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A Phase II Trial of Plitidepsin (Aplidin®) in Combination with Bortezomib and Dexamethasone in Multiple Myeloma Patients Double Refractory to Bortezomib and Lenalidomide

STATISTICAL ANALYSIS PLAN

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATC-WHO	Anatomical Therapeutic Chemical Drug Classification by the World Health Organization
BM	Bone Marrow
BSA	Body Surface Area
CBR	Clinical Benefit Rate
CI	Confidence Interval
CMV	Cytomegalovirus
CPK	Creatine Phosphokinase
CPK-MB	Serum CPK Isoenzymes (Found In Cardiac Muscle)
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DB	Data Base
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
e-CRF	Electronic Case Report Form
EFS	Event-free Survival
EOT	End-of-treatment
G-CSF	Granulocyte Colony Stimulating Factor
GGT	ɣ-glutamyl Transpeptidase
H	Hour
HBV	Hepatitis B virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDT	High Dose Chemotherapy
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization
IMWG	International Myeloma Working Group
Ig	Immunoglobulin

IMIDs	Immunomodulatory Drugs
IMP	Investigational Medicinal Product
ISS	International Staging System
i.v	Intravenous
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA AE	Medical Dictionary for Regulatory Activities for Adverse Events
MM	Multiple Myeloma
MOA	Mechanism of action
MR	Minimal Response
MUGA scan	Multiple Uptake Gated Acquisition Scan
NA	Not Applicable
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria
NOS	Not Otherwise Specified
ORR	Objective Response Rate
OS	Overall Survival
OS6	Overall Survival Rate at 6 Months
OS12	Overall Survival Rate at 12 Months
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PDy	Pharmacodynamics
PFS	Progression-free Survival
PGx	Pharmacogenomics
PI	Proteasome Inhibitor
PK	Pharmacokinetics
PN	Peripheral Neuropathy
PR	Partial Response
PS	Performance Status
R-ISS	Revised International Staging System
RR	Response Rate
SAE(s)	Serious Adverse Event(s)
s.c.	Subcutaneous
sCR	Stringent Complete Response
SD	Stable Disease
SFLC	Serum Free Light Chains
SOC	System Organ Class
StD	Standard Deviation
TTP	Time To Progression
VGPR	Very Good Partial Response
WBC	White Blood Cells
wk	Week(s)
WOCBP	Woman/Women of Childbearing Potential

1 STUDY RATIONALE

- Multiple myeloma (MM) is a malignant plasma-cell disorder characterized by the production of a monoclonal protein from plasma cells in the bone marrow (BM).
- In the Western hemisphere, about 1% of cancer-related deaths are due to myeloma.
- MM is still an incurable disease. As front-line treatment to reduce tumor burden, hematopoietic stem cell transplantation (HSCT) as well as emergent drugs used in newly diagnosed patients offer the best chance for long-term survival. However, while many studies have shown the benefits of this approach, most patients will relapse. Thus, additional therapeutic options are needed for these patients.

A full rationale for the study design including the choice of the double refractory patient population and the use of the combination of plitidepsin with bortezomib and dexamethasone may be found in the appropriate sections of the study clinical protocol (section 1.5).

2 STUDY DESIGN

This is a multi-center, open-label, single arm, non-comparative phase II trial, designed to evaluate the efficacy of plitidepsin in combination with bortezomib and dexamethasone in patients with MM double refractory to bortezomib and lenalidomide. Plitidepsin will be administered as a 3-hour (h) i.v. infusion at a dose of 5 mg/m^2, on Day (D) 1 and 15, q4wk, bortezomib will be administered as a s.c. injection at a dose of 1.3 mg/m^2 on D1, 4, 8 and 11, q4wk and dexamethasone will be taken orally at a dose of 40 mg/day on D1, 8, 15 and 22, q4wk.
Patients will be evaluated at scheduled visits in three trial periods: pre-treatment, treatment and follow-up.

The **pre-treatment period** includes screening and baseline visits. Baseline assessment consists of a detailed history of pre-existing diseases, physical examination and clinical neurological assessment, ECOG PS, ECG, LVEF and laboratory tests, urinalysis, hepatitis B and C virus screening and serum pregnancy tests for WOCBP.

During the **treatment period**, all patients are to attend trial center visits on Day 1, 4, 8, 11 and 15 on an every four-week basis to assess safety and toxicity. All patients are to attend an end-of-treatment (EOT) visit 30 (±5) days after the last dose of trial therapy.

A cycle is defined as 28 days, plus any additional days required for dosing delays due to any reason.

After completion of the treatment period or in case of discontinuation, patients are to attend **follow-up visits**. Patients will be followed for AEs during 30 days after the last administration of trial drug and until their resolution. In addition, patients will be followed every three months to assess disease status.

A full description for the study may be found in the appropriate sections of the study clinical protocol.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To evaluate the efficacy of plitidepsin in combination with bortezomib and dexamethasone in patients with MM double refractory to bortezomib and lenalidomide in terms of overall response rate (ORR), including stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR).

3.2 Secondary Objectives

- To evaluate time-to-event efficacy endpoints of plitidepsin in combination with bortezomib and dexamethasone, i.e., duration of response (DOR), time to progression (TTP), progression-free survival (PFS) and event-free survival (EFS).
- To evaluate overall survival (OS) and OS rate at 6 and 12 months (OS6 and OS12, respectively).
- To evaluate the safety and tolerability of plitidepsin in combination with bortezomib and dexamethasone.
- To study the pharmacokinetics (PK) and pharmacodynamics (PDy) of plitidepsin in combination with bortezomib and dexamethasone.
- To obtain pharmacogenomic information (Pharmacogenomics [PGx]) on markers of response to plitidepsin and bortezomib treatment.

3.3 Endpoints

Primary endpoint:

- ORR, defined as the percentage of patients with sCR , CR , VGPR or PR according to IMWG response criteria.

Secondary endpoints:

- DOR, defined as the time from the first observation of response to the time of PD, with censoring of deaths due to causes other than PD
- TTP, defined as the time from the date of first drug administration to the date of PD.
- PFS, defined as the time from the date of first drug administration to the date of PD or death (of any cause).
- EFS, defined as the time from the date of first drug administration to the date of drug-related events leading to treatment discontinuation, PD or death (of any cause), whichever comes first.
- OS, defined as the time from the date of the first dose to the date of death or last patient contact.
- OS6 / OS12, defined as the Kaplan-Meier estimate of the percentage of patients who are alive at six/twelve months after first drug administration.

Treatment safety [AEs, SAEs and laboratory abnormalities] graded according to the NCI-CTCAE, v. 4. Dose reductions, skipped doses or dose delays required due to treatment-related AEs, and reasons for treatment discontinuations will be analyzed.
Other supportive exploratory endpoints are defined in section 6.1.3.

4 PATIENTS EVALUABILITY CRITERIA

The study population will include patients with MM double refractory to bortezomib and lenalidomide. To be enrolled in this study, the patients must meet all inclusion criteria and no exclusion criteria.

4.1 Definition of Patient Sets for Analysis

"All Included Patients" analysis set is defined as all patients who are included in the study (excluding screening failures), independent of whether they received the study drug.

"All Evaluable for Safety Patients" analysis set is defined as all included patients who receive at least part of one dose or infusion of plitidepsin.

"All Evaluable for Efficacy Patients" analysis set is defined as all included patients who receive at least one complete treatment cycle (two plitidepsin infusions, four bortezomib injections, four doses of dexamethasone), or the equivalent doses over two cycles and must have had at least one disease assessment.

