comparison of the study and description of censoring reasons for OS have been added in order to get a better understanding of the results. Clarification regarding evaluability has been done in order to make clearer how patients are classified as Evaluable for efficacy.

New exploratory efficacy analyses have been added according to the refractory status to prior therapies such as bortezomib, lenalidomide/thalidomide, last prior therapy, IMiD therapy and PIs therapy and according to the genetic risk.

Minor corrections and analysis clarifications have been added.

CHANGES:

Included changes are highlighted in *Italic Bold.*

PAGE 5: ABBREVIATIONS AND GLOSSARY

ADDED

IMiD	***Immunomodulatory Drug***
…	
IPCW	***Inverse Probability of Censoring Weighting***
…	
PIs	***Proteasome Inhibitors***
…	
RPSFT	***Rank Preserving Structural Failure Time***

PAGE 10: Section 4.1 Analysis sets definitions

Original text:

"All Evaluable Patients" analysis set is defined as all randomized patients who have completed at least one full cycle of treatment or have received two incomplete cycles followed by at least one response assessment not less than eight weeks (± one week) after

treatment onset. Patients withdrawn from the study due to early disease progression or treatment-related toxicity will be considered as "early progression" or "treatment failure", respectively. …

Changes to:

"All Evaluable Patients" analysis set is defined as all randomized patients who have completed at least one full cycle of treatment or have received two incomplete cycles followed by at least one response assessment not less than eight weeks (± one week) after treatment onset. Patients withdrawn from the study due to early disease progression or treatment-related toxicity will be considered as "early progression" or "treatment failure", respectively***, even though they have not received a full cycle***. ...

PAGE 13: Section 6.1.2 Final analyses - Primary Endpoint.

Original text:

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of documented progressive disease (PD) by IMWG criteria or death (regardless of the cause of death). If the patient receives further antitumor therapy before PD and within the timeframe expected for first follow-up, PFS will be censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient is lost to follow-up for the assessment of progression, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS will be censored at the date of last valid tumor assessment before the missing evaluations.

An external review committee blinded to treatment arm will assign the objective response and a progression or censoring date for each patient based on laboratory data, radiologic and bone marrow assessments when required and evaluation of all relevant clinical information; then, this information will be merged with the date of death from the death report forms for the calculation of PFS. Patients with missing IRC evaluations will have their PFS censored at randomization date.

Changes to:

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of documented progressive disease (PD) by IMWG criteria or death (regardless of the cause of death). If the patient receives further antitumor therapy before PD ~~***and within the timeframe expected for first follow-up***~~, PFS will be censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient is lost to follow-up for the assessment of progression, or has more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS will be censored at the date of last valid tumor assessment before the missing evaluations.

An external review committee blinded to treatment arm will assign the objective response and a progression or censoring date for each patient based on laboratory data, radiologic and bone marrow assessments when required and evaluation of all relevant clinical

information; then, this information will be merged with the date of death from the death report forms ***and with further antitumor therapy data*** for the calculation of PFS. Patients with missing IRC evaluations will have their PFS censored at randomization date.

PAGE 15: Section 6.1.2 Final analyses. Subsection Sensitivity analyses of PFS.

Original text:

In the first sensitivity analysis, the midpoint of the last two assessment dates on or prior to the documented disease progression will be used to impute the actual date of the disease progression. For patients without documented disease progression, the PFS will be censored at the date of last disease assessment.

Changed to:

In the first sensitivity analysis, the midpoint of the last two assessment dates on or prior to the documented disease progression will be used to impute the actual date of the disease progression. ***Those patients who have disease progression in the first assessment, the midpoint of randomization date and the documented disease progression will be used. Those patients who die, the midpoint between last disease assessment without PD and the date of death will be used.*** For patients without documented disease progression, the PFS will be censored ~~***at the date of last disease assessment***~~ ***following the same rules than in the main analysis***.

PAGE 15: Section 6.1.2 Final analyses – Sensitivity analyses of PFS

ADDED

A sensitivity analysis of PFS in the "All Evaluable Patients" population according to IRC and investigator assessment will be performed in order to present the results in the population described in the protocol.

Due to the variability of the protein used for the disease assessment, a sensitivity analysis of PFS requiring the confirmation of the disease progression by IRC assessment will be performed. Patients who dies within the timeframe expected for the confirmation of PD, will be considered as PD confirmed by death. Those patients without confirmation of PD with a second disease assessment due to crossover, further antitumor therapy, lost to follow-up or other reason, will be censored. The same censoring rules described above for PFS calculation will be considered.

PAGE 16: Section 6.2.3 Secondary analyses – Overall survival

Original text:

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of

crossover by means of, rank preserving structural failure time models for correcting for treatment changes (2) and by the inverse probability of censoring weighting method (6) in order to try to control any bias caused by treatment crossover.

Changes to:

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of crossover ***in a first sensitivity analysis excluding the patients who crossed over and a second analysis censoring survival at the time of crossover. Estimates of the unbiased effect in survival will be studied*** by means of, rank preserving structural failure time ***(RPSFT)*** models for correcting for treatment changes (2) and by the inverse probability of censoring weighting ***(IPCW)*** method (6) in order to try to control any bias caused by treatment crossover.

ADDED

The following time-dependent covariates will be included in the IPCW analysis: ECOG, Body Surface Area (BSA), m-protein value (serum/urine), number of adverse events grade≥3, bone marrow plasma cells, creatinine, LDH, hemoglobin and corrected serum calcium. Also, baseline covariates such us gender, age, MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed vs. relapsed/refractory), refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, presence of plasmacytomas, presence of lytic lesions, number of plasmacytomas, sum of the dimensions of plamacytomas, will be included.

ADDED

The reasons for censoring of OS will be shown using counts and percentages.

PAGE 17: Section 6.2.3 Secondary analyses – Multivariate analyses

Original title:

Multivariate analyses

Changes to:

Analysis of prognostic factors, subgroup analysis and multivariate analyses

Original text:

Cox proportional hazard models for PFS and OS and logistic regression models for RR will include the following prognostic factors: Gender, age, baseline ECOG, Body Surface Area (BSA), MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed *vs.* relapsed/refractory), previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, bone marrow plasma cells, creatinine (≥2 mg/dl *vs.* < 2 mg/dl), LDH, hemoglobin and corrected serum calcium (>11.5 mg/100ml *vs.* ≤11.5 mg/100ml). Further covariates may be included in the analyses according to the oncologist's criteria.

