PM104-B-003-10

Phase II Multicenter, Open-label, Clinical and Pharmacokinetic Study of Zalypsis® (PM00104) in Patients with Unresectable Locally Advanced and/or Metastatic Ewing Family of Tumors (EFT) Progressing After at Least One Prior Line of Chemotherapy

Statistical Analysis Plan

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BPD	Blood Diastolic Pressure
BPS	Blood Systolic Pressure
BSA	Body Surface Area
CA	Calcium
CI(s)	Confidence Interval(s)
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CTC(s)	Circulating Tumor Cells
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DB	Data Base
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFT	Ewing Family of Tumors
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IND	Investigational New Drug
i.v.	Intravenous(ly)
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LNL	Lower Normal Limit
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MedRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression Disease
PFS	Progression-Free Survival
PGx	Pharmacogenomic

PK	Pharmacokinetic(s)
PNET	Primitive Neuroectodermal Tumor
PR	Partial Response
PS	Performance Status
Q4wk	Every Four Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Stable Disease
TCR	Tumor Control Rate
ULN	Upper Limit of Normal
v.	Version
WHO	World Health Organization
WPP	Worst Per Patient

1. Introduction

1.1. Study rationale

This Statistical Analysis Plan (SAP) explains in detail the statistical analyses that will be carried out for PharmaMar PM104-B-003-10 study. The analyses described in this SAP are based upon and supplement those described in the study protocol (dated 30-07-2010).

1.2. Information on study drug

PM00104 is a new synthetic alkaloid that has been selected for clinical development based on its *in vitro* activity against human solid and non-solid tumor cell lines, its *in vivo* activity in xenografted human tumors, as well as an acceptable non-clinical toxicology profile.

2. Objectives

The study protocol states the following:

2.1. Primary

- To determine the antitumor activity of Zalypsis® administered as a 1-hour intravenous (i.v) infusion on Day 1, 8 and 15 every four weeks (d1, d8 and d15; q4wk) to patients with advanced and/or metastatic Ewing family of tumors (EFT).

2.2. Secondary

- To determine time-to-event efficacy parameters.
- To characterize the safety profile and tolerability of Zalypsis® in patients with unresectable advanced and/or metastatic EFT.
- To characterize the pharmacokinetics (PK) of Zalypsis® when administered as a single-agent to patients with EFT.
- To determine the pharmacodynamic profile by measuring the effect of Zalypsis® on the number of Ewing's sarcoma circulating tumor cells (CTCs) at different times of treatment and its correlation with the clinical outcome.
- To determine the pharmacogenomic (PGx) profile. Hypothesis-generating exploratory PGx analyses will be conducted to correlate the molecular parameters found in the tumor and blood samples of the patients with the clinical results achieved with Zalypsis®.

3. Study design

Multicenter, open label, phase II clinical trial with single-agent PM00104 given as a 1-hour i.v. infusion on d1, d8 and d15, q4wk, to patients with advanced and/or metastatic EFT who failed at least to one line of standard chemotherapy.

The primary endpoint of the study is the overall response rate (ORR), defined as the percentage of patients with objective response (OR), either complete response (CR) or partial response (PR), as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

4. Study populations

4.1. Analysis populations

Patients with EFT progressing after at least one line of standard treatment with systemic chemotherapy are eligible for this trial. To be included in the study, patients have to fulfill all inclusion criteria and none of the exclusion criteria.

4.1.1. Efficacy population

To be evaluable for efficacy, eligible patients must have received at least four infusions of the six infusions corresponding to the first two cycles and have at least one disease measurement recorded not less than six weeks after treatment onset.

In addition, any eligible patient who receives at least two of the three infusions in one treatment cycle and develops disease progression or dies due to progressive disease (PD) prior to response evaluation will be considered evaluable for the main endpoint (ORR) and will be categorized as an "early progression".

Patients withdrawn due to toxicity without any tumor assessment after the start of study treatment will be considered as "treatment failures" and will not be replaced.

Patients withdrawn due to significant clinical deterioration of unknown reason, or due to hypersensitivity reactions or unrelated AEs, and patients who refuse to continue on study for any reason without any tumor assessment after the start of study treatment will be considered not evaluable for efficacy and will be replaced.

4.1.2. Safety population

All patients who have received at least one total or partial infusion of Zalypsis® will be included in the safety analysis.

5. Endpoints

5.1. Primary endpoints

- Overall response rate (ORR): is defined as the percentage of patients with confirmed OR, either CR or PR response according to the RECIST v1.1.

5.2. Secondary endpoints

- Duration of response (DOR): is defined as the time between the date when the response criteria (PR or CR, whichever is reached first) are fulfilled and the first date when disease progression, recurrence or death is objectively documented (taking the smallest measurements documented since the treatment started as reference for PD). DOR censoring rules are the same as for progression-free survival (PFS) and are described below.
- Progression-free survival (PFS): is defined as the time from the date of the first study drug administration to the date of documented progressive disease (PD) by RECIST v1.1 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. PFS at three and PFS at six months (PFS3 and PFS6) are defined as the Kaplan Meier estimates of PFS at these time points.

- Overall survival (OS): is defined as the time from the first day of study treatment administration to the date of death (or the last date when the patient is known to be alive). Survival will be followed every three months until death, or until the date of study termination, whichever occurs first. OS at 12 months (OS12) is defined as the Kaplan-Meier estimates of OS at this time point.
- Safety profile: adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, deaths and the reason for study discontinuations, dose delays, modifications or omissions will be analyzed. All AEs and SAEs will be classified according to the NCI-CTCAE, v4.0, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

5.3. Other endpoints

- Treatment exposure:
  - *Date of treatment start***:** Date of treatment administration in Cycle 1.
  - *Date of last dose*: Date of last treatment administration in the last cycle.
  - *End of treatment:* Day of the last study drug administration plus 30 days, or onset of subsequent therapy or death, whichever occurs first.
  - *Time on treatment*: Time from treatment start to the "end of treatment" date.
  - *A cycle*: Period of time (planned as 4 weeks plus the potential administration delays) between two dose infusions. *The duration of the last cycle* (for the purpose of exposure calculations) will be 4 weeks. Therefore, the *exposure duration* will be calculated as the time between the day of the first dose and the day of last dose + 4 weeks (28 days) (expressed in weeks).
  - *Body Surface Area (BSA):* The calculated surface of a human body (expressed in m^2). BSA will be calculated using the Dubois & Dubois formula:

$$BSA(m^2) = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$$

  - *Total cumulative dose*: The sum of all the study drug doses from the first cycle until last cycle, including the dose received in last cycle (expressed in mg/m²).
  - *Absolute dose intensity:* The actual cumulative dose divided by number of weeks of exposure (expressed in mg/m²/wk).
  - *Intended dose intensity*: The planned dose per cycle divided by the planned weeks by cycle (expressed in mg/m²/wk).
  - *Relative dose intensity:* The ratio of absolute dose intensity (x100) divided by the intended dose intensity (expressed in percentage).

- Pharmacokinetic (PK) and pharmacodinamic profile.
  - These analyses will be described in different documents not included in this SAP. For further details please refer to the study Protocol.

- Pharmacogenomic (PGx) profile.
  - The PGx analysis will be described in a different document not included in this SAP. For further details please refers to the study Protocol.

6. Sample size

6.1. Sample size determination

In this phase II trial, an optimum two-stage design to test the null hypothesis that the ORR is ≤ 3% versus the alternative that ORR ≥ 20% was selected. After testing the drug on 12 patients in the first stage, the trial will be terminated if there is not any responder. If the trial goes on to the second stage, a total of 29 patients will be studied, 12 from the first stage and 17 from the second stage. If the total number responding is less than or equal to 2 (two patients), the drug will be considered not interesting in the setting of patients treated with this disease and with this schedule.

This design has an expected sample size of 17.20 and a probability of early termination of 0.69 under the null hypothesis. If the drug is actually not effective, there is a 0.05 probability of concluding that it is (type I error). If the drug is actually effective, there is a 0.1 probability of concluding that it is not (type II error).

7. Statistical analysis

7.1. Treatment discontinuation and protocol deviations management

The study populations will be summarized and listed in Section 10 (Appendix I), including the number of patients in the following populations:

- Eligible patients.
- Included patients.
- All treated patients (safety population).
- Patients evaluable for the main endpoint (efficacy population).

Reasons for not belonging to any population will be detailed.

The accrual and study discontinuation details will be presented descriptively. The reasons for treatment discontinuation will be described by counts and percentages, overall and by number of cycles received. Reasons of treatment discontinuation other than disease progression will be detailed.

Reason for patient's study withdrawal will be also detailed. These may include:

- Study termination
- Patient refusal
- Investigator decision
- Lost to follow up
- Death
- Never treated
- Other reasons

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Protocol deviations will be summarized for all patients. A summary table with the number of patients with inclusion/exclusion deviations will be presented per criterion. These patients will be listed with the criteria that are not met. Deviations with no effects on the risk/benefit ratio of the clinical trial will be distinguished from those that might have an effect on this risk/benefit ratio.