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

5 SAMPLE CONSIDERATIONS

Patients will be treated to test the null hypothesis (H_0) that 20% or fewer patients achieve a response according to IMWG criteria ($p \leq 0.20$) versus the alternative hypothesis (H_1) that 40% or more patients achieve a response according to IMWG criteria ($p \geq 0.40$). The variance of the standardized test will be based on the empirical estimate. The type I error rate (alpha) associated with this one-sided test is 0.025 and the type II error rate (beta) is 0.1; hence, statistical power is 90%. In order to test these hypotheses, it is necessary to recruit 64 evaluable patients.

A futility analysis based on the primary endpoint (ORR) is planned for the time when the first 20 evaluable patients have been recruited. The futility analysis will commence once patient number 20 has completed two full treatment cycles. Patient recruitment will not be halted during the conduct of this futility analysis. A spending function defined by the Gamma family with parameter (-2) has been selected. If there are two or fewer responders according to boundaries and sample size assumptions, then the alternative hypothesis could be rejected and recruitment might be stopped at that time. Otherwise, patient accrual will continue to a total of 64 patients.

Overall, if ≥ 21 (i.e., 33%) patients achieve a response, then the null hypothesis can be rejected.

6 STATISTICAL METHODOLOGY FOR EFFICACY

6.1 Planned Analyses and Definitions

Frequency tables will be performed for categorical variables, whereas continuous variables will be described by means of summary tables that will include the mean, standard deviation (StD), median, minimum, and maximum of each variable.

The "All Evaluable for Efficacy Patients" analysis set will be used for the analyses of ORR, TTP, PFS, EFS, OS, clinical benefit rate (CBR) and disease control rate (DCR).

The "All Responder Patients" analysis set will be used for the analyses of the DOR and time to response.

6.1.1 Primary Endpoint

The ***ORR*** is calculated as the percentage of the number of responders, based on the IMWG response criteria, divided by the total number of patients.

6.1.2 Secondary Endpoints

The ***DOR*** will be analyzed for all patients in whom a response has been observed and is defined as the time, in months, from the date of first documentation of response to the date of disease progression. Response will be assessed according to the IMWG classification response criteria. Deaths due to causes other than PD will be censored.

TTP is defined as the time, in months, from the date of the first infusion to the date of documented PD or death due to PD. TTP will be censored on the date of the last tumor assessment or on the date of the first drug administration if there are no tumor assessments.

PFS is defined as the time, in months, from the date of first drug administration to the date of documented PD, or death (of any cause). If any patient is lost to follow-up before PD or receives another antitumor therapy, PFS will be censored on the date of the last tumor assessment. If there are no tumor assessments, these parameters will be censored on the date of the first drug administration.

EFS is defined as the time, in months, from the date of first drug administration to the date of onset of the first drug-related event leading to treatment discontinuation, documented PD or death. The censoring rules defined above for PFS will be used for EFS.

OS, defined as the time, in months, from the date of first drug administration to the date of death (of any cause) or last patient contact (in this case, survival will be censored on that date).

OS6/OS12, defined as the Kaplan-Meier estimate of the percentage of patients who are alive at six/twelve months after first drug administration.

6.1.3 Other Definitions

CBR was defined in the protocol as SD or better but to homogenize with nowadays standard practice it has been considered to report it as MR or better. Nevertheless, to maintain the definition in the protocol, it will be called ***DCR*** for the analyses and it is defined as SD or better.

Duration of Minor Response, defined as the time, in months, from the first observation of MR to the time of PD, with censoring of deaths due to causes other than PD.
Time to response, defined as the time, in months, from the first drug administration to the first documentation of response.

6.2 Efficacy Analysis Methods

6.2.1 Primary Analysis

For the evaluation of the primary endpoint, ***ORR,*** the exact binomial estimator (count and percentage) including its 95% confidence interval will be used.

6.2.2 Secondary Analyses

Time-to-event variables (DOR, TTP, PFS, EFS and OS) and their fixed time estimates (i.e. OS6 and OS12) will be analyzed according to the Kaplan-Meier method.

Multivariate analyses by logistic regression could be carried out for ORR, and Cox regression for time-to-event endpoints, as supportive analysis.

If appropriate, exploratory multivariate models (e.g. Logistic/Cox regression) will include prognostic factors/covariates widely reported and recognized by hematologist such as: sex, age at diagnosis, baseline ECOG, Body Surface Area, MM type, number of prior lines of anti-myeloma treatment, previous SCT, cytogenetics and/or other covariates according to the hematologist's criteria.

6.2.3 Other Exploratory Analyses

The CBR is calculated as patients with sCR, CR, VGPR, PR, MR divided by the number of patients. The DCR is calculated as patients with sCR, CR, VGPR, PR, MR or SD divided by the number of patients.

Duration of minor response and time to response will be analyzed according to the Kaplan-Meier method.

Waterfall plot will be used to describe the maximum reduction of M-protein in serum and urine.

7 STATISTICAL METHODOLOGY FOR SAFETY

The analysis of the secondary endpoint treatment safety will be based on the "All Evaluable for Safety Patients" analysis set.

7.1 Adverse Events

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

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

As far as all the adverse events 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. Adverse events will be described according to the worst NCI-CTC grade or, for events which do not form the subject of NCI-CTC classification, according to the worst severity.

AEs reported in EOT visit will be imputed to last cycle.

An overall summary of adverse events will be done by body system and preferred term, by severity (worst toxicity grade), by relationship to the study drug/s (drug related or relationship unknown / all adverse events regardless of relationship), and by AE outcome. Only events reported by the Investigator as 'not related to plitidepsin +/- bortezomib +/- dexamethasone' will be excluded from the trial analysis of drug-related events. A second set of tables including all events will also be presented, and a third set of tables including treatment emergent events will also be presented.

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

All events entered in Adverse Event form with the onset date before the first drug administration, will be reported as Signs and symptoms. Only those events with start date after or on the date of first infusion will be included in AE tables in Safety section (except those already present at baseline).

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.

Laboratory results reported during the EOT visit will be imputed to last cycle.

Overall cross tabulation will be used to present the worst grade during treatment versus the baseline toxicity grade for anemia, lymphopenia, leukopenia, neutropenia and thrombocytopenia, and also versus treatment-emergent events (i.e., those that worsened or appeared for the first time during treatment).

The worst grade per patient during treatment and per cycle will also be calculated for biochemical tests: ALT, AST, total bilirubin, AP, CPK, GGT, creatinine, calcium (corrected by albumin levels), potassium, sodium, magnesium, glucose and albumin.

Time and duration of AST, ALT and CPK increases, platelet count and neutrophil count 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 grade of AST, ALT, bilirubin, creatinine, AP, CPK and electrolytes; and also versus treatment-emergent events.

7.3 Vital Signs, Physical Examination, Left Ventricular Ejection Fraction (LVEF) and Electrocardiogram Findings

Tabulation will be used to summarize the performance status, body weight, and LVEF and electrocardiogram abnormalities at baseline and during the treatment, if appropriate, for each patient.

7.4 Deaths and Other Serious Adverse Events

Deaths and Serious Adverse Events will be tabulated according to their relationship with the study treatment and time from last dose (<=30d / > 30d).

8 OTHER ANALYSES

Categorical variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, mean, standard deviation, 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, 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/test, the last assessment before or on 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 delays, dose omissions and dose reductions will be described following standard tables detailed in Appendix I.

Total cumulative dose, is the sum of all the study drug doses from the first cycle until last cycle, including the dose received in the last cycle.

Patients will be considered to be on-treatment for the duration of their treatment and 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.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle.