Changed to:

Univariate evaluation of the influence of different prognostic factors on the main efficacy endpoints will be performed by using the following covariates: Gender, age, baseline ECOG, Body Surface Area (BSA), MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed vs. relapsed/refractory) refractory status to bortezomib, lenalidomide/thalidomide prior therapy, refractory status to last prior therapy, refractory status to IMiD therapy, refractory status to PIs therapy, genetic risk, previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, bone marrow plasma cells, bone lytic lesions (Y/N), plasmacytomas at baseline (Y/N), number of lesions at baseline, sum of the dimensions of plamacytomas, creatinine (≥2 mg/dl vs. < 2 mg/dl), LDH, hemoglobin and corrected serum calcium (>11.5 mg/100ml vs. ≤11.5 mg/100ml).

Exploratory subgroup analyses will be performed by means of logistic regression, Kaplan-Meier analysis and Cox regression. The different subgroup analyses will be summarized by means of Forest plots.

Cox proportional hazard models for PFS and OS and logistic regression models for RR will include the ~~***following***~~ prognostic factors~~***: Gender, age, baseline ECOG, Body Surface Area (BSA), MM type (i.e.: IgG, IgA, light chain myeloma, non-secretory), number of prior lines of anticancer treatment, status (relapsed vs. relapsed/refractory), previous SCT, time from diagnosis to randomization, time from last progression before randomization, International Staging System, Durie-Salmon stage, bone marrow plasma cells, creatinine (≥2 mg/dl vs. < 2 mg/dl), LDH, hemoglobin and corrected serum calcium (>11.5 mg/100ml vs. ≤11.5 mg/100ml). Further covariates may be included in the analyses according to the oncologist's criteria.***~~ ***specified for the univariate analysis. More relevant and explanatory covariates from the univariate analysis will be included in the multivariate analyses.***

PAGE 17: Section 6.2.3 Secondary analyses – Symmetry evaluations

TITLE ADDED:

Wilcoxon test will be used to compare time to disease assessments between treatment arms. Moreover, Kaplan-Meier curves of the time from randomization to first and second disease assessment will be plotted.

Sensitivity analyses of PFS.

For the three sensitivity analyses using imputation methods for the date of progression, similar unstratified log-rank test as for the key primary PFS analysis will be performed, based on the imputed data sets.

PAGE 20: Section 8.7 Subgroup analyses

Original text:

No specific subgroup analysis is planned for efficacy. However, the influence of the study strata and other prognostic factors on the efficacy endpoints will be studied in the multivariate analysis.

Changes to:

Analysis of efficacy profile by age in order to characterize a potential benefit of the drug in elderly population is planned. Exploratory efficacy subgroup analyses according to genetic risk the refractory status to prior therapies such as bortezomib, lenalidomide/thalidomide, last prior therapy, IMiD therapy and PIs are planned. No ***other*** specific subgroup analysis is planned for efficacy. However, the influence of the study strata and other prognostic factors on the efficacy endpoints will be studied in the multivariate analysis.

PAGE 29: Section 9. STATISTICAL SOFTWARE

Original text:

EAST v5.2 has been used to calculate sample size. SAS v9 (4) will be used for all statistical analysis outputs.

Changes to:

EAST v5.2 has been used to calculate sample size. SAS v9 (4) will be used for all statistical analysis outputs***. Stata v14 or greater will be used for the analysis of crossover by RPSFT method.***

PAGE 22: Section 10.1. Patient dispositions

Original text:

Main characteristics concerning inclusion in the study, withdrawal from the study and protocol deviations will be displayed in this section.

Changes to:

Main characteristics concerning inclusion in the study***, patient crossover from arm B to arm A***, withdrawal from the study and protocol deviations will be displayed in this section.

ADDED

Listing 10.1.2a Patients assigned to the wrong stratum by mistake

Patient id.	*Assigned stratum by randomization*	*Actual stratification values*
…		

Listing 10.1.2b Comparison of Durie-Salmon at IVRS and baseline value

Patient id.	*Durie-Salmon value at IVRS*	*Actual Durie-Salmon value*
…		

Listing 10.1.2c Comparison of ECOG PS at IVRS and baseline value

Patient id.	*PS ECOG value at screening*	*PS ECOG value at IVRS*	*Last ECOG before start of study treatment*
…			

Table 10.1.5 Last cycle in Arm A before crossover

Last cycle before crossover	*Crossover patients*	
	N	*%*
Cycle 1	*X*	*XX.X*
Cycle 2		
…		
Total		

PAGE 24: Table 10.2.5 Reasons for treatment discontinuation by cycles received

Footnote has been added.

Original table:

Reason	Arm A				Arm B				Total			
	Last cycle				Last cycle				Last cycle			
	1	2	…	Total	1	2	…	Total	1	2	…	Total
Progressive disease												
Toxicity												
Patient refusal												
Investigator decision												
Death (due to toxicity)*												
Death (non-treatment-related)**												
Other ***												
Total												

(*) Cause of death = Toxicity (study drug related) (**) Cause of death = Malignant disease or Other (***) Specify (see listing 10.2.6)

Changes to:

Reason	Arm A				Arm B				Total			
	Last cycle				Last cycle				Last cycle			
	1	2	…****	Total	1	2	…	Total	1	2	…	Total
Progressive disease												
Toxicity												
Patient refusal												
Investigator decision												
Death (due to toxicity)*												
Death (non-treatment-related)**												
Other ***												
Total												

(*) Cause of death = Toxicity (study drug related) (**) Cause of death = Malignant disease or Other (***) Specify (see listing 10.2.6) ***(****) Cycles > % will be grouped as 6-10, 10-20 and >20.***

PAGE 24: Listing 10.2.7 Treatment discontinuation due to AEs

FOOTNOTE ADDED:

Action taken: study drug withdrawal

PAGE 25: Table 11.1.1.3 Baseline characteristics: Age grouped

Original table:

	Arm A		Arm B		Total	
	N	%	N	%	N	%
18-XX	X	XX.X	X	XX.X	X	XX.X
XX-YY						
≥65						
Total						

Changes to:

	Arm A		Arm B		Total	
	N	%	N	%	N	%
18-***64***	X	XX.X	X	XX.X	X	XX.X
65-74						
75-84						
≥85						
Total						

PAGE 25: Table 11.1.2.2 Time from last PD/relapse by dose

DELETED:

Table 11.1.2.2 Time from last PD/relapse ~~*by dose*~~

PAGE 25: Section 11.1.2. Disease at diagnosis, time from diagnosis and current disease

ADDED:

Table 11.1.2. 7 Genetic risks at diagnosis.

Genetic Risks*	***Arm A***		***Arm B***		***Total***	
	N	***%***	***N***	***%***	***N***	***%***
High risk	***X***	***XX.X***	***X***	***XX.X***	***X***	***XX.X***
Intermediate risk						
Good prognostic						
Total						

(*)Patients will be classified in "high risk", "intermediate risk" or "good prognosis" according to their genetic results (cytogenetic or FISH) at by clinical review. Further details in section 11.3.7.