A study of the protocol deviations deemed relevant according to the Data Management Plan and Oncology review will be made following the International Conference on Harmonisation (ICH) guidelines. The protocol deviations will be listed by type of deviation, including (but not restricted to) the following categories:

- Patients not satisfying inclusion / exclusion criteria.
- Patients developing withdrawal criteria but not withdrawn.
- Patients receiving incorrect dose or at an incorrect schedule.
- Patients receiving forbidden concomitant treatment.
- Patients receiving treatment at the same dose and schedule but not satisfying criteria for treatment continuation.

7.2. Demographic analysis

Demographics and baseline characteristics will be summarized for all recruited patients following the standard tables detailed in Section 11 (Appendix II).

Continuous variables will be summarized and presented with summary statistics, i.e., median and range, mean, standard deviation and categorical variables will be summarized in frequency tables.

In case of pre-treatment characteristics with multiple measurements per patient before the start of treatment (laboratory assessments, vital signs) the baseline measurement will be considered the last value prior to or on the first day of treatment.

Age, sex, baseline weight, height, BSA, Eastern Cooperative Oncology Group performance status (ECOG-PS), vital signs (heart rate, blood pressure and body temperature), left ventricular ejection fraction (LVEF), electrocardiogram (ECG), signs and symptoms and concomitant medication results will be summarized descriptively. Age is calculated based on the date of birth at the time date of registration date.

Age will be calculated based on the date of birth and the date of informed consent and rounded to integer numbers (by defect).

$$Age = \frac{(\text{date of informed consent}) - (\text{date of birth})}{365.25}$$

Tumor characteristics: histology diagnosis, primary site, time from diagnosis, stage, number of organs involved and sites of disease, time from last documentation of PD before start of treatment with Zalypsis® will be described.

A frequency tabulation of the number of patients with the different types of previous cancer surgery, radiotherapy and systemic anticancer therapy will be given.

A summary of prior relevant history and signs and symptoms will be presented per patient.

Laboratory values at baseline will be tabulated. Median values, ranges and NCI-CTCAE grades will be displayed by laboratory parameters.

7.3. Statistical methodology for efficacy

The main efficacy analysis will be performed in the efficacy population. A sensitivity analysis of efficacy results will be done in the population of all treated patients (safety population).

Binomial estimates with exact 95% confidence intervals (CIs) will be calculated for the analysis of the main endpoint (ORR). Time-to-event endpoints (DOR, PFS3, PFS6 rates and OS rate at 12 months) will be analyzed according to the Kaplan-Meier method.

If relevant, efficacy parameters versus baseline covariates will be analyzed and appropriate test will be used (i.e., the Fisher exact test for categorical variables, the log-rank test or Cox regression for time-to-event variables, etc.).

Graphical representations of tumor shrinkage will be represented by waterfall plots or spider plots if applicable.

Statistical tests, if and when they are carried out, will only have an exploratory purpose and have a threshold of $\alpha = 5\%$.

See Section 11 (Appendix II) for further details on the efficacy analysis and Section 13 (Appendix IV) for graphic templates.

7.4. Statistical methodology for safety

Descriptive statistics, tabulation and graphic representation will be used for the evaluation of safety for this phase II study, as described in Section 12 (Appendix III) and Section 13 (Appendix IV).

7.4.1. Exposure

Cumulative dose, dose intensity and relative dose intensity, cycle delay, and dose modifications or omissions will be described following standard tables detailed in Section 12.1 (Appendix III).

7.4.2. Cycle delays, skipped doses and dose modifications

Patients who receive only one infusion of Zalypsis® and have treatment discontinuation within the first cycle due to any reason different from drug related adverse event (eg: disease progression, patient's refusal), will not be considered for the calculations of the number of dose administration delays, doses skipped or dose reductions.

Dose delay is defined by a delay in the administration of the first infusion of one cycle (Day 1 infusion). Infusions not administered on Days 8 and/or 15 of the cycle are considered skipped doses and are analyzed separately.

The item "Dose delayed: No/Yes" in the case report form (CRF) will be used to calculate the delay. For doses considered as delayed by the investigator, the delay will be calculated as:

Administration delay (in days) will be equal to the date of start of the actual cycle minus the date of start of previous cycle minus 28 days (planed cycle duration, in days).

A second analysis taking into account the drug administration dates rather than the item "dose delay" completed by the investigator will be performed in order to know the calculated delay in days.

The first cycle is excluded from all calculation of cycle delay (and the denominator used for calculations will be equal to the number of cycles susceptible to be delayed).

The distribution of delays will be studied by means of counts and percentages (the denominator used for calculations will be equal to the number of patients/cycles susceptible of delay). The reasons for infusion delay will be detailed, specifying how many were due to treatment and how many were not. Within delays attributable to treatment, hematological and non-hematological reasons will be outlined, and the specific reasons will be detailed (administrative reasons will be analyzed separately and additional tables will be prepared after exclusion of those delays).

Skipped dose or dose omission is defined as every infusion not administered on Day 8 and/or 15 of the cycle. The distribution of skipped doses will be studied by means of counts and percentages (the denominator used for calculations will be equal to the number of patients/cycles susceptible to have an omission) and a detailed listing of patients with skipped

dose and reason will be showed. Also reasons for dose omission will be detailed, specifying how many were due to treatment and how many were not.

Dose reduction refers to any dose modification occurred after the first drug administration. The distribution of reductions will be studied by means of counts and percentages (the denominator used for calculations will be equal to the number of patients/cycles susceptible to be reduced). All dose reductions will be considered and described (per cycle and patient), specifying the magnitude and the reason for reduction (hematological toxicity, non-hematological toxicity or other causes not due to treatment).

7.4.3. Adverse events

Adverse events (AEs) will be graded according to NCI-CTCAE v4.0 and will be coded using the MeDRA, v11.0. The incidence and grade of AEs and laboratory abnormalities will be calculated considering the most severe grade per patient and cycle. The numeric form of the NCI-CTCAE grade (Grade 0, 1, 2, 3, 4, 5) will be used for all tables and listings. Grades displayed in tables and figures will be grouped in categories to simplify reading (occurrence of grade 5 of the NCI-CTCAE will be in tables indicated by Grade 4* and the asterisk (*) will have associated with a footnote where further detail information is provided). Totals will be provided in all tables.

As far as all the events and abnormalities are concerned, the NCI-CTCAE grade will be used wherever an NCI-CTCAE 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-CTCAE grade reported or, for toxicities which do not form the subject of NCI-CTCAE classification, according to the worst severity.

Descriptive statistics will be used to present the profiles of drug-related AEs, drug-related deaths, SAEs and drug-related treatment discontinuations and the observed grade 1-4 toxicities, per patient and per cycle. The incidence and grade of AEs and laboratory abnormalities will be calculated considering the most severe grade per patient and infusion and will be displayed in frequency tables using counts and percentages.

7.4.4. Deaths and serious adverse events

Database listings of deaths and serious adverse events will be provided, including at least date of onset and resolution (if applicable), severity, relationship to study drug, significant consequences and action taken. Deaths on treatment (within 30 days from last study drug administration) will also be included.

7.4.5. Laboratory evaluations

Hematology

Hematological abnormalities classified according to the NCI-CTCAE will be calculated in all cycles. The worst grade reached by each patient during treatment will be also calculated.
If serious abnormalities occur, special follow-up including calculation of nadir values and median time to recover to baseline values with 95% confidence intervals (CIs) and descriptive tables will be made to find out the pattern of thrombocytopenia and neutropenia within and between the different cycles.
If appropriate, these tables might be complemented with boxplots for the nadir of neutrophils and platelets count by cycle along the treatment. Furthermore, graphs of the inter-cycle time course of neutropenia and thrombocytopenia will be provided. Graphs comparing the time course during the first and second or further cycles will be created, if required.

Serum Biochemistry

The non-hematological laboratory abnormalities (i.e., NCI-CTCAE grades) of transaminases, creatinine, creatine phosphokinase (CPK), bilirubin, alkaline phosphatase (AP), etc., by patient

and cycle, will be calculated as explained for hematological disorders. The worst grade reported for each patient during treatment be recorded.
If appropriate, the time to onset and recovery from selected non-hematological abnormalities (i.e., hepatic enzymes) will be illustrated graphically and by means of descriptive statistics.

Shift from baseline

The shift of severity grades from baseline to the worst occurrence during treatment will be tabulated. The time to onset and recovery from neutrophils, platelets, and hepatic enzymes elevations will be illustrated by means of descriptive statistics.

7.4.6. Other safety evaluations

Physical examination evaluation (normal/abnormal) and vital signs at baseline and during treatment will be described by means of frequency counts and summary statistics.

