CONFIDENTIAL INFORMATION

Statistical Analysis Plan (SAP)

Final Version v1
13th February 2019

NCT Number	NCT02562378
EudraCT Number	2014-001056-28
Protocol Number	MedOPP038 (THELMA study)
Protocol Version Date	23th November 2015
Title	Phase I multicenter clinical trial evaluating the combination of trastuzumab emtansine (T-DM1) and non-pegylated liposomal doxorubicin in HER2-positive metastatic breast cancer.
Sponsor	Medica Scientia Innovation Research MEDSIR ARO Rambla Cataluña, 2-4, 2D 08007 Barcelona (Spain)

STATISTICAL ANALYSIS PLAN (SAP)

Performed by:

SAIL Servicio de Asesoría a la Investigación y Logística

Avenida Meridiana 350, 9 D
08027 Barcelona (Spain)

www.sail-biometria.com

Signature Page

EudraCT Number: **2014-001056-28**
Protocol Number: **MedOPP038**

Written by:

Signature:

_____

Date:

_____

Xavier Masramon
Biostatistician
SAIL S.L.
Barcelona, Spain

Sponsor Signature:

The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

Signature:	Signature:
_____	_____
Date:	Date:
_____	_____
Name:	Name:
_____	_____
Title:	Title:
_____	_____

SAP Revision History:

Version Number	Date	Changes
v1	13th February 2019	Initial version

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
ARO	Academic Research Organization
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BLQ	Below the Limit of Quantification
BNP	B-type Natriuretic Peptide
CBR	Clinical Benefit Rate
CI	Confidence Interval
CL	Clearance
CMAX	Maximal Serum Concentration
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DV	distribution volume
ER	Estrogen Receptor
HER2	Human Epidermal Growth Factor Receptor 2
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IQR	Interquartile Range
ISH	In Situ Hybridization
ITT	Intention-To-Treat
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
M2	square meter
MBC	Metastatic Breast Cancer
MEDDRA	Medical Dictionary for Regulatory Activities
MG	Milligrams
MTD	Maximum Tolerated Dose
NYHA	New York Heart Association
ORR	Objective Response Rate
PD	Progressive Disease
PGR	Progesterone Receptor
PK	Pharmacokinetics
PP	Protocol Population
PR	Partial Response
PT	Preferred Term
RDI	Relative Dose Intensity
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class

Abbreviation	Definition
T1/2	half-life
T-DM1	Trastuzumab emtansine
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, Figures

TABLE OF CONTENTS

1 INTRODUCTION

1.1 General

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Protocol version dated: 27th June 2017
- electronic Case Report Form: 27th July 2016

1.2 Type of Study

This is a prospective dose-finding, multicenter and open-label phase I clinical trial.

1.3 Study Population

This study will enroll patients with histologically or cytologically confirmed HER2-positive metastatic breast cancer (mBC) that have relapsed or progressed on or after both taxane and trastuzumab-based therapy. Only patients whose human epidermal growth factor receptor 2 (HER2) tumor status was locally scored as Immunohistochemistry (IHC) 3+ or In Situ Hybridization (ISH) positive will be eligible. Evidence of measurable or evaluable metastatic disease is required.

1.4 Study Design

This is a prospective dose finding, multicenter and open-label phase I clinical trial. There are three planned cohorts. Trastuzumab emtansine (T-DM1) will be administered at a fixed dose of 3.6 mg/kg IV on Day 1 every 3 weeks and three cohorts of patients with three different dose levels of non-pegylated liposomal doxorubicin (45 mg/m2, 50 mg/m2 and 60 mg/m2) IV on Day 1 in cycles of 21 days each are planned.

Study Cohort	T-DM1	Non-pegylated liposomal doxorubicin
Cohort 1 (level 1)	3.6 mg/kg IV D1	45 mg/m^2 IV D1
Cohort 2 (level 2)	3.6 mg/kg IV D1	50 mg/m^2 IV D1
Cohort 3 (level 3)	3.6 mg/kg IV D1	60 mg/m^2 IV D1

No dose escalation between cohorts will be permitted. Patients assigned on each cohort will remain at their study cohort during all the study period.

Planned number of cohorts is currently 3 (3+3 design), including an expansion cohort of an additional 6 patients at the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

The Steering Committee will review toxicities and may decide to add the expansion cohort to level -1 in the situation where it is necessary to have a dose level -1.

The detailed rules for dose escalation are detailed at figure 1 of the protocol.

1.5 Study Schedule

Summary of study assessments is reported in Appendix 1 of the protocol: Schedule of assessments and study procedures.