Tables will be renumbered accordingly.

PAGE 25: Table 11.1.2. Disease at diagnosis, time from diagnosis and current disease

Original table:

Table 11.1.2.7 Baseline characteristics: MM protein measurements (Serum)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Total Ig G (mg/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Total Ig A (mg/dL)												
Total Ig M (mg/dL)												

Table 11.1.2.8 Baseline characteristics: MM protein measurements (Serum)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
M-spike(SPE)(g/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Kappa (mg/L)												
Lambda (mg/L)												
sFLC ratio												

Listing 11.1.2.9 Baseline characteristics: MM protein type

Arm	Patient id.	Serum / Urine	Type
…			

Table 11.1.2.10 Baseline characteristics: MM protein measurements (24h Urine analysis)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Protein -24h urine (mg/24 h)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Urine M-spike (UPE) (Bence Jones) (g/24 hrs)												
Urine M-protein (Bence Jones) (mg/L)												
Kappa (mg/L)												
Lambda (mg/L)												

Table 11.1.2.11 Baseline characteristics: Immunofixation urine

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Positive	X	XX.X	X	XX.X	X	XX.X
Negative						
Total						

Table 11.1.2.12 Baseline characteristics: Non-secretory myeloma

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
Total						

Changes to:

Table 11.1.2***.8*** Baseline characteristics: MM protein measurements (Serum*****)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Total Ig G (mg/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Total Ig A (mg/dL)												
Total Ig M (mg/dL)												

**** Based on central lab assessments.***

Table 11.1.2***.9*** Baseline characteristics: MM protein measurements (Serum*****)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
M-spike(SPE)(g/dL)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Kappa (mg/L)												
Lambda (mg/L)												
sFLC ratio												

**** Based on central lab assessments.***

Listing 11.1.2.***10*** Baseline characteristics: MM protein type*****

Arm	Patient id.	Serum / Urine	Type
…			

**** Based on central lab assessments.***

Table 11.1.2.***11*** Baseline characteristics: MM protein measurements (24h Urine analysis*****)

	Arm A				Arm B				Total			
	N	Median	Min	Max	N	Median	Min	Max	N	Median	Min	Max
Protein -24h urine (mg/24 h)	X	X.X	X.X	X.X	X	X.X	X.X	X.X	X	X.X	X.X	X.X
Urine M-spike (UPE) (Bence Jones) (g/24 hrs)												
Urine M-protein (Bence Jones) (mg/L)												
Kappa (mg/L)												
Lambda (mg/L)												

**** Based on central lab assessments.***

Table 11.1.2.***12*** Baseline characteristics: Immunofixation urine*****

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Positive	X	XX.X	X	XX.X	X	XX.X
Negative						
Total						

**** Based on central lab assessments.***

Table 11.1.2.***13*** Baseline characteristics: Non-secretory myeloma*****

	Arm A		Arm B		Total	
	N	%	N	%	N	%
Yes	X	XX.X	X	XX.X	X	XX.X
No						
Total						

**** Based on central lab assessments.***

ADDED

Table 11.1.2.16 Genetic risks at baseline.

Genetic Risks*	***Arm A***		***Arm B***		***Total***	
	N	***%***	***N***	***%***	***N***	***%***
High risk	***X***	***XX.X***	***X***	***XX.X***	***X***	***XX.X***
Intermediate risk						
Good prognostic						
Total						

(*)Patients will be classified in "high risk", "intermediate risk" or "good prognosis" according to their genetic results (cytogenetic or FISH) at by clinical review. Further details in Section 11.3.7.

PAGE 28 Section 11.1.3 Skeletal sites involved at baseline

Original listing:

Listing 11.1.3.1 Baseline characteristics: Skeletal/soft tissue evaluation

Arm	Patient id.	No lesion / NA	Type	Anatomic localization	Method	Measurements for soft tissue lesions (mm)	Diffuse osteoporosis
…						XXX x XXX	

Changes to:

Listing 11.1.3.1 Baseline characteristics: Skeletal/soft tissue evaluation

Arm	Patient id.	***Date of assessment***	No lesion / NA	Type	Anatomic localization	Method	Measurements for soft tissue lesions (mm)	Diffuse osteoporosis
…							XXX x XXX	

ADDED

Table 11.1.3.3 Baseline characteristics: Number of lesions

	Arm A		***Arm B***		***Total***	
	N	***%***	***N***	***%***	***N***	***%***
Plasmacytoma	***X***	***XX.X***	***X***	***XX.X***	***X***	***XX.X***
1						
2						
…						
Bone (Lytic lesion)						
1						
2						
…						
Total						

Table 11.1.3.4 Baseline characteristics: Sum of plasmacytomas dimensions

		N	***Median***	***Min***	***Max***
Sum of plamacytomas product of diameters	***Arm A***				
	Arm B				
	Total				

PAGE 28: Section 11.1.4 Prior anticancer therapy

ADDED

Table 11.1.4.2 Number of patients with prior radiotherapy

Prior radiotherapy	*Arm A*		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
Yes	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
No						
Total						

Table 11.1.4.6 Status regarding response to bortezomib therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior bortezomib regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last bortezomib therapy.
(***)Refractory myeloma: non responder to last bortezomib therapy.

Table 11.1.4.7 Status regarding response to lenalidomide therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior lenalidomide regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last lenalidomide therapy.
(***)Refractory myeloma: non responder to last lenalidomide therapy.

Table 11.1.4.8 Status regarding response to thalidomide therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior thalidomide regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last thalidomide therapy.
(***)Refractory myeloma: non responder to last thalidomide therapy.

Table 11.1.4.9 Status regarding response to bortezomib, lenalidomide/thalidomide therapy

(*)	*Arm A*		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies **	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib ***						
*Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide ****						
Other than the above						

(*) Resistant or refractory myeloma: non responder or relapse of disease while on salvage therapy, or progression within 60 days of therapy.

Table 11.1.4.10 Status regarding response to last therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of last therapy.
(***)Refractory myeloma: non responder to last therapy.

Table 11.1.4.11 Status regarding response to IMiD therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior IMiD regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of IMiD therapy.
(***)Refractory myeloma: non responder to IMiD therapy.