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 delayed infusions. 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 delays and cycle modification calculations.

8.3 Subsequent Therapy

A table summarizing all 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 first drug administration to treatment failure that leads to the need of a further treatment regimen.

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 and Pharmacodynamic Analyses

These analyses will be detailed in separate documents.

8.6 Pharmacogenomic Analyses

This analysis will be detailed in a separate document.

8.7 Decimal Places

By default, all results will be rounded to one decimal, except in the case where variables are integer; in that case, they will be reported without decimals, for example, age in years, number of sites. For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary.

8.8 Imputation of Incomplete Dates

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

Before registration

If day of a date is unknown then the imputed day will be the 15th of the month, 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 registration date; otherwise the imputed date will be the first day of the registration month (i.e. 1/Month of registration date/Year).

Between treatment start and end of treatment

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month is also unknown then the imputed date will 1/January. This assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date.

After end of treatment

To ensure the most conservative approach for time-to-event variables (i.e. DOR, TTP, PFS, EFS 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 the first of the month. 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.

8.9 Subgroup Analyses

Specific subgroup analysis will be developed according to those variables considered clinically relevant.

The influence of prognostic factors on the efficacy endpoints will be studied in the multivariate analysis. These prognostic factors to be considered are; multiple myeloma status (relapse, refractory or relapse and refractory), cytogenetic risk (high risk *vs* standard risk), number of prior lines, etc.

Analysis of safety profile based on age, race, body mass index (BMI) or other clinically relevant variables will be performed.

8.10 Methods for Handling Missing Data

Missing values will not be included in the calculation of outputs.

8.11 Interim and Group Sequential Analyses

A futility analysis based on the primary endpoint (ORR) is planned for the time when the first 20 evaluable patients have been recruited. The analysis will commence once the last of the 20 patients has completed two full treatment cycles.

8.12 Data Analysis Conventions

All data analysis conventions, data calculations and grouping needed to perform the Clinical Study Report outside of this statistical analysis plan will be described in a separate document.

9 STATISTICAL SOFTWARE

Medidata Rave® EDC will be used for data entry and clinical data management.

EAST v.6.3.1 has been used to calculate sample size.

SAS v.9.4 or superior will be used for all statistical analysis outputs.

APPENDIX I

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

Summary tables will have source data footnotes that will refer to the relevant listings. The tables' layout may change to adequately accommodate group size as appropriate.

If the number of categories or items does not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

10 Study Patients

These analyses will be performed in "All Included patients" analysis set.

10.1 Patient Disposition

Main characteristics concerning inclusion in the study, withdrawal from the study and protocol deviations will be displayed in this section.

Table 10.1.1 Number of Patients Included, Evaluable for Safety, and Evaluable for the Main Endpoint.

	N	%
All Included patients		
All evaluable patients for safety		
All evaluable patients for efficacy		

Listing 10.1.2 Patients who do not meet All Inclusion Criteria.

Patient id.	Criterion number(s) and description

Listing 10.1.3 Patients who meet Any Exclusion Criteria.

Patient id.	Criterion number(s) and description

Listing 10.1.4 Patients not Evaluable for Efficacy

Patient id.	Reason

Listing 10.1.5 Patient not Evaluable for Safety.

Patient id.	Reason

Table 10.1.6 Patients Accrual by Institution

	Country	Institution	N	%
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 10.1.7 Study Dates

Date of first registration	
Date of first dose of the first patient	
Date of last registration	
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

10.2 Reasons for Treatment and Study Discontinuation

Table 10.2.1 Treatment Discontinuation

	N	%
Progressive disease		
Treatment related adverse event		
Non treatment related adverse event		
Patient refusal to treatment		
Investigator decision		
Death		
Other *		
Total		

Note: This table will be based on treated patients .Other (*) Specify (see listing 10.2.2)

Listing 10.2.2 Reasons for Treatment Discontinuation Other than Progressive Disease.

Patient id.	Reason	Last cycle	Comments

Note: This table will be based on treated patients

Listing 10.2.3 Treatment Discontinuation due to AEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Seriousness criteria	Outcome

Note: This table will be based on treated patients

Table 10.2.4 Study Discontinuation

	N	%
Study termination (clinical cut-off)		
Patient's refusal		
Never treated		
Death		
Patient's follow-up completed		
Lost to follow-up		
Other *		
Total		

Other (*) See Listing 10.2.5

Listing 10.2.5 Study Discontinuation due to Other Reason

Patient id.	Reason	Specify

10.3 Protocol Deviations

Listing 10.3.1 Protocol Deviations

Patient id.	Deviation type	Description

11 Efficacy Evaluation

11.1 Demographic and Other Baseline Characteristics

These analyses will be performed in "All Included patients" analysis set.

11.1.1 Patient Characteristics at Baseline

Table 11.1.1.1 Baseline characteristics: Sex

	N	%
Male	X	XX.X
Female		
Total		

Table 11.1.1.2 Baseline characteristics: Age at treatment registration

N	Median	Mean	StD	Min	Max

Table 11.1.1.3 Baseline characteristics: Age grouped

	N	%
<65 years	X	XX.X
65-75 yeas		
≥75		
Total		

Table 11.1.1.4 Baseline characteristics: Race

	N	%
White	X	XX.X
…		

Total		

11.1.2 Disease at Diagnosis, Time from Diagnosis and Current Disease

Table 11.1.2.1 Time from diagnosis to first infusion (months)

N	Median	Mean	StD	Min	Max

Table 11.1.2.2 Time from last PD to first infusion (weeks)

N	Median	Mean	StD	Min	Max

Table 11.1.2.3 Multiple Myeloma Type.

	N	%
Secretory	X	XX.X
Oligosecretory		
Non-Secretory		
Total		

Table 11.1.2.4 Ig abnormality at diagnosis (for secretory and oligosecretory MM).

	N	%
IgG	X	XX.X
IgA		
IgD		
IgE		
IgM		
Kappa light-chain Disease		
Lambda light-chain Disease		
Total		

Table 11.1.2.5 Durie-Salmon Stage at First Diagnosis.

	N	%
IA	X	XX.X
IB		
IIA		
IIB		
IIIA		
IIIB		
Total		

Table 11.1.2.6 ISS Stage at First Diagnosis.

	N	%
I	X	XX.X
II		
III		
Not Done		
Total		

Table 11.1.2.7 Karyotype and FISH at First Diagnosis.

	N	%
Done	X	XX.X
Not Done		

Total		

Table 11.1.2.8 R-ISS Stage at Study Entry

	N	%
I (ISS stage I and standard-risk *CA by iFish and normal LDH)	X	XX.X
II (Not R-ISS stage or III)		
III(ISS stage III and either high-risk *CA by iFISH or high LDH)		
Total		

(*) Standard-risk (or standard prognosis) and high-risk as defined below

11.1.3 Cytogenetics

Table 11.1.3.1 Cytogenetics.

Result **	N	%
del13	X	XX.X
del17		
t(14;16)		
…		
Other *		
Total		

Other (*) Specify, see Listing 11.1.3.2

Listing 11.1.3.2 Cytogenetics: Result, 'Other'.

Patient id.	Other

Patients will be classified in "high risk" or "standard 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 single alterations of trisomies 3, 5, 6, 9, 11, 15, 19 or 21 will be classified as "standard prognosis". This classification will be done by clinical review.

Table 11.1.3.3 Cytogenetic Risk.

	N	%
High risk	X	XX.X
Standard risk		
Total		

11.1.4 Prior Anticancer Therapy

Table 11.1.4.1 Number of Lines of Prior Medical Therapy.