Electrocardiogram (ECG) evaluation (normal/abnormal) will be summarized with frequency counts.

Continuous variables (LVEF and LVEF Normal Range) will be summarized and presented with summary statistics, i.e., mean, standard deviation, median and range.

Tabulation of baseline values and evolution during treatment will be presented for PS, weight, and LVEF, troponin I measurement.

7.4.7. Concomitant Medication

Concomitant therapies will be categorized per the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) class and coded term. The number of patients receiving each type of therapy during the treatment phase will be tabulated in two separate tables: a frequency tabulation of the different therapies that started pre-study, and a frequency tabulation of the different therapies that started during the study. Each table will be generated by system, indication and agent family, WHO-ATC levels 1, 2 and 4 and once by coded term. The accompanying listing will contain all concomitant therapies.

See Section 12.2-12.5 (Appendix III) for further details on the safety analysis.

7.5. Pharmacokinetic (PK), Pharmacodynamic profile and pharmacogenomic (PGx) evaluation

These analyses will be described in two different documents not included in this SAP.

8. Other statistical analysis considerations

8.1. Missing value management

In case of missing values in the determination of protocol deviations (for instance, time from last anticancer treatment to start of treatment with Zalypsis®) the most conservative approach will be taken for the evaluation.

The cycles with missing information regarding laboratory values or adverse events will be subtracted from the denominator of the tables.

8.1.1. Imputation in incomplete dates

Before registration

If the day of a date is unknown (i.e, UK/Jan/09) then the imputed day will be the 15th. If the month is also unknown (i.e, UK/UK/09) then the imputed date will be July 1st. This assumption will be valid if the imputed date is earlier than the informed consent's date. Otherwise the imputed date will be the first day of the informed consent's month date (i.e., 01 / informed consent’s month / year).

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 the 1st; if the month is also unknown, then the imputed date will be July 1st. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise the imputed date will be either last drug administration date plus the planed cycle duration (28 days), or the last day of the reported month, whichever occurs first.

8.2. Data analysis conventions

Percentages in the summary tables will be rounded to one decimal unless otherwise specified, and, therefore, may not always add up to exactly 100%.

Calcium can be falsely low if hypoalbuminemia is present. Serum album is <4.0 g/dl, hypocalcemia will be reported after the following correction is performed:

Calcium corrected (mMol/l) = Calcium (mMol/l) + 0.2 x (4 – Albumin(g/dl))

Calcium corrected (g/dl) = Calcium (g/dl) + 0.8 x (4 – Albumin(g/dl))

In case of albumin and calcium results are not performed in the same date then the nearest albumin result to the calcium will be taken and if a calcium result falls at an equal time between two albumin results, then the earlier albumin result will be used for the calculation.
If there is no any albumin results or the result exceeds more than 30 days from calcium result then no correction will be used.

8.3. Multivariate analyses

If appropriate, exploratory Cox regression for multivariate analysis of main covariate effects will be used for time-dependent efficacy parameters, and logistic regression for the evaluation of covariates associated with best overall response.

8.4. Fixed, random or mixed effects models

Not applicable.

8.5. Subgroup Analysis

Not applicable.

8.6. Interim Analysis

A futility analysis is planned when 12 patients evaluable for efficacy are recruited according to the Simon's design. Other non-scheduled analyses might be performed exclusively for enhancing patient's safety.

8.7. Independent review committee

Because of safety reasons, an independent cardiologist will undertake a review of all the ECGs and echocardiograms performed to the patients during the course of the study, in order to evaluate the cardiotoxicity risk of PM00104. For this purpose, an independent cardiologist´s report not included in this SAP will be presented as an Appendix of the CSR.

9. Statistical software

Oracle Clinical will be used for double data entry and clinical data management.

SAS v9.2 will be used for all the statistical analysis.

TABLES, LISTINGS AND FIGURE SHELLS

NOTE: Each particular table, listing and figure will have a comprehensive header and/or footnotes. If the number of items would not yield appropriate tabular or graphic representations, detailed listings will be shown instead.

10. Appendix I. Patient disposition and protocol deviations

10.1. General characteristics

10.1.1. Patients disposition

Table 10.1.1.1 Patients disposition by institution.

	Institution 1		Institution 2		….		Total	
	N	%	N	%	N	%	N	%
N-eligible								
N-included								
N-treated								
N-evaluable for safety								
N-evaluable for efficacy								

NOTE: See listings from 10.1.1.2 to 10.1.1.5

Table 10.1.1.2 Listing of patients not eligible.

Patient ID	Reason

Table 10.1.1.3 Listing of patients included but not treated.

Patient ID	Reason

Table 10.1.1.4 Listing of patients not evaluable for safety.

Patient ID	Reason

Table 10.1.1.5 Listing of patients not evaluable for efficacy.

Patient ID	Reason

10.1.2. Study dates

Table 10.1.2.1 Study dates.

Event	Date
Date first consent	
Date first dose of first patient	
Date last consent	
Date first dose of last patient	
Date last dose	
Last follow up date	

10.1.3. Reasons for treatment discontinuation

Table 10.1.3.1 Reasons for treatment discontinuation.

	Total	
	N	%
Progressive disease		
Toxicity (Drug related AE)*		
Death**		
Patient refusal		
Investigator decision		
Other***		

(*) See tables 10.1.3.6; (**) Table 10.1.3.7; (***) Table 10.1.3.5

Table 10.1.3.2 Reasons for treatment discontinuation by number of cycles received.

	Cycle 1		Cycle 2		….		Total	
	N	%	N	%	N	%	N	%
Progressive disease								
Patient refusal								
….								

Table 10.1.3.3 Time on treatment (months).

	N	Median*	Min*	Max*

(*) Time from first infusion of the study drug to the day of the last study drug administration plus 30 days, or onset of subsequent therapy or death, whichever occurs first.

Table 10.1.3.4 Listings of patients and time on treatment.

Patient ID.	Day of first infusion	Day of last dose administered	Number of cycles received	Time on treatment (months)

Table 10.1.3.5 Listings of treatment discontinuation other than progressive disease.

Patient ID.	Cycle	Reason	Specify

Table 10.1.3.6 Listing of treatment discontinuation due to adverse events (AEs).

Patient ID.	PT MedDRA Code	Grade	…	Relationship	Significant consequence

Table 10.1.3.7 Listing of treatment discontinuation due to death.

Patient ID.	Cycle	Cause of death	Last study drug administration date	Death date	Time from last Study drug administration to death (days)

10.1.4. Reasons for patient's study discontinuation

Table 10.1.4.1 Reason for study discontinuation.

	Total	
	N	%
Study termination		
Investigator decision		
Lost to follow up		
Death		
Never treated		
Patient refusal		
Other*		

(*)See table 10.1.4.2

Table 10.1.4.2 Listing of other reasons study discontinuation.

Patient ID	Reason	Specify

10.1.5. Protocol deviations

Table 10.1.5.1 Eligibility: Patients who entered the study even though they did not satisfy the entry criteria.

Patient ID	Deviation type*	Deviation description**

(*) Including but not restricted to: Inclusion/Exclusion deviations, study procedures not performed, patients developing withdrawal criteria who were not withdrawn, patients who received incorrect dose or schedule, patients who received an excluded concomitant medication, and patients who do not satisfy criteria for treatment continuation.
(**) Deviations with no effects on the risk/benefit ratio of the clinical trial will be distinguished from those that might have an effect on this risk/benefit ratio.

11. Appendix II. Demographic analysis and efficacy evaluation

11.1. Baseline characteristics

11.1.1. Patients characteristics at baseline

Table 11.1.1.1 Baseline characteristics: Summary statistics.

	Total (N=XX)	
	N	**%**
Gender		
Male		
Female		
Age grouped:		
16 – XX years		
XX – YY years		
≥ YY years		

Table 11.1.1.2 Summary statistics: baseline characteristics.

	N	**Median**	**Min**	**Max**
Age (years)				

11.1.2. Histology and time from diagnosis

Table 11.1.2.1 Tumor histology.

	Total (N=XX)	
	N	**%**
Tumor diagnosis:		
Ewing's bone sarcoma		
Extraosseous Ewing:		
PNET		
Askin		
Other*		
Primary tumor site:		
Upper extremity		
Lower extremity		
Face and neck		
Trunk/abdominal wall		
Other**		
Current Disease		
Unresectable locally advanced disease		
Metastatic		
Number of sites involved (target-non target):		
1		
2		
3		
> 3		
Summary statistics of number of sites involved (target-non target):		
N		
Median		
Minimum		

Maximum

Programming Notes: Percentage is based on total patient included.
(*) and (**) See listing 11.1.2.3

Table 11.1.2.2 Sites for target and non-target lesions.

Sites	Total	
	N	%
Bone		
Lung		
….		

Table 11.1.2.3 Listing of patient histology.