Table 11.1.4.12 Status regarding response to PIs therapy

	Arm A		*Arm B*		*Total*	
	N	*%*	*N*	*%*	*N*	*%*
*Relapsed**	*X*	*XX.X*	*X*	*XX.X*	*X*	*XX.X*
*Relapsed/Refractory***						
*Refractory****						

(*)Relapsed myeloma: at least one prior PIs regimen, and not meeting criteria for relapsed and refractory / refractory myeloma.
(**) Relapsed/refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of PIs therapy.
(***)Refractory myeloma: non responder to PIs therapy.

Consequently, the rest of the tables have been renumbered.

FOOTNOTE ADDED:

Table 11.1.4.13 TTP to last prior anticancer therapy

In case of non-PD to last therapy, TTP will be calculated until the date of informed consent

Original table:

Table 11.1.4.8 Prior stem cell transplantation

	Arm A		Arm B		Total	
	N	%	N	%	N	%
0	X	XX.X	X	XX.X	X	XX.X
1						
≥2						
Type	N	%	N	%	N	%
Autologous	X	XX.X	X	XX.X	X	XX.X
Allogeneic						

Changes to:

Table 11.1.4.***16*** Prior stem cell transplantation

	Arm A		Arm B		Total	
	N	%	N	%	N	%
0	X	XX.X	X	XX.X	X	XX.X
1						
≥2						
Total						
Type	N	%	N	%	N	%
Autologous	X	XX.X	X	XX.X	X	XX.X
Allogeneic						

PAGE 30: Table 11.1.6.5 Baseline characteristics: Left Ventricular Ejection Fraction (LVEF)

Original table:

Arm	Patient id.	Cycle	Date	LVEF (%)	Institutional normal range (%)	Method
…						

Changes to:

Arm	Patient id.	***Not done***	Date	LVEF (%)	***Interpretation***	Institutional normal range (%)	Method
…							

PAGE 32: Table 11.1.8.2 Biochemical values at baseline

Original table:

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
AST (xULN)			
ALT (xULN)			
Total bilirubin (xULN)			
Direct bilirubin (xULN)			
AP (xULN)			
Creatinine (xULN)			
Cr. Clearance (Calculated) (ml/min)			
Cr. Clearance (Measured) (ml/min)			
CPK (xULN)			
CPK MB (IU/L)			
Cardiac Troponin I (ng/ml)			
Total proteins (g/dL)			
Albumin (g/dL)			
Uric acid (mg/dL)			
LDH (xULN)			
Beta-2-microglobulin (mg/L)			

Changes to:

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
AST (xULN)			
ALT (xULN)			
Total bilirubin (xULN)			
Direct bilirubin (xULN)			
AP (xULN)			
Creatinine (xULN)			
Cr. Clearance (Calculated) (ml/min)			
Cr. Clearance (Measured) (ml/min)*			
CPK (xULN)			
CPK MB (IU/L)			
Cardiac Troponin I (ng/ml)			
Total proteins (g/dL)			
Albumin (g/dL)			
Uric acid (mg/dL)			
LDH (xULN)			
Beta-2-microglobulin (mg/L)			

(*)If available

PAGE 32: Listing 11.1.8.3 Biochemical tests not assessed at baseline

FOOTNOTE ADDED

****CPKMB to be assessed as missing only if CPK>ULN***

PAGE 32: Listing 11.1.8.4 Biochemical abnormalities at baseline. Grade ≥ 2

Original table:

Arm	Patient id	Parameter	Value	Grade
…				

Changes to:

Arm	Patient id	Parameter	Value	***xULN***	Grade
…					

PAGE 33: Listing 11.1.9.4 Metabolic abnormalities at baseline. Grade ≥ 2

Original table:

Arm	Patient id	Parameter	Value	Grade
…				

Changes to:

Arm	Patient id	Parameter	Value	***xULN***	Grade
…					

PAGE 35: Section 11.3.2 Supportive PFS analyses

Original text:

In the 'time-to-event variables', the unstratified and stratified log-rank test will be used to evaluate the differences between treatment arms and the median values of time-dependent parameters. Their fixed-time estimations will be analyzed according to the Kaplan-Meier method. Median follow-up assessments will be calculated using the Kaplan-Meier method reversing the censoring values (5).

Changes to:

In the 'time-to-event variables', the unstratified and stratified log-rank test will be used to evaluate the differences between treatment arms and the median values of time-dependent parameters. Their fixed-time estimations will be analyzed according to the Kaplan-Meier method. Median follow-up assessments will be calculated using the Kaplan-Meier method reversing the censoring values (5). ***Whenever it is not specified, the unstratified test is used***.

FOOTNOTE ADDED:

Table 11.3.2.4 PFS – Concordance between Independent Review assessment and Investigator assessment ("All Randomized Patients" population)

XX, YY, ZZ = Patients evaluable for both Independent review assessment and investigator assessment

PAGE 37: Section 11.3.3 Sensitivity analyses of PFS

Original titles:

Table 11.3.3.1 PFS (first imputation of PD dates) (Independent Review assessment and "All Randomized Patients" population)

Table 11.3.3.2 PFS (second imputation of PD dates) (Independent Review assessment and "All Randomized Patients" population)

Table 11.3.3.3 PFS (third imputation of PD dates) (Independent Review assessment and "All Randomized Patients" population)

Changes to:

Table 11.3.3.1 PFS (***~~first~~ midpoint*** imputation ***method*** of PD dates) (Independent Review assessment and "All Randomized Patients" population)

Table 11.3.3.2 PFS (***~~second~~ weeks from randomization*** imputation ***method*** of PD dates) (Independent Review assessment and "All Randomized Patients" population)

Table 11.3.3.3 PFS (***~~third~~ missing assessment*** imputation ***method*** of PD dates) (Independent Review assessment and "All Randomized Patients" population)

ADDED

Table 11.3.3.6 PFS (Independent Review assessment and "All Evaluable Patients" population)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
PFS at 6 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.3.6)

Table 11.3.3.7 PFS (Investigator Assessment and "All Evaluable Patients" population)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
PFS at 6 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.3.7)

Table 11.3.3.8 PFS with confirmation of PD (Independent Review assessment and "All Randomized Patients" population)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
PFS at 6 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.3.8)

Table 11.3.3.9 PFS with confirmation of PD (Investigator Assessment and "All Randomized Patients" population)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
PFS at 6 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.3.9)

PAGE 38: Section 11.3.4.1 OS analyses

ADDED

Table 11.3.4.1.3 OS ("All Randomized Patients" population excluding crossover patients)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
OS at 12 months			***Diff:***	
OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.3).

Table 11.3.4.1.4 OS ("All Randomized Patients" population censoring crossover patients at cross-over date)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
OS at 12 months			***Diff:***	
OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.4).

Table 11.3.4.1.5 OS ("All Randomized Patients" population and IPCW method)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
OS at 12 months			***Diff:***	
OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.5).