	N	%
1	X	XX.X
2		
...		
Total		
Median (Range)		
Mean (Std)		

Table 11.1.4.2 Prior Anti-myeloma Agents

(ATC-level)		
	N	%
	X	XX.X
….		
Median (Range)		
Mean (Std)		

Table 11.1.4.3 Prior Stem Cell Transplantation

	N	%
Autologous HSCT	X	XX.X
Allogeneic HSCT		
Both		
Total		

Table 11.1.4.4 TTP to Last Prior Anti-myeloma Therapy

Time to progression. Last anticancer therapy (months)	N	Median	Mean	StD	Min	Max
Total						

Table 11.1.4.5 Best Response to Last Therapy

	N	%
CR		
sCR		
VGPR		
PR		
…		
NE / NA / UNK		

Table 11.1.4.6 Status to Last Therapy

	N	%
Relapse		
Refractory		
Relapse/Refractory		

11.1.5 Physical Examination, Vital Signs, Electrocardiogram and Other Tests

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

Table 11.1.5.1 Baseline characteristics: Physical Exam.

Parameter	N	Median	Mean	StD	Min	Max
Weight (kg.)						
Height (cm.)						
BSA (m^2)						

Table 11.1.5.2 Number of Lesions (Plasmacytomas) at Baseline.

No.of lesion	N	%
1 lesion	X	
2 lesions		
3 lesions		
…		

See listing 11.1.5.3 for details

Listing 11.1.5.3 Plasmacytomas at Baseline

Patient id.	Lesion Number	New lesion	Anatomic Localization	Date	Method.	Lesion dim 1	Lesion dim 2	Product of the Cross-diameters	Sum of the product of the Cross-Diameters

Table 11.1.5.4 Baseline characteristics: Vital Signs.

Parameter	N	Median	Mean	StD	Min	Max
Heart rate (beats/min)						
Systolic blood pressure (mmHg)						
Diastolic blood pressure (mmHg)						
Temperature (ºC)						

Table 11.1.5.5 Baseline characteristics: Electrocardiogram

	N	%
Normal	X	XX.X
Significant abnormalities*		
Non-significant abnormalities		
Total		

(*)See listing 11.1.5.6 for details

Listing 11.1.5.6 ECG Abnormalities at Baseline

Patient id.	Result	QT interval (msec)	PR interval (msec)	QRS complex duration (msec)	Max Height of QRS (mm)	Heart Rate:	QTc (msec)

Table 11.1.5.7 Baseline Characteristics: ECOG Performance Status

	N	%
0	X	XX.X
1		
2		
…		
Total		

Table 11.1.5.8 Baseline characteristics: Neurological Examination

	N	%
Normal	X	XX.X
Abnormal*		
Total		

(*)See listing 11.1.5.9 for details

Listing 11.1.5.9 Neurological Examination Abnormalities at Baseline

Patient id.	Result	Specify

Table 11.1.5.10 Baseline characteristics: LVEF

	N	%
Normal	X	XX.X
Significant abnormalities*		
Non-significant abnormalities*		
Total		

(*)See listing 11.1.5.11 for details

Listing 11.1.5.11 Patients with Left Ventricular Ejection Fraction Abnormalities at Baseline

Patient id.	Date	Method	LVEF (%)	Institutional normal range (%)	Result	Abnormalities

Table 11.1.5.12 Baseline Characteristics: Adequate Contraception

	N	%
Yes	X	XX.X
No		
NA*		
Total		

(*) Specify reasons

Table 11.1.5.13 Baseline Characteristics: Pregnancy test

	N	%
Positive	X	XX.X
Negative		
NA*		
Not done		
Total		

(*) Specify reasons

11.1.6 Viral Serology

Table 11.1.6.1 Viral Serology

	N	%
Viral serology Yes	X	XX.X
Hepatitis B (HBC)		
Surface antigen (HBsAg) Positive Negative Not Done		
Surface antibody (HBsAb or Anti-HBs): Positive Negative Not Done		
Core antibody (HBcAb or anti-HBc): Positive Negative Not Done		
Hepatitis C (HCV)		
HCV Positive Negative Not Done		
Cytomegalovirus		
CMV pp65 antigen Positive Negative Not Done		
Quantitative CMV DNA PCR Positive Negative Not Done		

11.1.7 Hematological Values at Baseline

Table 11.1.7.1 Hematological Abnormalities at Baseline

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

(*)Any grade

Listing 11.1.7.2 Hematological Tests not Assessed at Baseline

Patient id.	Lab. test

Listing 11.1.7.3 Hematological Abnormalities at Baseline. Grade ≥ 2

Patient id	Parameter	Value	Grade

11.1.8 Biochemical Values at Baseline

Table 11.1.8.1 Biochemical Abnormalities at Baseline

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

(*)Any grade

Table 11.1.8.2 Biochemical Values at Baseline

	N	%
LDH > 2 .5× ULN		
B2-microglobulin>ULN		

Listing 11.1.8.3 Biochemical Tests not Assessed at Baseline

Patient id.	Lab. test
…	

Listing 11.1.8.4 Biochemical Abnormalities at Baseline. Grade ≥ 2

Patient id	Parameter	Value	Grade

11.1.9 Other Metabolic Values at Baseline

Table 11.1.9.1 Other Metabolic Abnormalities at Baseline

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

(*)Any grade

Listing 11.1.9.2 Metabolic Tests not Assessed at Baseline

Patient id.	Lab. test
…	

Listing 11.1.9.3 Metabolic Abnormalities at Baseline. Grade ≥ 2

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

	N	%
No. signs and symptoms per patient		
0 1 2 ≥ 3		
Median (Range)		
Mean (Std)		

Table 11.1.10.2 Signs and Symptoms at Baseline

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

(*)Any grade

Listing 11.1.10.3 Signs and Symptoms at Baseline

Patient id.	Sign/symptom	Grade	Onset date	Treated

11.1.11 Concomitant Medication/Procedures at Baseline

Concomitant medication at baseline according to the ATC classification.

Table 11.1.11.1 Agents of Concomitant Medication started at Baseline

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Preferred Name	N	%
				X	XX.X

Listing 11.1.11.2 Concomitant Medication Therapy at Baseline

Patient id.	Type	Drug name /Procedure	ATC Code	Route	Dose	Start date	End date	Ongoing	Indication

Listing 11.1.11.3 Concomitant Procedures Therapy at Baseline

Patient id.	Test	Date	Result

11.2 Efficacy Analysis

Efficacy analysis will be carried out on the "All Evaluable for Efficacy Patients" population.

11.2.1 Primary Analysis

Table 11.2.1.1 Overall Response

Response		
	N	%
sCR		
CR		
VGPR		
PR		
MR		
SD		
PD		

Table 11.2.1.2 Overall Response Rate

	Proportion	Lower 95% limit	Upper 95% limit
Response rate			

Binomial exact estimator and 95% confidence interval

11.2.2 Secondary Analyses

Table 11.2.2.1 Duration of Response

N	
Events	
Censored	
Median DR	

Kaplan-Meier plot will be also shown (Figure 11.2.2.1)

Table 11.2.2.2 Time-To-Progression

N	
Events	
Censored	
Median TTP	
TTP at 3 months	
TTP at 6 months	
TTP at 12 months	

Kaplan-Meier plot will be also shown (Figure 11.2.2.2)

Table 11.2.2.3 Progression-Free Survival

N	
Events	
Censored	
Median PFS	
PFS at 3months	
PFS at 6 months	
PFS at 12 months	

Kaplan-Meier plot will be also shown (Figure 11.2.2.3)

Table 11.2.2.4 Event-Free Survival

N	
Events	
Censored	
Median EFS	
EFS at 3 months	
EFS at 6 months	
EFS at 12 months	

Kaplan-Meier plot will be also shown (Figure 11.2.2.4)

Table 11.2.2.5 OS

N	
Events	
Censored	
Median OS	
OS at 6 months	
OS at 12 months	

Kaplan-Meier plot will be also shown (Figure 11.2.2.5).