Patient ID.	Tumor diagnosis	Primary tumor site	TNM at Diagnosis	Stage at Diagnosis	Other, Specify	Current stage

Table 11.1.2.4 Listing of target and non target lesions.

Patient ID.	Target/non-target	Site/Subsite	Method

Table 11.1.2.5 Summary statistics of cancer diagnosis characteristics: Time from diagnosis and time from last progression disease (PD) to first infusion of study drug.

	N	Median	Min	Max
Time from first diagnosis to first infusion (months)				
Time from last progression to first infusion (months)				

11.1.3. Prior anticancer therapy

Table 11.1.3.1 Surgery (palliative + curative).

	N	%
Yes		
No		

Table 11.1.3.2 Radiotherapy.

	N	%
Yes		
No		

Table 11.1.3.3 Patients with prior surgery.

Patient ID.	Intention	Site and Procedures	Surgery Date	Residual disease

Table 11.1.3.4 Summary statistics of prior systemic anticancer therapy.

	N	Median	Min	Max
Number of lines				
Number of agents				

Table 11.1.3.5 Number of lines and agents of systemic anticancer therapy.

	Total (N=XX)	
	N	%
Number of lines		
1		
2		
3		
> 3		
Number of agents		
1		
2		
3		
> 3		

Table 11.1.3.6 Summary of lines and agents of systemic anticancer therapy.

Antineoplastic and immunomodulating agents (ATC-clas. Levels 1-4)	N	%
Antineoplastic Agents (L01)		
…..		
…..		

11.1.4. Prior history

Table 11.1.4.1 Prior history.

Patient ID.	Description	Onset date	Resolved date

11.1.5. Physical examination, vital signs, electrocardiogram and other tests

Table 11.1.5.1 Physical examination at baseline.

	Total (N=XX)	
	N	**%**
Physical Examination:		
Normal		
Abnormal		
ECOG-PS:		
0		
1		
2		
…		
ECG:		
Normal		
Abnormal		
LVEF		
Normal		
Abnormal		

(*) NA stands for "Not applicable" and specify reasons will be giving in a supportive listing.

Table 11.1.5.2 Listings of patients with positive pregnancy test.

Patient ID.	Sample date

Table 11.1.5.3 Listings of patients with no adequate contraception.

Patient ID.	Sample date

Table 11.1.5.4 Listing of ECOG performance status.

Patient ID.	ECOG	Specify*

(*) If available details will be extracted from signs and symptoms.

Table 11.1.5.5 Listing of patients with abnormal ECG at baseline.

Patient ID.	ECG result	Specify*

(*) If available details will be extracted from signs and symptoms.

Table 11.1.5.6 Listing of patients with LVEF lower than the normal range.

Patient ID.	LVEF (%)	Result	Method	Institutional normal range

Table 11.1.5.7 Summary statistics: Physical examination and vital signs.

Parameter	N	Median	Min	Max
Weight (Kg)				
Height (cm)				
Heart rate (beats/min)				
BPS (mmHg)				
BPD (mmHg)				
Temperature (ºC)				

11.1.6. Hematological values at baseline

Table 11.1.6.1 Hematological abnormalities at baseline.

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
Anemia										
Lymphopenia										
Neutropenia										
Thrombocytopenia										

(*) All hematological abnormalities susceptible to be graded in NCI-CTCAE v4.0

Table 11.1.6.2 Hematology at baseline. Last value before treatment.

Parameter*	N	Median	Min	Max
Hemoglobin				
Lymphocytes				
Neutrophils				
Platelets				

(*) Units for Leukocytes, Lymphocytes, Neutrophils and Platelets are in 10^9/l. Hemoglobin in g/dl

Table 11.1.6.3 Hematology at baseline: Patients with hematological parameters missing.

Patient ID.	Parameter

Table 11.1.6.4 Hematology at baseline. Abnormalities grade ≥ 2.

Patient ID.	Parameter	Value	Grade

11.1.7. Biochemical values at baseline

Table 11.1.7.1 Biochemical abnormalities at baseline.

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
AST										
ALT										
*…..										

(*) Total bilirubin, AP, CPK and Creatinine. All biochemical abnormalities susceptible to be graded in NCI-CTCAE v4.0

Table 11.1.7.2 Biochemistry at baseline. Last value before treatment.

Parameter*	N	Median	Min	Max
AST				
ALT				
Total Bilirubin				
….				

(*) Units for AST, ALT, AP, CPK are IU/l. Units for Total Bilirubin and Creatinine are mg/dl.

Table 11.1.7.3 Biochemistry at baseline. Patients with missing biochemical parameters.

Patient ID.	Parameter

Table 11.1.7.4 Biochemistry at baseline. Abnormalities grade ≥ 2.

Patient ID.	Parameter	Value	Grade

11.1.8. Other metabolic values at baseline

Table 11.1.8.1 Other metabolic abnormalities at baseline (hyper-hypo).

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
Hyperglycemia										
*…..										

(*) Hyper and hypo abnormalities and all metabolic parameters susceptible to be graded as per NCI-CTCAE v4.0; i.e, Glucose, Sodium, Potassium, Calcium, Magnesium and Albumin.

Table 11.1.8.2 Other metabolic abnormalities at baseline. Last value before treatment.

Parameter*	N	Median	Min	Max
Glucose				

(*) Units for Glucose, Sodium, Clorhide, Potassium, Calcium, Magnesium are in mmol/l; Albumin and Total proteins in g/dl and LDH in IU/l; Creatinine Clearance (CrCl) in ml/min.

Table 11.1.8.3 Patients with missing metabolic parameters.

Patient ID.	Parameter

Table 11.1.8.4 Other metabolic at baseline. Abnormalities grade ≥ 2.

Patient ID.	Parameter	Value	Grade

11.1.9. Signs and symptoms at baseline

Table 11.1.9.1 Summary statistics: Signs and symptoms.

SOC/MedDRA	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=XX)

Preferred term		N	%	N	%	N	%	N	%	N	%
General Disorders	Abdomina Distension										
	…..										
… Pain											

Table 11.1.9.2 Median of signs and symptoms

	N	Median	Min	Max

Table 11.1.9.3 Listing of baseline characteristics: Signs and symptoms (Grade ≥ 2).

Patient ID	SOC	Sign/symptom (PT)	Verbatim term	Grade	Onset date	Relationship	Treated

11.1.10.Concomitant therapy

Table 11.1.10.1 Agents of concomitant therapy started at baseline.

Concomitant medication (ATC1/ATC2/ATC4)				
System(ATC1)	Indication(ATC2)	Agents(ATC4)	N	%
Alimentary tract and metabolism	Stomatological preparations	Antiinfectives for local oral treat. Other agents for …. ……		
	Antiacids			
…….	……			

Table 11.1.10.2 Concomitant medication characteristics started at baseline.

	Total (N=XX)	
	N	%
No of systems (ATC1)		
0		
1		
2		
3		
> 3		
No of indications (ATC2)		
0		
1		
2		
3		
> 3		
No of agents (ATC4)		
0		
1		
2		

3	
> 3	

Table 11.1.10.3 Concomitant therapy started at baseline. Summary of number, indications and systems involved.

Concomitant medication (ATC1/ATC2/ATC4)	N	Median	Min	Max
Number of systems involved (ATC1)				
Number of indications involved (ATC2)				
Number of agents involved (ATC4)				

11.2. Efficacy

11.2.1. Response

Table 11.2.1 1 Patients evaluable for efficacy.

Evaluable	Total (N=XX)	
	N	%
Yes		
No		
Total		

Table 11.2.1.2 Listing of patients excluded from the efficacy analysis.

Patient ID	Reason

Table 11.2.1.3 Overall response rate.

Response	N	%
First stage		
CR+PR		
Total		
CR+PR		

Table 11.2.1.4 Best response in all evaluable patients.

Response	N	%
Complete Response (CR)		
Partial Response (PR)		
Stable Disease (SD)		
Progression Disease (PD)*		
Treatment Failure		

Programming Notes: Percentage is based on the total of patient evaluable for efficacy.
(*) Patients with early PD will also be included in this category (provided that they receive at least two infusions of Zalypsis®)

Table 11.2.1.5 Best response in all treated patients.

Response	**N**	**%**
Complete Response (CR)		
Partial Response (PR)		
Stable Disease (SD)		
Progression Disease (PD)*		
Treatment failure		
Not Evaluable (NE)		

Programming Notes: Percentage is based on total patient of patients treated
(*) Patients with early PD will also be included in this category (provided that they receive at least two infusions of Zalypsis®)

Table 11.2.1.6 Characteristics of responders

Patient characteristics*	**Outcome prior treatment****	**PM00104 treatment*****

(*)Patient ID, Sex/Age/PS and Histology. (**)No. prior CT lines, last prior treatment, cycles received and best response. *** TTP, Cycles with PM104, PFS, OS.

11.2.2. Time-to-event variables

Table 11.2.2.1 Duration of response.