Table 11.3.4.1.6 OS ("All Randomized Patients" population and RPSFT method)

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
OS at 12 months			***Diff:***	
OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.4.1.6).

Table 11.3.4.1.8 OS – Reason of censoring ("All Randomized Patients" population)

Reason of censoring	*Arm A*		*Arm B*	
	N	*%*	*N*	*%*
Alive				
Lost to follow-up				
Withdrawal of consent				

PAGE 39: Section 11.3.4.2 Response rate by independent review committee

ADDED

Table 12.1.2.2.1 Response rate by IMWG at early futility analysis (Independent Review assessment and "All Evaluable Patients" population)

Response	*Arm A*		*Arm B*	
	N	*%*	*N*	*%*
sCR ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD***				

PAGE 42: Section 11.3.4.7 Symmetry of evaluations

ADDED

Table 12.1.2.2.2 Time to first assessment

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median to first assessment			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.7.2)

Table 12.1.2.2.3 Time to second assessment

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Median second assessment			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 11.3.4.7.3)

Page 43: New section 11.3.4.8 Univariate analyses

ADDED

15.1.1.1 Univariate analyses

Table 11.3.4.8.1 Univariate analysis of PFS (Independent Review assessment and "All Randomized Patients" population)

	Arm A			***Arm B***			
Prognostic factors**	***Median (months)***	***Lower 95% Confidence Limit***	***Upper 95% Confidence Limit***	***Median (months)***	***Lower 95% Confidence Limit***	***Upper 95% Confidence Limit***	***p-value****
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.1)

Table 11.3.4.8.2 Univariate analysis of PFS (Investigator Assessment and "All Randomized Patients" population)

	Arm A			***Arm B***			
Prognostic factors**	***Median (months)***	***Lower 95% Confidence Limit***	***Upper 95% Confidence Limit***	***Median (months)***	***Lower 95% Confidence Limit***	***Upper 95% Confidence Limit***	***p-value****
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.2)

Table 11.3.4.8.3 Univariate analysis of OS (Independent Review assessment and "All Randomized Patients" population)

	Arm A			*Arm B*			
*Prognostic factors***	*Median (months)*	*Lower 95% Confidence Limit*	*Upper 95% Confidence Limit*	*Median (months)*	*Lower 95% Confidence Limit*	*Upper 95% Confidence Limit*	*p-value**
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.3)

Table 11.3.4.8.4 Univariate analysis of OS (Investigator Assessment and "All Randomized Patients" population)

	Arm A			*Arm B*			
*Prognostic factors***	*Median (months)*	*Lower 95% Confidence Limit*	*Upper 95% Confidence Limit*	*Median (months)*	*Lower 95% Confidence Limit*	*Upper 95% Confidence Limit*	*p-value**
Gender							
Age							
…							

(*) Cox regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of HR will be also shown (Figure 11.3.4.8.4)

Table11.3.4.8.5 Univariate analysis of RR (Independent Review assessment and "All Randomized Patients" population)

	Arm A				*Arm B*				
*Prognostic factors***	*N*	*RR*	*Proportion (%)*	*95% CI*	*N*	*RR*	*Proportion (%)*	*95% CI*	*p-value**
Gender									
Age									
…									

(*) Logistic regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of ORR confidence intervals will be also shown (Figure 11.3.4.8.5)

Table 11.3.4.8.6 Univariate analysis of RR (Investigator Assessment and "All Randomized Patients" population)

	Arm A				*Arm B*				
*Prognostic factors***	*N*	*RR*	*Proportion (%)*	*95% CI*	*N*	*RR*	*Proportion (%)*	*95% CI*	*p-value**
Gender									
Age									
…									

(*) Logistic regression. (**) See covariate listing in section 6.2.3. A forest plot with the summary of ORR confidence intervals will be also shown (Figure 11.3.4.8.6)

Rest of sections and tables have been renumbered.

Page 43: Section 11.3.4.8 Multivariate analyses

This section was renumbered to 11.3.4.9.

FOOTNOTE ADDED

In tables 11.3.4.9.1, 11.3.4.9.2 and 11.3.4.9.5:

**** Cox regression***

In tables 11.3.4.9.3 and 11.3.4.9.4:

**** Logistic regression***

PAGE 44: Section 11.3.6 Efficacy analysis by age

ADDED

11.3.6 Efficacy analysis by age
If there is a group of patients with scarce percentage of patients (i.e.5%), it will be joined to the nearest group of age. Age ≥ 85 to Age 75-84, age 75-84 to age 65-74 and age 65-74 to age 18-64

Table 11.3.6.1PFS (Independent Review assessment and "All Randomized Patients" population) by age

Age		*Arm A*	*Arm B*	*Parameter*	*p-value*
Age 18-64	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age 65-74	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age 75-84	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age ≥85	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.6.1a/b/c/d)

Table 11.3.6.2PFS (Investigator Assessment and "All Randomized Patients" population) by age

Age		*Arm A*	*Arm B*	*Parameter*	*p-value*
Age 18-64	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age 65-74	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age 75-84	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Age ≥85	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.6.2a/b/c/d)

Table 11.3.6.3OS ("All Randomized Patients" population) by age

Age		*Arm A*	*Arm B*	*Parameter*	*p-value*
Age 18-64	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Age 65-74	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Age 75-84	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Age ≥85	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	

	OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.6.3a/b/c/d).

Table 11.3.6.4Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by age

Age	***Response***	***Arm A***		***Arm B***	
		N	***%***	***N***	***%***
Age 18-64	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Age 65-74	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Age 75-84	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Age ≥85	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				

(*) Including NE and insufficient data available.

Table 11.3.6.5Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by age

Age		***Arm A***			***Arm B***		
		Proportion	***Lower 95% limit***	***Upper 95% limit***	***Proportion***	***Lower 95% limit***	***Upper 95% limit***
Age 18-64	***Response rate***						
Age 65-74	***Response rate***						
Age 75-84	***Response rate***						
Age ≥85	***Response rate***						

Binomial exact estimator and 95% confidence interval

11.3.7 Efficacy analysis based on genetic risks

Patients will be classified in "high risk", "intermediate risk" or "good prognosis" according to their genetic results (cytogenetic or FISH) at diagnosis or study entry.

Patients with translocations such as t(4;14), t(14;16), t(14;20), del 17, del 13 or single alterations such as +1q or +1p will be classified as "high risk"; patients with translocations such as t(11;14), t(6;14) or other will be classified "intermediate risk"; and finally, those patients with single alterations of trisomies 3, 5, 6, 9, 11, 15, 19 or 21 will be classified as "good prognosis". This classification will be done by clinical review.