Study Period	Screening	Study Treatment (T-DM1 + non-pegylated liposomal doxorubicin)				End of Study Treatment	Follow-up		
		Cycles 1-2		Cycles 3-6			While on T-DM1 treatment		End of Study visit
Day	-28 to -1	1	21	1	21	28±7 last dose TMD1 + Non-pegylated liposomal doxorubicin	Every 3 weeks	28 (-42) days after last T-DM1 dose[a]	
Informed Consent	X								
HER2 status	X								
Medical History	X								
Physical Examination and ECOG status	X	X		X		X	X	X	
Weight	X	X		X			X		
Vital signs[b]	X	X		X		X	X	X	
Concomitant Medication Reporting	←----------								→----------
AE reporting	←----------								→----------
ECHO	X		X		X		X[c]	X[c]	
12-lead ECG	X		X		X		X[c]	X[c]	
DLT assessment			X						
Tumor Assessments	X		X[d]		X[d]	X[do]	X[d]	X[d]	
Overall survival	←----------								→----------
Standard Laboratory Procedures:									
Pregnancy test[e]	X						X[e]	X[e]	
Hematology[f]	X	X[g] (Days 8 and 15)		X[g]			X[g]		
Biochemistry[h]	X	X[g] (Days 8 and 15)		X[g]			X[g]		
INR/aPTT	X	As clinically indicated					As clinically indicated		
Troponin I determination	X	X[ij] (Day 8)		X[ij]			X[ij]		
B-type natriuretic peptide (BNP)	X	X[kl] (Day 8)		X[kl]			X[kl]		
Experimental laboratory (to be performed in a central lab)									
PK samples[m]		X		X					
Single Nucleotide Polymorphisms (SNP)	X								
Drug Administrations									
Trastuzumab Emtansine (T-DM1)		X		X			X[no]		
Non-pegylated liposomal doxorubicin		X[p]		X[p]					

AE = Adverse Event; aPTT = Activated Partial Thromboplastin Time; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = International

AE = Adverse Event; aPTT = Activated Partial Thromboplastin Time; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = International Normalized Ratio

[a] Patients will be followed for new or worsening adverse events for 28 (+/- 7 days) days following the last dose of any study IMP. All ≥ grade 2 adverse events will be followed up until improvement to baseline levels, grade 1 or complete recovery, initiation of another anti-cancer therapy, the patient withdraws consent, patient's death or up to a maximum of 24 months after the first dose of study combination treatment whichever occurs first. Additionally, patients will be contacted regarding the occurrence of any new SAE considered to be treatment-related at 60 and 90 days following the last study treatment administration or until initiation of another anti-cancer therapy, whichever occurs first.

[b] Vital signs will include measurements of respiratory rate, heart rate, blood pressure, and temperature. Abnormal or significant changes to vital signs from baseline should be recorded as adverse events, if appropriate.

[c] ECHO and ECG will be performed every 1 cycle (cycles 1-6) during treatment with T-DM1 + non-pegylated liposomal doxorubicin. Thereafter, ECHO and ECG will be performed every 9 weeks until 12 months since last dose of study treatment (T-DM1+ non-pegylated liposomal doxorubicin)

[d] During study treatment (T-DM1+ non-pegylated liposomal doxorubicin) tumor assessment wil be performed at the end of cycle 2, cycle 4, and cycle 6. Thereafter, the tumor response assessment will be performed every 9 weeks up to progression or up to 24 months for patients

who discontinue all study IMP for reasons other than PD. Response assessments will be assessed by the investigator, based on physical examinations, CT or MRI scans, and bone scans using RECIST v. 1.1

[e] Serum β-HCG test must be performed during screening, every 3 cycles and at 3 and 7 months following the last dose of T-DM1 and/or non-pegylated liposomal doxorubicin for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal. Testing should be performed at a local laboratory within 7 days prior to the first administration of study treatment. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

[f] Hematologic assessments include hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cells (WBC) with differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils)

[g] Assessments should be performed at screening, within 72 hours prior to any IMP administration, at days 8 and 15 after any IMP administration during the first 2 cycles, weekly following any hematologic adverse event. If non-pegylated liposomal doxorubicin is discontinued due to toxicity, assessments should be performed weekly (minimum) until resolution of the adverse event (Grade ≤ 1 or baseline levels), and on Day 1 of subsequent cycles thereafter. All assessments at Day 1 should be performed within 72 hours preceding administration of any study IMP; results must be reviewed and documented prior to administration of study treatment. Assessments at days 8 and 15 should be performed 7 (±2) and 14 (±2) days after any IMP administration

[h] Biochemistry assessments include: sodium, potassium, chloride, calcium, magnesium, glucose, urea or blood urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), G-GT, LDH, total bilirubin (and direct bilirubin where total bilirubin > ULN).