Summary*
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median XX 95% CI (XX.X-X.X)

(*) Responder patients by RECIST v1.1, i.e, CR and PR.

Table 11.2.2.2 Progression-free survival (Kaplan-Meier estimates in all evaluable patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median XX 95% CI (X.X-X.X)
PFS rate at 3 months XX.X% 95% CI (XX.X%-XX.X%)
PFS rate at 6 months XX.X% 95% CI (XX.X%-XX.X%)

Table 11.2.2.3 Overall survival. (Kaplan-Meier estimates in all evaluable patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (XX.X-X.X)
OS rate at 12 months XX.X% 95% CI (XX.X%-XX.X%)

Table 11.2.2.4 Progression-free survival (Kaplan-Meier estimates in all treated patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median XX 95% CI (X.X-X.X)
PFS rate at 3 months XX.X% 95% CI (XX.X%-XX.X%)
PFS rate at 6 months XX.X% 95% CI (XX.X%-XX.X%)

Table 11.2.2.5 Overall survival. (Kaplan-Meier estimates in all treated patients).

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (XX.X-X.X)
OS rate at 12 months XX.X% 95% CI (XX.X%-XX.X%)

Table 11.2.2.6 Follow-up period.

Parameter	Median	95% CI Lower bound	95% CI Upper bound
PFS			
OS			

12. Appendix III. Safety evaluation

12.1. Extent of exposure

12.1.1. Treatment administration

Table 12.1.1.1 Cycles administered.

Cycles per patient: n (%)	N	%
1		
2		
3		
…		

Table 12.1.1.2 Summary of cycles administered.

	N	Median	Min	Max

Table 12.1.1.3 Dose intensity.

	N	Median	Min	Max
Cumulative dose (mg/m²)				
Dose intensity (mg/m² wk)				
Relative dose intensity (%)				

12.1.2. Dose administration delays

Note: Dose delays refer to delays in the administration of the first infusion of one cycle (Day 1 infusion).

Table 12.1.2.1 Dose delay

	N	%
Number of patients treated		
Number of patients susceptible of delay*		
Number of cycles administered		
Number of cycles susceptible of delay*		
Patients** with		
No delays		
1 cycle delayed		
2 cycles delayed		
≥ 3 cycles delayed		
Number of cycles with dose delay***		

Programming Notes: Percentage is based on number of cycle susceptible to be delayed.
(*) Patients who receive only one cycle of Zalypsis®.
(**) Denominator: Number of patients susceptible of delay = (Total number of patients* – Number of patients with first cycle only)
(***) Denominator: Number of cycles susceptible of delay = (Number of cycles administrated – Total number of first cycles)

Table 12.1.2.2 Dose delay according to their relation to study drug.

	Treatment related***		Non – Treatment related	
	N	%	N	%
Patients* with				
No delays				
1 cycle delayed				
2 cycles delayed				
≥ 3 cycles delayed				
Number of cycles with dosing delay *				

Programming Notes:
(*) Patients who receive only one infusion of Zalypsis® and have treatment discontinuation within the first cycle due to any cause except for drug related AE are not susceptible of delay.
(**) Denominator = Number of cycles susceptible to be delayed.
(***) Hematological reason / Non-hematological reason.

Table 12.1.2.3 Length of dose delay.

	Treatment related**		Non – Treatment related		Total	
	N	%	N	%	N	%
Length of delay*						
No delay						
≤ 7 days						
8 – 14 days						
> 14 days						

Programming Notes:
(*) Denominator = Number of cycles susceptible to be delayed.
(**) Hematological reason / Non-hematological reason.

Table 12.1.2.4 Dose delay and reason by cycle.

	Cycle 2		Cycle 3		…		Total	
	N	%	N	%	N	%	N	%
Number of delays								
No delay								
Treatment related*								
Hematological reason								
Non-hematological reasor								
Non-treatment related*								

Programming Notes: (*) Denominator = Number of cycles susceptible to be delayed.

Table 12.1.2.5 Listing of patient with dose delay.

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

Table 12.1.2.6 Listing of patients with dose interruption and/or re-administration

Patient ID.	Cycle	Reason	Date	Intended dose	Total dose	Total volume

12.1.3. Skipped doses

Note: Infusions not administered on Days 8 and/or 15 of the cycle are considered skipped doses.

Table 12.1.3.1 Skipped doses.

	N	%
Number of patients treated with at least 2 infusions		
Number of patients susceptible to have a omission		
Number of patients with any skipped dose*		
Number of patients with any skipped dose (drug related)		
Number of cycles administered		
Number of cycles with at least one skipped dose (drug related)		
Day 8		
Day 15		
Day 8 +15		

Number of cycles with at least one skipped dose	Treatment related**		Non–treatment related	
	N	% (of all cycles)	N	% (of all cycles)

Day 8
Day 15
Day 8 +15

(*) Patients who receive only one infusion of Zalypsis® and have treatment discontinuation within the first cycle due to any cause except for drug related AE are not susceptible of dose omission
(**) Hematological reason / Non-hematological reason.

Table 12.1.3.2 Listing of patients with skipped doses.

Patient ID.	Cycle/infusion (skipped dose)	Reason (drug related/other)	Comments

12.1.4. Dose reduction

Note: All dose reductions will be considered and described, specifying the reason for reduction (hematological toxicity, non-hematological toxicity or other causes not related to study drug).

Table 12.1.4.1 Dose reduction.

	N	%
Number of patients treated		
Number of patients susceptible of reduction*		
Number of cycles administered		
Number of cycles susceptible of reduction*		
Patients ** with		
No reductions		
1 cycle reduction		
2 cycle reductions		
≥ 3 cycle reductions		
Number of cycles with dose reduction ***		

Programming Notes: Percentage is based on number of cycle susceptible to be reduced.
(*) Patients who receive only one infusion of Zalypsis® and have treatment discontinuation within the first cycle due to any cause except for drug related AE are not susceptible of delay.
(**) Denominator = Number of patients susceptible of reduction = (Total number of patients – Number of patients with first cycle only)
(***) Denominator = Number of cycles susceptible of reduction = (Number of cycles administered – Total number of first cycles)

Table 12.1.4.2 Dose reduction according to their relation to study drug.

	Treatment related**		Non – Treatment related	
	N	%	N	%
Patients* with				
No dose reductions				
1 dose reduction				
2 dose reductions				
≥ 3 dose reductions				

Number of cycles with dose reduction*

Programming Notes: (*) Denominator = Number of patients/cycles susceptible to have had a dose reduced. (**) Hematological reason/Non-hematological reason.

Table 12.1.4.3 Dose reduction and reason by cycle.

	Cycle 2		Cycle 3		…		Total	
	N	%	N	%	N	%	N	%
Number of patients								
Number of reductions								
No reductions								
Treatment-related*								
Hematological reason								
Non-hematological reasc								
Non-Treatment related*								

Programming Notes. (*) Denominator = Number of patients susceptible to have had a dose reduced (who have received more than one cycle).

Table 12.1.4.4 Patients with dose reduction.

Patient ID	Reason for dose reduction	Dose reduction Spec	Dose in Reduction cycle	Dose in Previous cycle	Dose reduction Calculated (%)

Table 12.1.4.5 Patients with dose delay and reduction.

Patient ID.	Cycle	Reason	Comments	Dose delay (days)	(%) Reduction

12.2. Safety

12.2.1. Adverse events

Table 12.2.1.1 Summary of adverse events.

Number of patients* with	N	%
Any AE		
Any drug-related* AE		
Any AE grade ≥ 3		
Any drug-related AE grade ≥ 3		
Any SAE		
Any drug-related SAE		
Deaths associated with AEs		
Deaths associated with drug-related AEs		
Discontinuations associated with AEs		
Discontinuations associated with drug-related AEs		
Dose delays associated with AEs		
Dose delays associated with drug-related AEs		
Dose skipped associated with AEs		

Dose skipped associated with drug-related AEs
Dose reduction associated with AEs
Dose reduction associated with drug-related AEs

(*) Safety Population ; (**) Drug related and unknown

Table 12.2.1.2 Summary of hematological laboratory abnormalities.

Number of patients* with**	**N**	**%**
Any hematological abnormality		
Any hematological abnormality grade ≥ 3		

(*) Safety Population.(**) Includes only Hemoglobin, absolute neutrophil count (ANC) and Platelets.

Table 12.2.1.3 Summary of non-hematological laboratory abnormalities.

Number of patients* with**	**N**	**%**
Any non-hematological abnormality		
Any hematological abnormality grade ≥ 3		

(*) Safety Population. (**) Includes only ALT, AST, AP, Total Bilirubin, CPK, Creatinine.

Table 12.2.1.4 Drug-related adverse events. Worst case per patient

Table 12.2.1.5 Drug-related adverse events occurring in > 10% Worst case per patient.

Table 12.2.1.6 All adverse events regardless relationship. Worst case per patient.