11.2.3 Other Exploratory Analyses

Table 11.2.3.1 Clinical Benefit Rate

	Proportion	Lower 95% limit	Upper 95% limit
Clinical Benefit Rate			

Binomial exact estimator and 95% confidence interval.
CBR defined as MR or better according to IMWG.

Table 11.2.3.2 Disease Control Rate

	Proportion	Lower 95% limit	Upper 95% limit
Disease Control Rate			

Binomial exact estimator and 95% confidence interval.
DCR defined as SD or better according to IMWG.

Table 11.2.3.3 Duration of Minor Response

N	
Events	
Censored	
Median Duration of Minor Response	

Kaplan-Meier plot will be also shown (Figure 11.2.3.3)

Table 11.2.3.4 Time to Response

N	
Events	
Censored	
Median Duration of Time to Response	

Kaplan-Meier plot will be also shown (Figure 11.2.3.4)

11.2.4 Characteristics of Responders

A summary of the main characteristics of patients with sCR, CR, VGPR, PR, MR or SD as best response will be shown.

Listing 11.2.4.1 Characteristics of Responders

Patient id.	Sex	Age	PS	MM type	Relapse /Refractory	No. of prior lines	Cycles received	Best response	PFS	DOR	...	OS

11.2.5 Multivariate analyses

Multivariate analyses could be carried out as supportive analysis.

Table 11.2.5.1 Multivariate analysis of ORR

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

List of covariates will be provided by the medical responsible

Table 11.2.5.2 Multivariate analysis of TTP

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

List of covariates will be provided by the medical responsible

Table 11.2.5.3 Multivariate analysis of PFS

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

List of covariates will be provided by the medical responsible

Table 11.2.5.4 Multivariate analysis of EFS

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

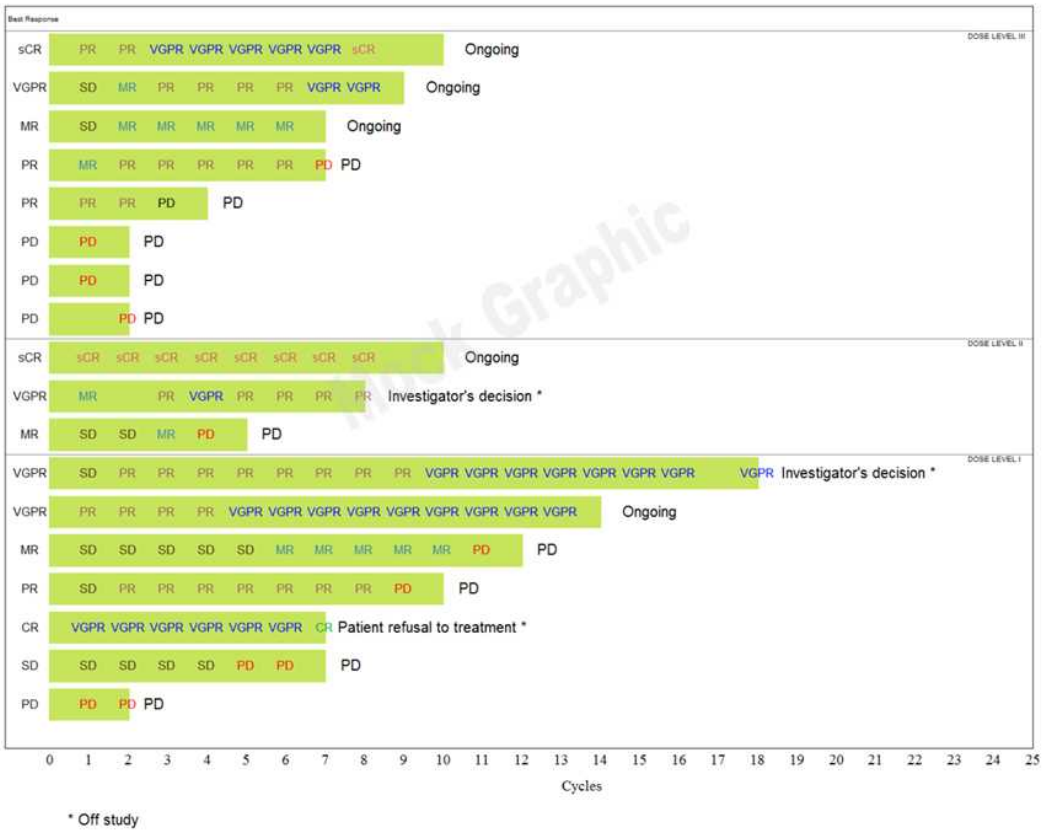
List of covariates will be provided by the medical responsible

Table 11.2.5.5 Multivariate analysis of OS

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

List of covariates will be provided by the medical responsible

Figure 11.2.5.6 . Response to Treatment per Cycle in All Patients Evaluable for Efficacy



12 Safety Analysis

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

12.1 Extent of Exposure

12.1.1 Treatment Administration

Table 12.1.1.1 Number of Cycles Administered and Dose Intensity

No. of cycles administered per patient	N	%
1 2 3 …		
Median (Range)		
Mean (Std)		
Time on treatment (weeks) Median (Range) Mean (Std)		
Plitidepsin cumulative dose (mg/m²) Median (Range) Mean (Std)		
Plitidepsin dose intensity (mg/m²/wk) Median (Range) Mean (Std)		
Plitidepsin relative dose intensity (%) Median (Range)		
Bortezomib cumulative dose (mg/m²) Median (Range) Mean (Std)		
Dexa cumulative dose (mg) Median (Range) Mean (Std)		
…….		

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

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

Table 12.1.2.1.2 Number of Patients and Cycles with Dosing Delay, any Relationship

	N	%
No. of patients susceptible of dose delay		
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 plitidepsin delays 1 cycle with plitidepsin delayed 2 cycles with plitidepsin delayed ≥ 3 cycles with plitidepsin delayed No BTZ delays …….		

BTZ, bortezomib (*) All cycles excluding first cycle. (**) Denominator= Number of cycles susceptible to be delayed

Table 12.1.2.1.3 Number of Patients and Cycles with Dosing Delay according to the Relationship

	Drug Related AE*		Non-Drug Related AE*		Relationship Unknown*		Other*	
	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.

Table 12.1.2.1.4 Length of Dosing Delay.

		Treatment-related**		Non-treatment-related***		Total	
Length of delay	Median (Range) /Mean(Std)						
Length of delay		N	%	N	%	N	%
<= 7 days							
>7 days and <=14 days							
> 14 days							

(*) Denominator= Number of cycles susceptible to be delayed. .(**) Drug Related AE, Relationship unknown (***)Non-drug related AE, other

12.1.2.2 Number of Delays according to Cycle Number

Listing 12.1.2.2.1 Cycle Delays due to AEs

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

AEs with action = 'Dose delayed' or 'Dose delayed/reduced' or 'Dose delayed/omitted' or 'Dose delayed/omitted/reduced'

12.1.3 Dose Omissions

12.1.3.1 Number of Patients and Cycles with Dose Omissions

Listing 12.1.3.1.1 Dose Omissions

Patient id.	Cycle	Day	Cycle start date	Reason for dose omission	Dose omission Spec.