[i] TPN I determination will be performed 7 days (with a window of ± 2 days) after every infusion of every cycle.

[j] TPN I determination will be performed every 1 cycle (cycles 1-6) during treatment with T-DM1 + non-pegylated liposomal doxorubicin. Thereafter, TPN I will be performed every 9 weeks until 12 months since last dose of study treatment (T-DM1+ non-pegylated liposomal doxorubicin).

[k] BNP determination will be performed 7 days (with a window of ± 2 days) after every infusion of every cycle.

[l] BNP determination will be performed every 1 cycle (cycles 1-6) during treatment with T-DM1 + non-pegylated liposomal doxorubicin. Thereafter, BNP will be performed every 9 weeks until 12 months since last dose of study treatment (T-DM1+ non-pegylated liposomal doxorubicin)

[m] Pharmacokinetic assessments will be performed during the Dose Finding part of the study on Cycles 1 and 2 and also on cycle 4.

[n]: Every 3 weeks from last dose of study treatment (combination T-DM1+ Non-pegylated liposomal doxorubicin) until disease progression or development of intolerable toxicity, whichever occurs first.

[o] Optional as per investigator's criteria

[p] At the Level -1, non-pegylated liposomal doxorubicin will be administered in a weekly schedule.

1.6 Sample Size

The total sample size was dependent on the number of dose levels required to determine the maximum tolerated dose (MTD). A minimum of 12 and up to 24 patients was planned.

The inclusion of patients has already been completed. The total number of patients is 15.

Study Cohort	N
Cohort 1	3
Cohort 2	3
Cohort 3	9

2 STUDY OBJECTIVES

2.1 Primary objective

To determine the MTD of the combination of T-DM1 and non-pegylated liposomal doxorubicin.

2.2 Secondary Objectives

- To assess the overall objective response rate (ORR).
- To assess the clinical benefit rate (CBR)
- To assess the number of progressions.
- To assess the number of deaths and reasons.

- To assess the safety profile of the combination of T-DM1 and non-pegylated liposomal doxorubicin.
- To assess the cardiac safety of the combination of T-DM1 and non-pegylated liposomal doxorubicin.
- To explore the potential role of single nucleotide polymorphisms (SNP) in the predisposition for developing cardiotoxicity.
- To analyze the pharmacokinetics (PK) profile of T-DM1 and non-pegylated liposomal doxorubicin.

3 ANALYSIS POPULATIONS

The following populations will be analyzed:

- Screening Population: All patients who were present at the screening visit will be included in the screening population.
- DLT population: all patients who complete the first two cycles of treatment or who stop treatment during this time because of dose-limiting toxicity (DLT).
- The Safety / Intention-To-Treat (ITT) population: all included patients receiving any dose of study treatment.
- Per protocol population (PP): all patients who receive the protocol required study drug exposure and required protocol processing.

  To determine the Per Protocol Population, all protocol deviations will be reviewed prior to database lock to determine which ones should be classified as major deviations.

4 DEFINITION OF ENDPOINTS

4.1 Primary Endpoint

- MTD is defined as the highest dose level at which no more than one of six patients (i.e. less or equal than 16,7%) experience DLT during the first two cycles of study treatment.

4.2 Secondary Endpoints

- ORR, according RECIST v1.1
- CBR according RECIST v1.1
- Number and Rate of patients with progression
- Number and Rate of patients who died
- The extent of exposure
- Grade 3 and 4 AEs, SAEs, AESIs, deaths, and study discontinuations for each study group will be described and assessed.
- Number and Rate of patients with left ventricular dysfunction IV NYHA, defined as LVEF decline >10 percentual points or LVEF <50%

- Number and Rate of patients who discontinue any of the study drugs due to cardiac function or die due to cardiac cause.
- Number and Rate of patients with cardiac troponin I elevation, according to CTCAE v4.0 criteria.
- Number and Rate of patients with B-type Natriuretic Peptide (BNP) levels, according to CTCAE v4.0 criteria.
- Number and Rate of patients with segmental wall-motion abnormalities.
- Association between HER2 Ile655Val single nucleotide polymorphism and LVEF changes.
- Association between HER2 Ile655Val single nucleotide polymorphism and prevalence of a cardiac toxicity.
- PK profile: AUC, clearance (CL), distribution volume (dV), apparent half-life (t1/2) and maximal serum concentration (Cmax).
- Clinically relevant tests, concomitant medications, and reported AEs will be described in every study subgroup. For AEs, severity, expectedness, causality, relationship, body system, action taken, and outcome will be reported.