Table 12.2.1.7 All adverse events regardless relationship occurring in > 10% Worst case per patient.

Table 12.2.1.8 Drug-related adverse events. Worst case per cycle.

Table 12.2.1.9 Drug-related adverse events occurring in > 10% Worst case per cycle.

Table 12.2.1.10 All adverse events regardless relationship. Worst case per cycle.

Table 12.2.1.11 All adverse events regardless relationship occurring in > 10% Worst case per cycle.

Table 12.2.1.12 Listing of AEs leading to death.

Table 12.2.1.13 Listing of AEs treatment related leading to death.

Table 12.2.1.14 Listing of AEs leading to dose delay.

Table 12.2.1.15 Listing of AEs leading to dose reduction.

Table 12.2.1.16 Listing of AEs leading to dose delay and reduction.

Tables from 12.2.1.4 to 12.2.1.11 will have the following format and grades could be grouped into categories if required.

System Organ Class/ Preferred Term	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total (G1-G4)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
System Organ Class 1 (Total)										
Preferred Term 1										
System Organ Class 2 (Total)										

Preferred Term 1

……..

Percentages are based on the safety population. Table shows number of distinct patients with events.

Tables from 12.2.1.12 to 12.2.1.16 have the following format*:

Patient ID.	Verbatim name	MedDRA Preferred term	Cycle	Grade	…….	Onset date	End Date	.....

(*) Delays and reductions will be checked with information in drug administration.

12.2.2. Grade 3-4 adverse events

Table 12.2.2.1 Listing of patients with grade 3-4 AEs (treatment-related).

Patient ID.	Cycle	MedDRA preferred term	Verbatim name	Grade	Relationship	Onset date	….

(*)End date, Action taken and serious criteria

Table 12.2.2.2 Listing of patients with grade 3-4 AEs (treatment-related).

Patient ID.	Cycle	MedDRA preferred term	Verbatim name	Grade	Relationship	Onset date	….

(*)End date, Action taken and serious criteria

12.2.3. Deaths and serious adverse events (SAEs)

All serious adverse events will be listed only for the purpose of reconciliation with the database of the Pharmacovigilance department. The listings provided by the Pharmacovigilance department will be used for the clinical study report.

Table 12.2.3.1 Listing of SAEs.

Patient ID.	Cycle	MedDRA preferred term	Verbatim name	Grade	Relationship	Onset date	End date

(*) Also Action taken and serious criteria

Table 12.2.3.2 Listing of all deaths.

Patient ID.	Cycle	MedDRA preferred term	Verbatim name	Grade	Relationship	Onset date	End date

(*)Taken from death report form.(**)Also 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 and Time from last dose defined as death date minus last infusion date.

12.3. Laboratory evaluation

12.3.1. Hematological abnormalities

Table 12.3.1.1 Hematological abnormalities during treatment, worst grade per patient.

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
Anemia										
Lymphopenia										
Neutropenia										
Thrombocytopenia										

Programming Notes: Percentages are based on the safety population. (*) All hematological abnormalities susceptible to be graded in NCI-CTCAE v4.0.

Table 12.3.1.2 Hematological abnormalities during treatment, worst grade per cycle.

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
Anemia										
Lymphopenia										
Neutropenia										
Thrombocytopenia										

Programming Notes: Percentages are based on the safety population.
(*) All hematological abnormalities susceptible to be graded in NCI-CTCAE v4.0.

Table 12.3.1.3 Patients with any hematological abnormalities grade 3-4.

Patient ID	Cycle	Event/ Parameter	Value at BL*	Grade at BL	Onset day	Onset value	Onset value	…**	Days with Grade 3-4

(*) Units for Leukocytes, Lymphocytes, Neutrophils and Platelets are in 10^9/l units in % and Hemoglobin in g/dl. (**) Also Nadir day, nadir value, recovery date, recovery value, recovery grade.

Table 12.3.1.4 Listing of patients and cycles with hematological evaluations missing.

Patient ID	Cycle	Parameter

Table 12.3.1.5 Time course and recovery from hematological toxicities.

	All cycles		
	N	**Median**	**Range**
Neutrophils			
Day of nadir neutrophils count			
Nadir of neutrophils count (/mm^3)			
Day of neutropenia G3-4 onset			
Day of recovery to grade ≤2*			
Number of days with grade 3-4 neutropenia			
Platelets			
Day of nadir platelets count			
Nadir of platelets count (/mm^3)			
Day of thrombocytopenia G3-4 onset			
Day of recovery to grade ≤2*			
Number of days with grade 3-4 thrombocytopenia			

Programming notes: (*) Denominator = No of cycles with Grade 3-4. Also recovery to grade 1 or an specific value if required.

Table 12.3.1.6 Baseline grade and evolution of hematological toxicities.

	Worst grade per patient during treatment									
Baseline	**Grade 0**		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Anemia										
Grade 0										
Grade 1										
Grade 2										
Grade 3										
Grade 4										
Neutropenia										
Grade 0										
Grade 1										
Grade 2										
Grade 3										
Grade 4										
…….										

12.3.2. Biochemical abnormalities

Table 12.3.2.1 Biochemical abnormalities during treatment, worst grade per patient.

Parameter*	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total (G1-G4)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
AST										
ALT										
*…..										

Programming Notes: Percentages are based on the safety population. (*) All biochemical abnormalities susceptible to be graded by NCI-CTCAE v4.0.

Table 12.3.2.2 Biochemical abnormalities during treatment, worst grade per cycle.

Parameter*	Grade 1		Grade 2		Grade 3		Grade 4		Total (G1-G4)	
	N	%	N	%	N	%	N	%	N	%
AST										
ALT										
*…..										

Programming Notes: Percentages are based on the safety population. (*) All biochemical abnormalities susceptible to be graded by NCI-CTCAE v4.0.

Table 12.3.2.3 Supportive listing: Patients with any biochemical abnormalities grade 3-4.

Patient ID	Cycle	Event/ Parameter	Value at BL	Grade at BL	Onset day	Onset value	…..*	Days with Grade 3-4

(*) Nadir day, nadir value, recovery date, recovery value and recovery grade to grade ≤ 2.

Table 12.3.2.4 Listing of patients and cycles with biochemical evaluations missing.

Patient ID	Cycle	Lab test

Table 12.3.2.5 Time course and recovery from biochemical toxicities.

	All cycles		
	N	Median	Range
ALT			
Day of peak ALT count			
Peak of ALT count (/mm^3)			
Day of ALT G3-4 onset			
Day of recovery to grade ≤2			
Number of days with grade 3-4 ALT increase			
AST			
Day of peak AST count			
Peak of AST count (/mm^3)			
Day of AST G3-4 onset			
Day of recovery to grade ≤2*			
Number of days with grade 3-4 AST increase			

Programming notes: (*) Denominator= Number of cycles with Grade 3-4. Also recovery to grade 1 if required.

Table 12.3.2.6 Baseline grade and evolution of biochemical toxicities.

	Worst grade per patient during treatment									
Baseline	**Grade 0**		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
AST										
Grade 0										
Grade 1										
Grade 2										
Grade 3										
Grade 4										
ALT										
Grade 0										
Grade 1										
Grade 2										
Grade 3										
Grade 4										
…….										

12.3.3. Other metabolic abnormalities

Table 12.3.3.1 Metabolic abnormalities during treatment, worst grade per patient

Parameter*	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total (G1-G4)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia										
….										

(*) All metabolic parameters susceptible to be graded as per NCI-CTCAE v4.0

Table 12.3.3.2 Metabolic abnormalities during treatment, worst grade per cycle.

Parameter*	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total (G1-G4)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia										
….										

(*) All metabolic parameters susceptible to be graded as per NCI-CTCAE v4.0

Table 12.3.3.3 Metabolic abnormalities grade per cycle.

Parameter*	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total (G1-G4)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hyperglycemia										
….										

(*) All metabolic parameters susceptible to be graded as per NCI-CTCAE v4.0

Table 12.3.3.4 Listing of patients and cycles with metabolic evaluations missing.

Patient ID.	**Cycle**	**Lab. test**

12.4. Vital Signs

Table 12.4.1 Vital signs.

Vital Signs	Baseline	Cycle 1	Cycle 2	…	Cycle (X)
PS					
BPS (mmHg)					
BPD (mmHg)					
Weigth (Kg)					

12.5. Prophylactic and concomitant medication during treatment

Table 12.5.1 Patients who received prophylactic medication.

No patients treated	No patients with Adequate prophylaxis	%	N Cycles administered	No Cycles with adequate prophylaxis	%

Table 12.5.2 Prophylactic therapy by patient.

Patient ID	Cycles	Dexamethasone Y/N	Dose	Ondansetron Y/N	Dose	Other	Specify
	Cycle 1 Cycle 2 Cycle n						

Table 12.5.3 Agents of concomitant therapy started during treatment.