Listing 12.1.3.1.2 Dose Omissions due to AEs

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

AEs with action = 'Dose Omitted' or 'Dose delayed/omitted' or 'Dose omitted/reduced' or 'Dose delayed/omitted/reduced'

12.1.4 Dose Reductions

All dose reductions should be considered and described, specifying the reason for reduction (drug related AE, non-drug related AE, relationship unknown and other).

Listing 12.1.4.1 Dose Reductions

Patient id.	Cycle	Day	Cycle start date	Previous dose	Reduced dose	Reason for dose reduction	Dose reduction Spec.

Table 12.1.4.2 Number of Patients and Cycles with Dose Reduction, any Relationship

	N	%
No. of patients treated	X	XX.X
No. of patients with any dose reduced		
No. of patients with:		
No plitidepsin reduction		
1 cycle with plitidepsin dose reduced		
2 cycles with plitidepsin dose reduced		
….		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced*		
No. of cycles with plitidepsin dose reduced **		
No. of cycles with plitidepsin 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 reduction

Table 12.1.4.3 Number of Patients and Cycles with Dose Reduction according to the Relationship

No. of cycles with dose reductions*	N	%
Treatment-related		
Drug Related AE	X	XX.X
Relationship Unknown		
Non–treatment-related		
Non-Drug Related AE		
Other *		

(*) Denominator= Number of cycles susceptible to have a dose reduction

Listing 12.1.4.4 Dose Reductions due to AEs

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

AEs with action = 'Dose Reduced' or 'Dose delayed/reduced or 'Dose omitted/reduced' or 'Dose delayed/omitted/reduced'

12.2 Adverse Events (AEs)

12.2.1 Display of Adverse Events

Table 12.2.1.1 Summary of Adverse Events.

	N (%)
Patients with at least one AE regardless relationship	
Any treatment-related AE	
Any plitidpesin-related AE	
Any BTZ -related AE	
Any DXM -related AE	
Any plitidepsin and DXM –related AE	
Any plitidepsin and BTZ –related AE	
Any DXM and BTZ –related AE	
Any plitidepsin&DXM&BTZ –related AE	
Any grade 3/4 AE	
Any grade 3/4 treatment-related AE	
Any grade 3/4 plitidpesin -related AE	
Any grade 3/4 BTZ -related AE	
Any grade 3/4 DXM -related AE	
Any grade 3/4 plitidepsin and DXM –related AE	
Any grade 3/4 plitidepsin and BTZ –related AE	
Any grade 3/4 DXM and BTZ –related AE	
Any grade 3/4 plitidepsin&DXM&BTZ –related AE	
AEs leading to death	
AEs treatment-related leading to death	
AEs plitidpesin -related leading to death	
AEs BTZ -related leading to death	
AEs DXM -related leading to death	
AEs plitidepsin and DXM -related leading to death	
AEs plitidepsin and BTZ -related leading to death	
AEs DXM and BTZ -related leading to death	
AEs plitidepsin&DXM&BTZ -related leading to death	
AEs leading to dose delay	
AE treatment-related leading to dose delay	
AE plitidpesin -related leading to dose delay	
AE BTZ -related leading to dose delay	
AE DXM -related leading to dose delay	
AE plitidepsin and DXM -related leading to dose delay	
AE plitidepsin and BTZ -related leading to dose delay	
AE DXM and BTZ -related leading to dose delay	
AE plitidepsin&DXM&BTZ -related leading to dose delay	
AEs leading to dose omission	
AEs treatment-related leading to dose omission	

	N (%)
AEs plitidpesin -related leading to dose omission	
AEs BTZ -related leading to dose omission	
AEs DXM -related leading to dose omission	
AEs plitidepsin and DXM -related leading to dose omission	
AEs plitidepsin and BTZ -related leading to dose omission	
AEs DXM and BTZ -related leading to dose omission	
AEs plitidepsin&DXM&BTZ -related leading to dose omission	
AEs leading to treatment discontinuation	
AEs treatment-related leading to treatment discontinuation	
AEs plitidpesin -related leading to treatment discontinuation	
AEs BTZ -related leading to treatment discontinuation	
AEs DXM -related leading to treatment discontinuation	
AEs plitidepsin and DXM -related leading to treatment discontinuation	
AEs plitidepsin and BTZ -related leading to treatment discontinuation	
AEs DXM and BTZ -related leading to treatment discontinuation	
AEs plitidepsin&DXM&BTZ -related leading to treatment discontinuation	
AEs treatment-related leading to dose reduction	
AEs plitidpesin -related leading to dose reduction	
AEs BTZ -related leading to dose reduction	
AEs DXM -related leading to dose reduction	
AEs plitidepsin and DXM -related leading to dose reduction	
AEs plitidepsin and BTZ -related leading to dose reduction	
AEs DXM and BTZ -related leading to dose reduction	
AEs plitidepsin&DXM&BTZ -related leading to dose reduction	

BTZ, bortezomib; DXM, dexamethasone

Table 12.2.1.2 Summary of Main Adverse Events.

Main Adverse Events*	N (%)
Fatigue	
Diarrhea	
Peripheral Neuropathy	
Alanine aminotransferase increased	
……	

* Main AEs will be defined by medical responsible (or will be defined as the most common AEs)

Table 12.2.1.3 Treatment-related* Adverse Events. Worst Grade by Patient

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

(*) or Unknown relationship (**) Any grade

Table 12.2.1.4 Treatment-related* Adverse Events. Worst Grade by Cycle

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

(*) or Unknown relationship (**) Any grade

Table 12.2.1.5 Adverse Events regardless of Relationship. Worst Grade by Patient

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

(*) Any grade

Table 12.2.1.6 Adverse Events regardless of Relationship. Worst Grade by Cycle

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

(*) Any grade

Table 12.2.1.7 Treatment Emergent Adverse Events* .Worst Grade by Patient

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

(*)Treatment Emergent AE: Event that first appears during treatment, which was absent before or which worsens relative to the pre-treatment state (**) Any grade

Table 12.2.1.8 Treatment Emergent Adverse Events. Worst Grade by Cycle

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

(*) Any grade

Listing 12.2.1.9 Treatment-related* Grade 3-4 Adverse Events. Worst Grade by Patient

Patient id.	SOC Name	Preferred term	Grade

(*) or Unknown relationship (**) Any grade

Listing 12.2.1.10 Treatment-related* Grade 3-4 Adverse Events. Worst Grade by Cycle

Patient id.	Cycle	SOC Name	Preferred term	Grade

(*) or Unknown relationship (**) Any grade

Listing 12.2.1.11 Adverse Events Grade 3-4 regardless of Relationship. Worst Grade by Patient

Patient id.	SOC Name	Preferred term	Grade

Listing 12.2.1.12 Adverse Events Grade 3-4 regardless of Relationship. Worst Grade by Cycle

Patient id.	Cycle	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

Table 12.3.1.1 Summary of Serious Adverse Events.

	N (%)
Patients	
Any SAE	
Any treatment-related* SAE	
Any grade 3/4 SAE	
Any grade 3/4 treatment-related* SAE	

(*)Broken down by drug/drugs

Table 12.3.1.2 Treatment-related* SAEs. Worst Grade by Patient

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

(*) or Unknown relationship (**) Any grade

Table 12.3.1.3 Treatment-related* SAEs. Worst Grade by Cycle

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

(*) or Unknown relationship (**) Any grade

Table 12.3.1.4 SAEs Regardless of Relationship. Worst Grade by Patient

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

(*) Any grade

Table 12.3.1.5 SAEs Regardless of Relationship. Worst Grade by Cycle

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

(*) Any grade

Listing 12.3.1.6 SAEs

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

SAEs narratives will be provided by the pharmacovigilance department.