Table 11.3.7.1 PFS (Independent Review assessment and "All Randomized Patients" population) by genetic risks

Cytogenetic profile		*Arm A*	*Arm B*	*Parameter*	*p-value*
High risk	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Intermediate risk	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Good prognosis	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.7.1a/b/c)

Table 11.3.7.2 OS ("All Randomized Patients" population) by genetic risks

Cytogenetic profile		*Arm A*	*Arm B*	*Parameter*	*p-value*
High risk	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Intermediate risk	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Good prognosis	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.7.2a/b/c).

Table 11.3.7.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by genetic risks

Cytogenetic profile	*Response*	*Arm A*		*Arm B*	
		N	*%*	*N*	*%*
High risk	*sCR* *CR* *VGPR* *PR* *MR* *SD* *PD* *Unknown*[*]				
Intermediate risk	*sCR* *CR* *VGPR* *PR* *MR* *SD* *PD* *Unknown*[*]				
Good prognosis	*sCR* *CR* *VGPR* *PR* *MR* *SD* *PD*				

	Unknown*				

(*) Including NE and insufficient data available.

Table 11.3.7.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by genetic risks

Cytogenetic profile	*Arm A*			*Arm B*		
	Proportion	*Lower 95% limit*	*Upper 95% limit*	*Proportion*	*Lower 95% limit*	*Upper 95% limit*
High risk						
Intermediate risk						
Good prognosis						

Binomial exact estimator and 95% confidence interval

11.3.8 Efficacy analysis in patients resistant or refractory to last lenalidomide/thalidomide or last bortezomib therapy

Patients will be classified in four groups according to their response to prior lenalidomide/thalidomide or bortezomib therapies.

-Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies
-Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib
-Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide
-Other than the above

Table 11.3.8.1 PFS (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies		*Arm A*	*Arm B*	*Parameter*	*p-value*
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Other than the above	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.8.1a/b/c/d)

Table 11.3.8.2 OS ("All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies		*Arm A*	*Arm B*	*Parameter*	*p-value*
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Other than the above	*N*				
	Events				
	Censored				

	Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
	OS at 12 months			***Diff:***	
	OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.8.2a/b/c/d).

Table 11.3.8.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies	***Response***	***Arm A***		***Arm B***	
		N	***%***	***N***	***%***
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Other than the above	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				

(*) Including NE and insufficient data available.

Table 11.3.8.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by lenalidomide/thalidomide or bortezomib prior therapies

Prior therapies	*Arm A*			*Arm B*		
	Proportion	*Lower 95% limit*	*Upper 95% limit*	*Proportion*	*Lower 95% limit*	*Upper 95% limit*
Resistant or refractory to lenalidomide/thalidomide and bortezomib therapies						
Resistant or refractory to lenalidomide/thalidomide therapy but not refractory to bortezomib						
Resistant or refractory to bortezomib therapy but not refractory to lenalidomide and thalidomide						
Other than the above						

Binomial exact estimator and 95% confidence interval

11.3.9 Efficacy analysis in patients refractory to last prior therapy

Patients will be classified as refractory to last prior therapy or other.

Table 11.3.9.1 PFS (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to last prior therapy	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Other	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.9.2 OS ("All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to last prior therapy	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	

	OS at 24 months			***Diff:***	
Other	***N***				
	Events				
	Censored				
	Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
	OS at 12 months			***Diff:***	
	OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.9.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy	***Response***	***Arm A***		***Arm B***	
		N	***%***	***N***	***%***
Refractory to last prior therapy	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Other	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				

(*) Including NE and insufficient data available.

Table 11.3.9.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) by refractory patients to last prior therapy

Prior therapy	***Arm A***			***Arm B***		
	Proportion	***Lower 95% limit***	***Upper 95% limit***	***Proportion***	***Lower 95% limit***	***Upper 95% limit***
Refractory to last prior therapy						
Other						

Binomial exact estimator and 95% confidence interval

11.3.10 Efficacy analysis in patients exposed to IMiD therapies

Patients who were exposed to IMiD therapies (pomalidomide, thalidomide or lenalidomide) will be classified as responders or refractory

Table 11.3.10.1 PFS (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to IMiD therapy	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Responders	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.10.2 OS ("All Randomized Patients" population) in patients exposed to IMiD

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to IMiD therapy	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	
Responders	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.10.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy	*Response*	*Arm A*		*Arm B*	
		N	*%*	*N*	*%*
Refractory to IMiD therapy	*sCR* *CR* *VGPR* *PR* *MR* *SD* *PD* *Unknown*[*]				
	sCR *CR* *VGPR*				

Responders	*PR* *MR* *SD* *PD* *Unknown*[*]				

(*) Including NE and insufficient data available.

Table 11.3.10.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to IMiD

Prior therapy	*Arm A*			*Arm B*		
	Proportion	*Lower 95% limit*	*Upper 95% limit*	*Proportion*	*Lower 95% limit*	*Upper 95% limit*
Refractory to IMiD therapy						
Responders						

Binomial exact estimator and 95% confidence interval

11.3.11 Efficacy analysis in patients exposed to PIs therapies

Patients who were exposed to PIs therapies (bortezomib or carfilzomib) will be classified as responders or refractory

Table 11.3.11.1 PFS (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to PIs therapy	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	
Responders	*N*				
	Events				
	Censored				
	Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.9.1a/b)

Table 11.3.11.2 OS ("All Randomized Patients" population) in patients exposed to PIs

Prior therapy		*Arm A*	*Arm B*	*Parameter*	*p-value*
Refractory to PIs therapy	*N*				
	Events				
	Censored				
	Median OS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
	OS at 12 months			*Diff:*	
	OS at 24 months			*Diff:*	

Responders	***N***				
	Events				
	Censored				
	Median OS			***Log-Rank:*** ***HR (95% CI) :***	***LR:*** ***HR:***
	OS at 12 months			***Diff:***	
	OS at 24 months			***Diff:***	

Kaplan-Meier plot will be also shown (Figure 11.3.9.2a/b).

Table 11.3.11.3 Response rate by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy	***Response***	***Arm A***		***Arm B***	
		N	***%***	***N***	***%***
Refractory to PIs therapy	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				
Responders	***sCR*** ***CR*** ***VGPR*** ***PR*** ***MR*** ***SD*** ***PD*** ***Unknown****				

(*) Including NE and insufficient data available.