Concomitant medication (ATC1/ATC2/ATC4)				
System(ATC1)	Indication(ATC2)	Agents(ATC4)	N	%
Alimentary tract and metabolism	Stomatological preparations	Antiinfectives for local oral treat. Other agents for …. ……		
	Antiacids			
…….	…….			

Table 12.5.4 Concomitant medication characteristics during treatment.

	Total (N=XX)	
	N	%
Number of Systems (ATC1)		
1		
2		
3		
> 3		
Number of indications (ATC2)		
1		
2		
3		

> 3
Number of agents (ATC4)
1
2
3
> 3

Programming Notes: Percentage is based on total patient included.

Table 12.5.5 Summary of concomitant medication during treatment.

Concomitant medication (ATC1/ATC2/ATC4)	**N**	**Median**	**Min**	**Max**
Number of systems involved (ATC1)				
Number of indications involved (ATC2)				
Number of agents involved (ATC4)				

12.6. Cardiac safety

Table 12.6.1 Listing of patients with Cardiac AEs and characteristics.

Patient ID.	**Cycle***	**MedDRA PT**	**Grade ****	**Relationship**	**….*****

*Cycle in witch the AE occurred. **According to NCI-CTCAE v.4.0 *** Also Seriousness Criteria, Action taken…

Table 12.6.2 Listing of ECG evolution per patient.

Patient ID	**Baseline**	**Cycle 1**	**Cycle 2**	…..	**Cycle (X)**

Table 12.6.3 Listing of patients with abnormal ECG.

Patient ID	**Result at baseline**	**Cycle**	**Specify***

(*) If applicable information obtained from AE.

Table 12.6.4 Median change in LVEF (%).

	N	**Median**	**Min**	**Max**

Table 12.6.5 Listing of LVEF/ECG evolution per patient.

Patient ID.	**Value at baseline**	**Cycle 1***	**Cycle 2***	…..	**Cycle (X)***

* ECG for day 1, day 8 and day 15.

Table 12.6.6 LVEF characteristics per patient.

Patient ID.	Value at baseline	Minimum value	Cycle (minimum value)

Table 12.6.7 Median change in Troponin I.

	N	Median	Min	Max
Baseline to nadir value (%)				
Baseline to last value (%)				

(*) Also tables in (x ULN) values if applicable.

Table 12.6.8 Listing of Troponin I evolution.

Patient ID.	Value* at Baseline (ng/ml)	Cycle 1	Cycle 2	…..	Cycle (X)

(*) Also tables in (x ULN) values if applicable

Table 12.6.9 Troponin I characteristics per patient.

Patient ID.	Value* at baseline (ng/ml)	Maximum value	Cycle (maximum value)

(*) Also tables in (x ULN) values if applicable

12.7. Other tests and procedures

Table 12.7.1.1 Other tests and procedures.

Patient ID.	Cycle	Test Date	Test name	Result(Normal/Abnormal)	Findings

13. Appendix IV. Figures

NOTE: Figures here showed are examples and may vary in the format and will be showed for "all evaluable patients" and "all treated patients" when applicable.

Figure 13.1 Evolution of laboratory abnormalities (ANC, Platelets, AST, ALT,……)

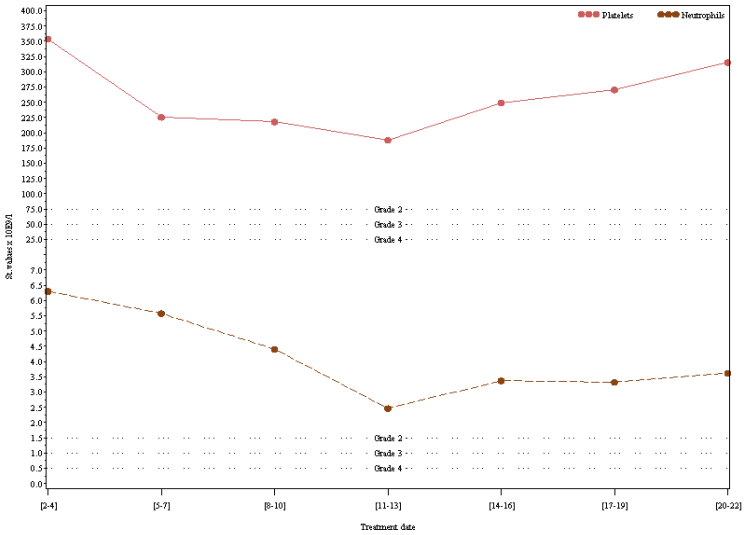


Figure 13.2 Overall survival.

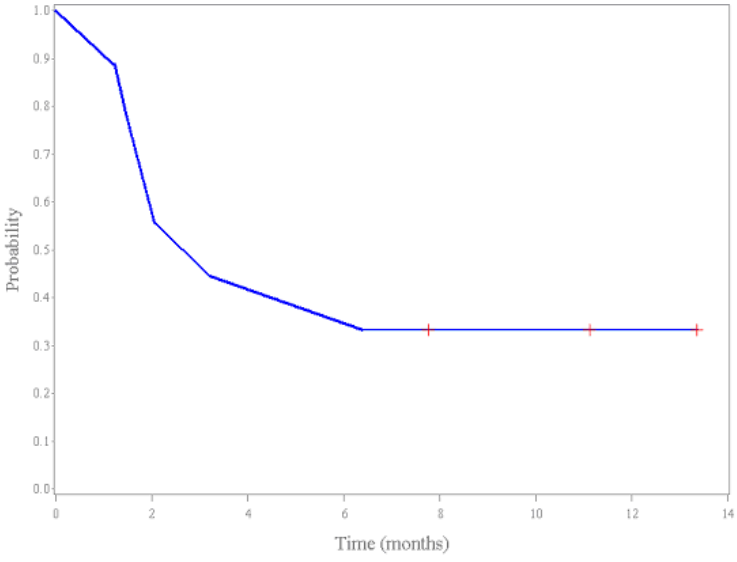


Figure 13.3 Progression-free survival.

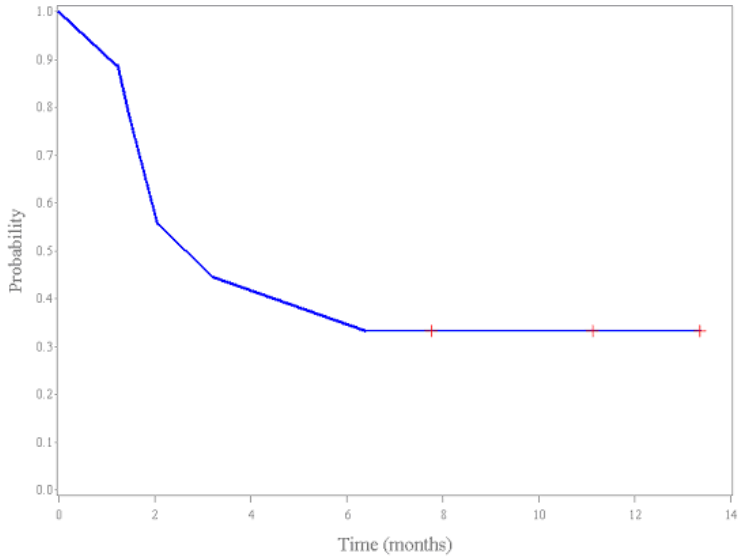
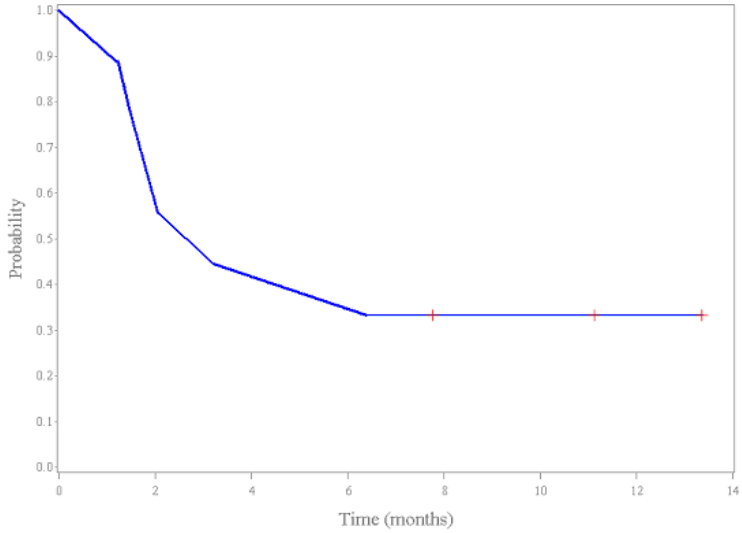
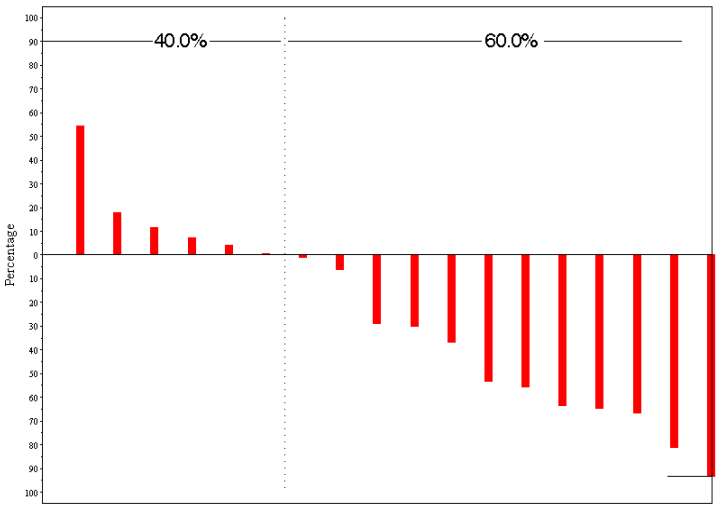


Figure 13.4 Duration of response.