12.3.2 Deaths

Table 12.3.2.1 Cause of Death

Reason*	N	%
Malignant disease		
Study drug related AE		
Non study drug related AE		
Other		
Total		

(*) Denominator=Number of patients who died.

Listing 12.3.2.2 Deaths

Patient id.	Death date	Cause	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

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

12.4 Clinical laboratory evaluation

12.4.1 Hematological Abnormalities

Table 12.4.1.1 Hematological Abnormalities during Treatment, Worst Grade per Patient

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

(*) Any grade

Table 12.4.1.2 Hematological Abnormalities during treatment, Worst Grade per Cycle

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

(*) Any grade

Listing 12.4.1.3 Grade 3-4 hematological Abnormalities during Treatment. Worst Grade per Patient

Patient id.	Test	Grade

Listing 12.4.1.4 Grade 3-4 hematological Abnormalities during Treatment. Worst Grade per Cycle

Patient id.	Test	Grade

Listing 12.4.1.5 Hematological Tests not Assessed at any Treatment Visit per Patient

Patient id.	Lab. test

Listing 12.4.1.6 Hematological Tests not Assessed by Patient and Cycle

Patient id.	Cycle	Lab. test

Table 12.4.1.7 Blood Products during the study

	N	%
Packed red cells	X	XX.X
Platelets		
Plasma		
Cryoprecipitates		
Clotting factors		

These tables will be complemented with plots for the median nadir of neutrophils (Figure 12.4.1.8), platelets count (Figure 12.4.1.9) and hemoglobin values (Figure 12.4.1.10) by cycle along the treatment. Furthermore, if appropriate, graphs of the intercycle time course of neutropenia and thrombocytopenia will be provided.

12.4.2 Biochemical Abnormalities

Table 12.4.2.1 Biochemical Abnormalities during Treatment, worst Grade per Patient

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

(*) Any grade

Table 12.4.2.2 Biochemical Abnormalities during Treatment, Worst Grade per Cycle

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

(*) Any grade

Listing 12.4.2.3 Grade 3-4 biochemical Abnormalities during Treatment. Worst Grade per Patient

Patient id.	Test	Grade

Listing 12.4.2.4 Grade 3-4 biochemical Abnormalities during Treatment. Worst Grade per Cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.2.5 Biochemical tests not Assessed at any Treatment Visit by Patient

Patient id.	Lab. test

Listing 12.4.2.6 Biochemical Tests not Assessed by Patient and Cycle

Patient id.	Cycle	Lab. test

These tables will be complemented with plots for the median peak of ALT (Figure 12.4.2.7, AST (Figure 12.4.2.8) and CPK values (Figure 12.4.2.9) by cycle along the treatment. If appropriate, graphs of the intercycle time course of ALT, AST and CPK will be provided.

12.4.3 Other metabolic parameters

Table 12.4.3.1 Metabolic Abnormalities during Treatment, Worst Grade per Patient

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

(*) Any grade

Table 12.4.3.2 Metabolic Abnormalities during Treatment, Worst Grade per Cycle

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

(*) Any grade

Listing 12.4.3.3 Grade 3-4 metabolic Abnormalities during Treatment. Worst Grade by Patient

Patient id.	Test	Grade

Listing 12.4.3.4 Grade 3-4 metabolic Abnormalities during Treatment. Worst Grade by Cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.3.5 Metabolic Tests not Assessed at any Treatment Visit by Patient

Patient id.	Lab. test

Listing 12.4.3.6 Metabolic Tests not Assessed by Patient and Cycle

Patient id.	Cycle	Lab. test

12.4.4 Laboratory values over time

Table 12.4.4.1 Evolution of Hematological Abnormalities from Baseline, Worst Case per Patient.

			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								

		……								

Table 12.4.4.2 Worsening of Hematological Abnormalities from Baseline, Worst Case per Patient.

			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								
		……								

Table 12.4.4.3 Evolution of Biochemical Abnormalities from Baseline, Worst Case per Patient.

			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								
		……								

Table 12.4.4.4 Worsening of Biochemical Abnormalities from Baseline, Worst Case per Patient.

			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								
		……								

Table 12.4.4.5 Grade 3-4 laboratory Abnormalities in the First Cycle and in all Other Cycles

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

Table 12.4.4.6 ALT,AST and CPK Time-Course Pattern

Laboratory abnormalities	Onset day grade 3/4	Days in grade 3/4	Time to recovery to grade <=2		
			Median	95%CI Lower limit	95%CI Upper limit
ALT					
AST					
CPK					

If considered relevant CPK relationship with muscular toxicity will be studied by means of descriptive tables/listings.

Table 12.4.4.7 Platelet Count and Neutrophil Count Time-Course Pattern

Laboratory abnormalities	Onset day grade 3/4	Days in grade 3/4	Time to recovery to grade <=2		
			Median	95%CI Lower limit	95%CI Upper limit
Platelet count					
Neutrophil count					

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	..	..	..
Patient id.							
…					.	.	.
…					.	.	.

(*) Worst ECOG PS of the cycle determinations.

Table 12.5.1.2 Physical Examination during the Study.

	Cycle/Physical examination result*						
	0	1	2	3	4	…	
Patient id.							
…							

(*) Worst result per cycle.

Table 12.5.1.3 Weight by Patient per Cycle

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

(*) % of changes respect to baseline

Table 12.5.1.4 Number of Lesions (Plasmacytomas) during the Study.

	Cycle/Nº of lesions*						
	0	1	2	3	..	..	..
Patient id.							
…					.	.	.
…					.	.	.

(*)Max.number of lesions of the cycle determinations.

12.5.2 LVEF and ECG

Listing 12.5.2.1 LVEF Evolution during the Study

Patient id.	LVEF(%)		
	Baseline*	Minimun*	End of treatment*
Median(Range)			
Mean(Std)			

(*) LVEF (%) value and method

Listing 12.5.2.2 Electrocardiogram Results . Evolution during the Study.

Patient id.	Cycle	ECG result

12.6 Concomitant Medication / Procedures according to the ATC Classification.

Table 12.6.1 Concomitant Medication during Treatment (ATC levels)

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Preferred Name		
				N	%
				X	XX.X

Table 12.6.2 G-CSF, transfusions and Bisphosphonates during Treatment

	N	%
G-CSF		

…		

Table 12.6.3 Subsequent Therapy

	N	%
Type		
Chemotherapy		
…		
Subsequent chemotherapy agents (ATC)		
…		

Table 12.6.4 Time to subsequent therapy or death

N	X
Events	X
Censored	X
Median Time	X.X

Kaplan-Meier plot will be also shown (Figure 12.6.4)

12.7 Safety Analysis in Special Subgroups.

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

	White			Other		
	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
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 MM Serum/Urine Protein Measurements