Table 11.3.11.4 Response rate estimates by IMWG (Independent Review assessment and "All Randomized Patients" population) in patients exposed to PIs

Prior therapy	***Arm A***			***Arm B***		
	Proportion	***Lower 95% limit***	***Upper 95% limit***	***Proportion***	***Lower 95% limit***	***Upper 95% limit***
Refractory to PIs therapy						
Responders						

Binomial exact estimator and 95% confidence interval

PAGE 45: Section 12.1.1 Treatment administration

Original footnote table 12.1.1.1:

NA: Not applicable. If appropriate, the dose intensity of plitidepsin and dexamethasone will be calculated in those patients who crossover to the Arm B.

Changes to:

NA: Not applicable. ~~***If appropriate, the dose intensity of plitidepsin and dexamethasone will be calculated in those patients who crossover to the Arm B***~~. ***Cycles after crossover will be excluded.***

ADDED

Table 12.1.1.2 Number of cycles administered and dose intensity after crossover

	After crossover	
No. of cycles administered per patient	***N***	***%***
1 ***2*** ***3*** ***…***		
Median (range)		
Time on treatment (weeks) ***Median*** ***Range***		
Plitidepsin cumulative dose (mg/m²) ***Median*** ***Range***		
Plitidepsin dose intensity (mg/m²/wk) ***Median*** ***Range***		
Plitidepsin relative dose intensity (%) ***Median*** ***Range***		
Dexamethasone cumulative dose (mg) ***Median*** ***Range***		
Dexamethasone dose intensity (mg/wk) ***Median*** ***Range***		
Dexamethasone relative dose intensity (%) ***Median*** ***Range***		

PAGE 45: Section 12.1 Extent of exposure

FOOTNOTES ADDED

The following footnote has been added in listing 12.1.2.1.1, 12.1.2.2.3, 12.1.3.1.1, 12.1.3.2, 12.1.4.1.1, 12.1.4.4, 12.1.5.1.

Results after crossover will be highlighted

The following footnote has been added in tables 12.1.2.1.2, 12.1.2.1.3, 12.1.2.1.4, 12.1.2.2.1, 12.1.2.2.2, 12.1.3.1.2, 12.1.3.1.3, 12.1.3.1.4, 12.1.4.2, 12.1.4.3.

Cycles after crossover will be excluded

PAGE 54: Listing 12.1.6.1 Patients and cycles without prophylactic medication administration

Original table:

Patient id.	Cycle	Infusion	Prophylactic medication not taken*	Reason
…				

(*) Ondansetron, diphenhydramine or ranitidine.

Changes to:

Arm	Patient id.	Cycle	Infusion	Prophylactic medication not taken*	Reason
	…				

(*) Ondansetron, diphenhydramine or ranitidine.

PAGE 54: Section 12.2 Averse Events (AEs)

FOOTNOTE ADDED

The following footnote has been added in tables and listings 12.2.2.1, 12.2.2.2, 12.2.2.3, 12.2.2.4, 12.2...2.6, 12.2.2.7, 12.2.2.9, 12.2.2.10, 12.2.2.11, 12.2.2.12.

Events with onset date after crossover will be excluded

Original footnote:
Tables 12.2.2.5 and 12.2.2.8.

(*)All toxicities with onset date ≥ administration date after crossover (**) Any grade.

Changes to:

(*)All ***events*** with onset date ≥ administration date after crossover (**) Any grade.

ADDED

Listing 12.2.2.13 Treatment-related grade 3-4 adverse events in “All Crossover Patients” population. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

Listing 12.2.2.14 Adverse Events grade 3-4 regardless of relationship in “All Crossover Patients” population. Worst grade by patient

Arm	Patient id.	SOC Name	Preferred term	Grade
…				

PAGE 58: Listing 12.3.2.3 Deaths due to AEs

ADDED:
* AEs with Seriousness=Death ….

PAGE 56: Section 12.4 Clinical laboratory evaluation

FOOTNOTE ADDED

The following footnote has been added in tables and listings 12.4.1.1, 12.4.1.2, 12.4.1.4, 12.4.1.5 12.4.1.8, 12.4.2.1, 12.4.2.2, 12.4.2.4, 12.4.2.5, 12.4.3.1, 12.4.3.2, 12.4.3.4, 12.4.3.5, 12.4.4.1, 12.4.4.2, 12.4.4.3, 12.4.4.4, 12.4.4.5.

Events with onset date after crossover will be excluded

ADDED

Listing 12.4.1.12 Grade 3-4 hematological abnormalities during treatment in the “All Crossover Patients” population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.1.13 Grade 3-4 hematological abnormalities during treatment in the “All Crossover Patients” population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

Listing 12.4.2.11Grade 3-4 biochemical abnormalities during treatment in the “All Crossover Patients” population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.2.12 Grade 3-4 biochemical abnormalities during treatment in the “All Crossover Patients” population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

Listing 12.4.3.8 Grade 3-4 metabolic abnormalities during treatment in the “All Crossover Patients” population. Worst grade per patient

Arm	Patient id.	Test	Grade
…			

Listing 12.4.3.9 Grade 3-4 metabolic abnormalities during treatment in the “All Crossover Patients” population. Worst grade per cycle

Arm	Patient id.	Test	Grade
…			

PAGE 61: Section 12.5 Vital signs, physical findings, LVEF, ECG and other tests related to safety

FOOTNOTE ADDED

The following footnote has been added in tables 12.5.1.1, 12.5.1.2, 12.5.2.2 and 12.5.2.4.

Results after crossover will be highlighted

PAGE 68: Table 12.7.2 Worst grade 3-4 by patient in special subgroups (Age)

Original table:

Events	Arm A						Arm B					
	<65 years old			≥65 years old			<65 years old			≥65 years old		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												
ALT												
CPK												
Nausea												
Vomiting												
Fatigue												
Other*												

(*)Any treatment-related toxicity present in >=5% of patients in any group

Changes to:

Events	Arm A						Arm B					
	<65 years old			…**			<65 years old			…**		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia												
Neutropenia												
AP												
Total bilirubin												
AST												

Events	Arm A						Arm B					
	<65 years old			…**			<65 years old			…**		
	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%	N	Grade 3-4	%
ALT												
CPK												
Nausea												
Vomiting												
Fatigue												
Other*												

(*)Any treatment-related toxicity present in >=5% of patients in any group

(**) Age 65-74, Age 75-84, Age ≥85. If there is a group of age with less than 5% of patients, it could be join with the previous/next group of age.

PAGE 85: Section 13 DB Listings

ADDED:

Listing 13.31 Investigator comments

Rest of listings were renumbered accordingly**.**

From Statistical Analysis Plan v2.0 to v3.0:

A new "substantial" protocol amendment was included; therefore, the Statistical Analysis Plan v2.0 was changed in accordance with the new version of the protocol as follows:

- In accordance with the correction in the bibliography in Appendix 5 of the protocol regarding the IMWG Response Criteria for Multiple Myeloma, progressive disease does not have to be confirmed with a second assessment. Sections of Sensitivity analyses have been modified accordingly.
- A new substudy to assess the potential effect of plitidepsin on the QTc interval of patients enrolled in clinical trial APL-C-001-09 will be performed. Reference to a separate SAP for the substudy has been added.
- A new method to estimate and control the effect of crossover in OS has been added.
- Other minor corrections have also been done.