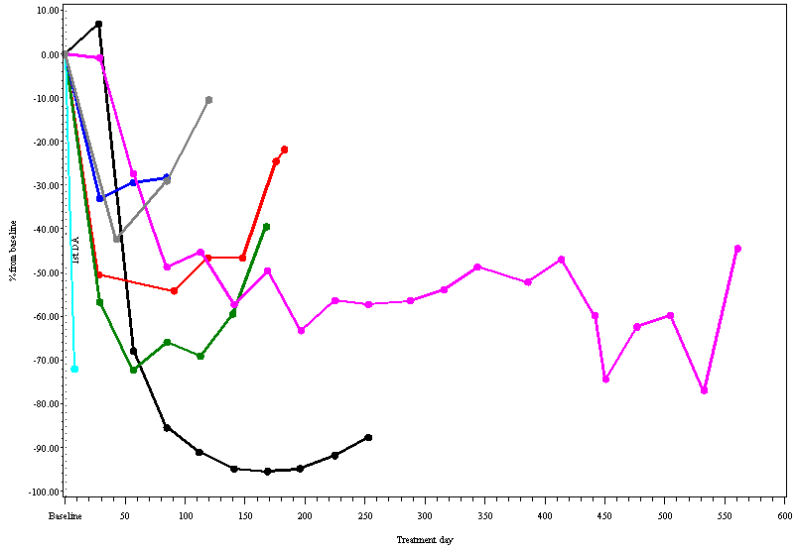
Kaplan-Meier curve of duration of response (if any response is observed).

Figure 13.5 Waterfall plots.



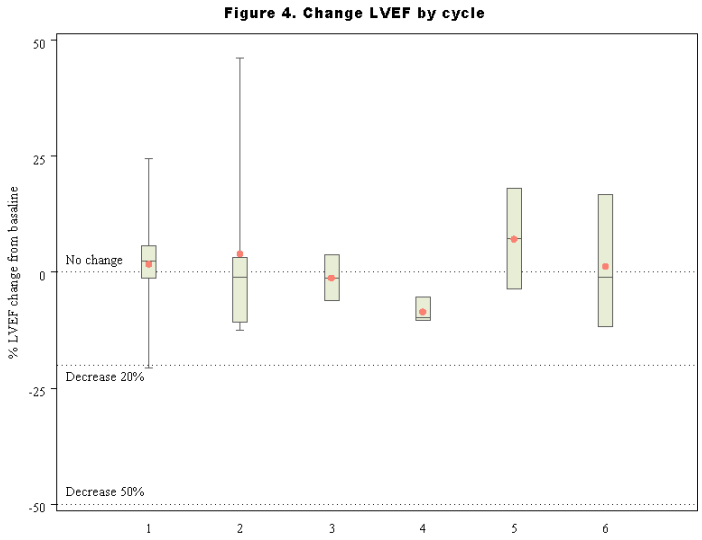
Maximum tumor shrinkage in measurable lesions by RECIST v1.1 will be displayed. Additional graphs by histology or RECIST response will also be provided when applicable.

Figure 13.6 Spider plot (SLD)



(*) Sum of longest diameters for all target lesions.

Figure 13.7 Boxplot of LVEF evolution from BL.



Boxplot showing the change in LVEF from baseline, to worst value by cycle.

14. Appendix V. DB listings.

-Listing 14.1.1. Cover

-Listing 14.1.2. Study registration

-Listing 14.1.3. Demography

-Listing 14.1.4. Pregnancy test

-Listing 14.1.5. Prior history

-Listing 14.1.6. Ewing sarcoma history

-Listing 14.1.7. Prior anticancer therapy: surgery

-Listing 14.1.8. Prior anticancer therapy: radiotherapy

-Listing 14.1.9. Prior anticancer systemic therapy: chemotherapy/biological therapy

-Listing 14.1.10. Drug administration

-Listing 14.1.11. Hematology laboratory values

-Listing 14.1.12. Biochemical laboratory values

-Listing 14.1.13. Other metabolic laboratory values

-Listing 14.1.14. Physical examination

-Listing 14.1.15. Performance status

-Listing 14.1.16. Vital signs

-Listing 14.1.17. Electrocardiogram

-Listing 14.1.18. LVEF

-Listing 14.1.19. Troponin I

-Listing 14.1.20. Other tests and procedures

-Listing 14.1.21. Adverse events (including signs and symptoms)

-Listing 14.1.22. Concomitant therapy/procedures

-Listing 14.1.23. Antiemetic prophylactic medication

-Listing 14.1.24. Tumor evaluation

-Listing 14.1.25. Radiological evaluation response assessment by cycle

-Listing 14.1.26. Clinical evaluation response assessment by cycle

-Listing 14.1.27. Overall response assessment by cycle

-Listing 14.1.28. Best overall response

-Listing 14.1.29. End of treatment

-Listing 14.1.30. Follow up

-Listing 14.1.31. Death report form

-Listing 14.1.32. Off study

-Listing 14.1.33. Signature report

15. SAP Version History.

Due to safety reasons, an independent cardiologist will undertake a review of all the ECGs and echocardiograms performed to the patients during the course of the study, in order to evaluate the cardiotoxicity risk of PM00104. This analysis was originally included in the first version of the SAP but due to logistical reasons, this analysis will be performed lately the database analyses, consequently it will be done in a separate document. The Statistical Analysis Plan is changed in accordance to the new version (version 2) as follows:

- All graphs and listings referred in the first version of the statistical plan will be presented in a separate document and will include data from CRF database and independent review database.

- In addition some minor changes and corrections in the text and to the mock shells have been done in order to improve a clear, unambiguous communication of the science and statistics of the trial.

Major changes:

Section 8.7 Independent review committee:

Original text: "Because of safety reasons, an independent cardiologist will undertake a review of all the ECGs and echocardiograms performed to the patients during the course of the study, in order to evaluate the cardiac risk of Zalypsis®. For this purpose all tables, graphs and listings will be presented in duplicate and all results will specify from which database are obtained, that is, CRF database and independent review database.
See section 12.6 Cardiac Safety."

Change to: "Because of safety reasons, an independent cardiologist will undertake a review of all the ECGs and echocardiograms performed to the patients during the course of the study, in order to evaluate the cardiotoxicity risk of PM00104. For this purpose, ***an independent cardiologist´s report not included in this SAP will be presented as an Appendix of the CSR***"

Section 12.6 Cardiac Safety:

Original text: **"**As an independent cardiologist will undertake a review of all the ECGs and echocardiograms performed to the patients during the course of the study, tables and listings defined in this section will be duplicated and will have a comprehensive header indication which date base were obtained, i.e, CRF database and Independent review database.
In this section additional tables and listings will be provided under request if clinical interest.**"**
Change to: ~~**"**As an independent cardiologist will undertake a review of all the ECGs, echocardiograms and troponin I determinations performed to the patients during the course of the study, tables and listings defined in this section will be duplicated and will have a comprehensive header indication which datebase were obtained, i.e, case report form (CRF) database and Independent review database.~~
~~In this section additional tables and listings will be provided under request if clinical interest.**"**~~

Section 13 Appendix IV.

Original text: Figure 13.8 Boxplot of LVEF (baseline, nadir and last value available).
Change to: ~~Figure 13.8 Boxplot of LVEF (baseline, nadir and last value available).~~

Section 14 Appendix V.

Original text: Listing 14.1.17 Electrocardiogram*, 14.1.18 LVEF* and Listing 14.1.19 Troponin I* and (*) Also will be included information for the independent review mentioned in section 8.7 of this document.
Change to: Listing 14.1.17 Electrocardiogram, 14.1.18 LVEF and Listing 14.1.19 Troponin I and ~~(*) Also will be included information for the independent review mentioned in section 8.7 of this document.~~

Section 15 SAP Version History has been included in order to be consistent with the SAP amendment of this study and in accordance with PharmaMar's SOP.