Figure 12.8.1 Individual M-protein Values of Responder Patients

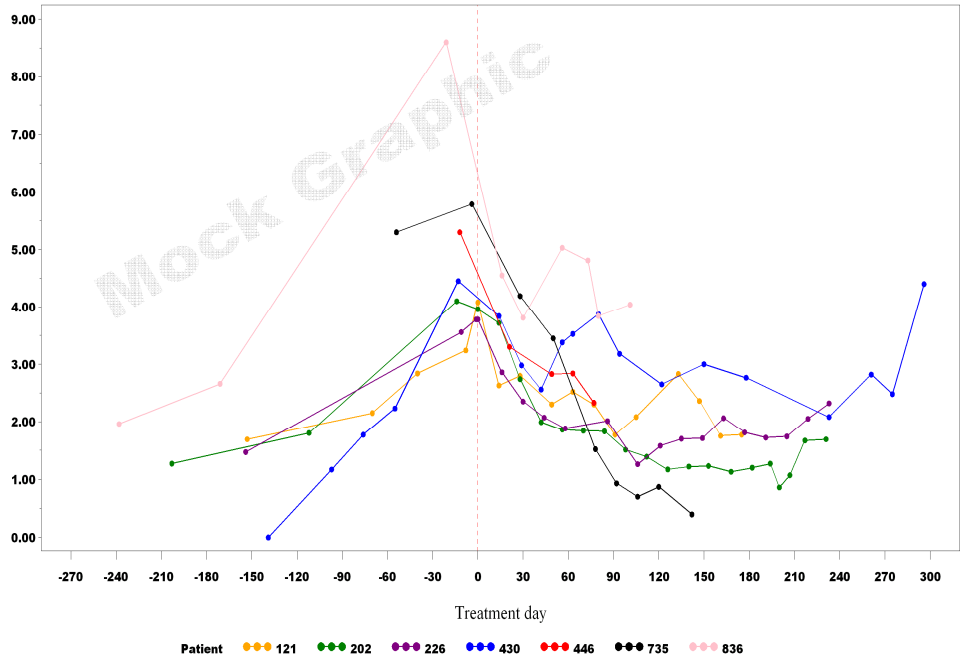
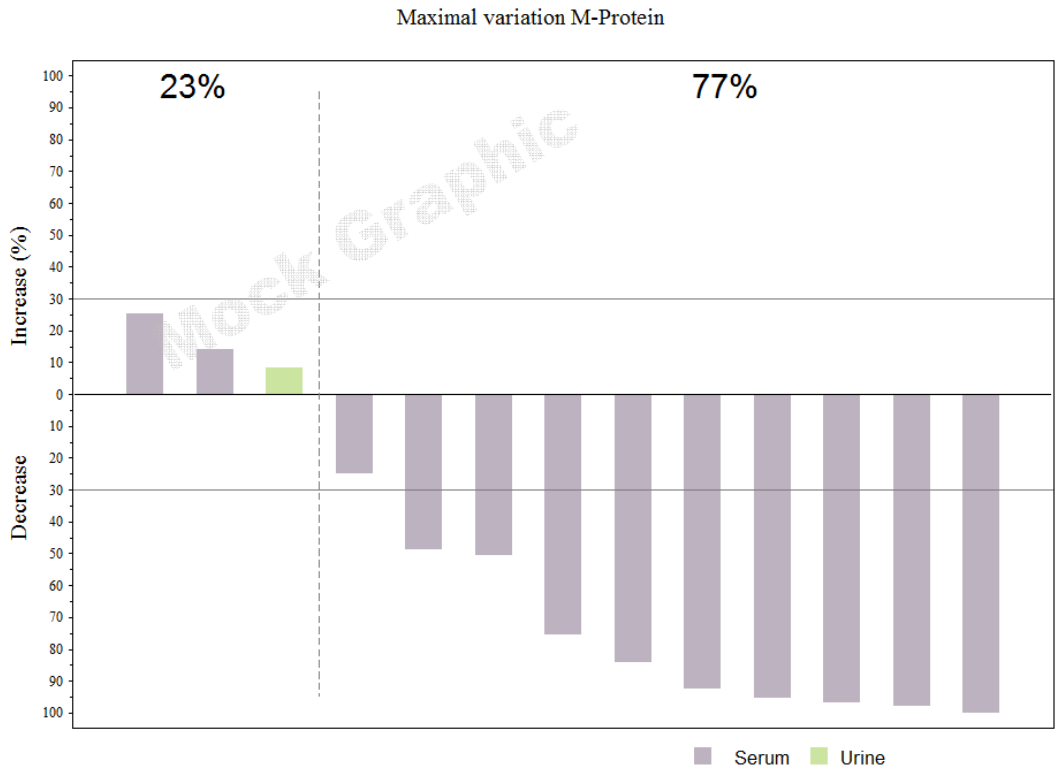


Figure 12.8.2 Waterfall Plot. (Maximum Reduction of M-Protein in Serum/Urine)



APPENDIX II

13 DB Listings

CRF Listings.

-Listing 13.1.1: Screening
-Listing 13.1.2: Demographics
-Listing 13.1.3: Contraception/Pregnancy test
-Listing 13.1.4: Medical history
-Listing 13.1.5: MM history
-Listing 13.1.6: Cytogenetics
-Listing 13.1.7: Prior AntiCancer Therapy: Surgery
-Listing 13.1.8: Prior AntiCancer Therapy: Palliative RadioTherapy
-Listing 13.1.9: Prior AntiCancer Medical Therapy for Study Disease
-Listing 13.1.10: Hematology laboratory values
-Listing 13.1.11: Coagulation Test
-Listing 13.1.12: Biochemical laboratory values
-Listing 13.1.13: Other metabolic laboratory values
-Listing 13.1.14: Urinalysis
-Listing 13.1.15: Physical examination
-Listing 13.1.16: Clinical neurological assessment
-Listing 13.1.17: Performance status
-Listing 13.1.18: Vital signs
-Listing 13.1.19: Electrocardiogram
-Listing 13.1.20: Left Ventricular Ejection Fraction
-Listing 13.1.21: Viral Serology
-Listing 13.1.22: Prophylactic medication
-Listing 13.1.23: Oral Dexamethasone Administration
-Listing 13.1.24: Plitidepsin Administration
-Listing 13.1.25: Plitidepsin Readministration
-Listing 13.1.26: Bortezomib Administration
-Listing 13.1.27: Treatment Continuation
-Listing 13.1.28: Adverse events (including signs and symptoms)
-Listing 13.1.29: SAE Summary
-Listing 13.1.30: Concomitant Medication/Procedures/Other Test
-Listing 13.1.31: Blood products use
-Listing 13.1.32: End of treatment
-Listing 13.1.33: Unscheduled
-Listing 13.1.34: Follow up
-Listing 13.1.35: Radiotherapy (after End of Treatment)
-Listing 13.1.36: Medical Treatment (after End of Treatment)
-Listing 13.1.37: MM Serum Protein Measurements
-Listing 13.1.38: MM Urine Protein Measurements
-Listing 13.1.39: Disease Evaluation
-Listing 13.1.40: C-Reactive Protein

-Listing 13.1.41: Beta-2-microglobulin
-Listing 13.1.42: Tumor Evaluation (Plasmacytomas)
-Listing 13.1.43: Skeletal Evaluation
-Listing 13.1.44: Bone Marrow Evaluation
-Listing 13.1.45: Evaluation of Response
-Listing 13.1.46: Death Report Form
-Listing 13.1.47: Off Study

APPENDIX III

14 ICH Listings

In accordance with ICH E-3 guidelines, the patient listings specified as Section 16.2 will be prepared.

- 16.2.1 Discontinued Patients
- 16.2.2 Protocol Deviations
- 16.2.3 Patients Not Included in the Efficacy Analysis
- 16.2.4 Demographic Data
- 16.2.5 Compliance and/or Drug Concentration Data
- 16.2.6 Individual Efficacy Response Data
- 16.2.7 Adverse Event Listing (each patient)
- 16.2.8 Listing of Individual Laboratory Measurements by Patient