CHANGES:

Included changes are highlighted in *Italic Bold.*

PAGE 14: Section 6.1.2 Final Analyses – Primary endpoint

DELETED:

> ~~***Those patients in the control arm (Arm B) who crossed over to the combination arm (Arm A) before a proper confirmation of progressive disease by IMWG will be censored at the date of first drug administration of the combination arm for the primary analysis of PFS in the control arm.***~~

PAGE 15: Section 6.1.2 Final Analyses – Sensitivity analyses

DELETED:

> In the third sensitivity analysis, disease progression will be assumed for the first missing scheduled assessment following the last evaluation without progression.
>
> ~~***In addition, two other sensitivity analyses of PFS will be done. The first one will be done using the IRC progression or censoring date for those patients who were crossed over without a proper confirmation of progressive disease. The second one will be done using the first documented progressive disease, even if it was not properly confirmed with a second determination.***~~

PAGE 16: Section 6.2.3 Secondary analyses – Overall survival

ADDED:

It is anticipated that an indeterminate number of patients in the control arm will switch treatment after progression to plitidepsin plus dexamethasone. This could cause the size of the effect on OS to be difficult to interpret. Consequently, if the OS results show to be substantially influenced by crossover, the Sponsor will study the estimated effect of crossover by means of rank preserving structural failure time models for correcting for treatment changes (2) ***and by the inverse probability of censoring weighting method (6) in order to try to control any bias caused by treatment crossover.***

PAGE 21: Section 8.12 Analyses of the effects of plitidepsin on the QTc interval

ADDED:

8.12 Analyses of the effects of plitidepsin on the QTc interval

A substudy will be conducted to assess the potential effects of plitidepsin on the QTc interval of patients with relapsed/refractory multiple myeloma enrolled in clinical trial APL-C-001-09. These analyses will be specified in a separate document.

PAGE 30: Mock table 11.1.6.5

CHANGES:
Original title:

Listing 11.1.6.5 Baseline characteristics: Left Ventricular Ejection Fraction (LVEF)

Arm	Patient id.	Cycle	Date	LVEF (%)	Institutional normal range (%)	Method
…						

Changes to:

Table 11.1.6.5 Baseline characteristics: Left Ventricular Ejection Fraction (LVEF)

Arm	Patient id.	Cycle	Date	LVEF (%)	Institutional normal range (%)	Method
…						

PAGE 32: Mock table 11.1.8.2

CHANGES:
Original table:

Table 11.1.8.2 Biochemical values at baseline

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
AST (IU/L)			
ALT (IU/L)			
Total bilirubin (mg/dL)			
Direct bilirubin (mg/dL)			

AP (IU/L)			
Creatinine (mg/dL)			
Cr. Clearance (Calculated) (ml/min)			
Cr. Clearance (Measured) (ml/min)			
CPK (IU/L)			
CPK MB (IU/L)			
Cardiac Troponin I (ng/ml)			
Total proteins (g/dL)			
Albumin (g/dL)			
Uric acid (mg/dL)			
LDH (IU/L)			
Beta-2-microglobulin (mg/L)			

Changes to:

Table 11.1.8.2 Biochemical values at baseline

	Arm A	Arm B	Total
	Median (range)	Median (range)	Median (range)
AST (***xULN***)			
ALT (***xULN***)			
Total bilirubin (***xULN***)			
Direct bilirubin (***xULN***)			
AP (***xULN***)			
Creatinine (***xULN***)			
Cr. Clearance (Calculated) (ml/min)			
Cr. Clearance (Measured) (ml/min)			
CPK (***xULN***)			
CPK MB (IU/L)			
Cardiac Troponin I (ng/ml)			
Total proteins (g/dL)			
Albumin (g/dL)			
Uric acid (mg/dL)			
LDH (***xULN***)			
Beta-2-microglobulin (mg/L)			

PAGE 37: Mock tables 11.3.3.6 and 11.3.3.7

DELETED:

Table 11.3.3.6 PFS (Independent Review assessment and "All Randomized Patients" population) without censoring those patients who were crossed over without a proper confirmation of progressive disease.

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.3.6).

Table 11.3.3.7 PFS (Investigator assessment and "All Randomized Patients" population) using the first documented progressive disease even if it was not

properly confirmed.

	Arm A	*Arm B*	*Parameter*	*p-value*
N				
Events				
Censored				
Median PFS			*Log-Rank:* *HR (95% CI) :*	*LR:* *HR:*
PFS at 6 months			*Diff:*	

Kaplan-Meier plot will be also shown (Figure 11.3.3.7).

PAGE 45: Mock listing 12.1.2.1.1

DELETED COLUMN:

Listing 12.1.2.1.1 Delays

Arm	Patient id.	Cycle	Day	Agent	Previous cycle	Previous cycle start date	~~***Delayed cycle***~~	Delayed cycle start date	Dose Delay calculated. (days)	Reason for dose delay	Dose Delay Spec.
…											

PAGE 47: Mock table 12.1.2.2.2

DELETED:

Table 12.1.2.2.2 Dose reduction in cycles delayed

		Reduction				~~***Reduction***~~			
		Yes		No		~~***Yes***~~		~~***No***~~	
		N	%	N	%	~~***N***~~	~~***%***~~	~~***N***~~	~~***%***~~
Arm A	Cycle 2 … Cycle nth Total								
Arm B	Cycle 2 … Cycle nth Total								

PAGE 60: Mock table 12.4.4.2

CHANGES:
Original table:

Table 12.4.4.2 Evolution of transaminases abnormalities from BL by treatment arm, worst case per patient.

	Arm A		Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								

	ALT increase	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								
	Arm B									
	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	…	Grade 0								
		Grade 1								
		……								

Changes to:

Table 12.4.4.2 Evolution of ***transaminase*** abnormalities from BL by treatment arm, worst case per patient.

	Arm A		Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	Arm B									
	AST increase	Grade 0								
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								

PAGE 66: Listing 13.1.13

CHANGES:
Original title:

-Listing 13.1.13: Other metabolic laboratory values

Changes to:

-Listing 13.1.13: ***Coagulation*** laboratory values

PAGE 67: Section 14: References

ADDED:

6. Robins JM, Finkelstein DM: Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 56:779-788, 2000.