5 STATISTICAL METHODS

5.1 General Methodology

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, maximum, and first and third quartiles, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n as the denominator, for frequency tables not assessed by time point the population will be used as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g. clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a p-value is only presented to four decimal places (by SAS) it will not be rounded again but will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001".

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 5% will be used for confidence intervals.

All report outputs will be produced using SAS® version 9.4 version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document.

5.2 Subject Disposition

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening population, the number of patients eligible to participate in the study, and number of screen failures.
- Number and percent of subjects in each of the analysis populations (DLT, Safety/ITT, PP).
- Number and percent of subjects excluded from each of the analysis populations along with reason for exclusion.
- Listing of subjects excluded from each of the analysis populations along with reason for exclusion.
- Listing of protocol deviations.
- Study termination:
    - Number and percent of subjects who completed the study.
    - Frequency of premature termination reasons.
    - Listing of all dropouts along with reason for termination, treatment group and time of termination.

No statistical tests are planned for these data.

5.3 Baseline Characteristics

Baseline characteristics will be provided overall for the Safety/ITT.

Descriptive statistics, including number of subjects, mean, standard deviation (SD), median and range for continuous variables and frequency and percent for categorical variables will be provided.

Baseline Characteristics:

- Demographic characteristics
- Physical examination
- Medical history
- Prior concomitant medication
- Estrogen receptor (ER)
- Progesterone receptor (PgR)

- Human epidermal growth factor receptor 2 (HER2)
- Previous treatment for local breast cancer
- Previous surgeries for breast cancer
- ECOG performance status
- TNM staging
- Tumor physical exam
- Metastases sites
- Vital signs
- Electrocardiogram
- Left Ventricular Ejection Fraction (LVEF)

No statistical tests are planned for these data.

A by-subject listing of all demographic and other baseline characteristics will be provided.

5.4 Efficacy

5.4.1 Secondary Efficacy Analysis

All secondary efficacy analysis will be based on the Safety/ITT and PP population.

Confidence intervals will be calculated for efficacy data, according to Clopper-Pearson.

Estimates for efficacy data, 95% confidence intervals (CIs) were constructed based on an exact binary distribution.

- Tumor response rate by MRI, according to the RECIST criteria version 1.1, is defined as best overall response in terms of:
    - Complete response (CR)
    - Partial response (PR)
    - Stable disease (SD)
    - Progressive disease (PD)

  Best overall response is obtained, from target lesion response, non-target lesion response and new lesions, as follows:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

For each response category, the number and proportion of patients, with its 95% Pearson-Clopper confidence intervals, will be calculated.

- Overall Response Rate (ORR), based on local investigator's assessment according to RECIST 1.1, is defined as the proportion of patients with best overall response of CR or PR. The ORR with its 95% Pearson-Clopper confidence interval, will be calculated.
- Clinical Benefit Rate (CBR), based on local investigator's assessment according to RECIST 1.1, is defined as those patients who experience a complete response, partial response or stable disease (for at least 24 weeks). The CBR with its 95% Pearson-Clopper confidence interval, will be calculated.
- The number and proportion of patients with progression disease (PD) with its 95% Pearson-Clopper confidence intervals will be calculated.
- The number and proportion of deaths with its 95% Pearson-Clopper confidence intervals will be calculated.
- The number and proportion for each reason of death with its 95% Pearson-Clopper confidence intervals will be calculated.

5.4.2 Handling of Missing Data

Study variables could be missing for patients who withdrawn from the trial or for specific visits. We will report reasons for withdrawal. Patient with missing in response outcomes (ORR and CBR) will considered as no responders in intention to treat set. The other variables will be managed with simple imputations methods (last observation carried forward). The effect that any missing data might have on results will be assessed via sensitivity analysis of study sets.

5.5 Safety

All safety tables will list or summarize subjects on the entire Safety/ITT Population and by each cohort, except for the primary safety analysis.

5.5.1 Primary Safety Analysis

The primary outcome will be analyzed in DLT population.

For each cohort (treatment dose), see section 1.4, the number and the proportion of patients with DLT with its 95% Pearson-Clopper confidence intervals will be calculated.

A DLT is defined as any of the drug-related adverse events, described in the Table 1 of the protocol, occurring during the first two cycles of study treatment. It will be used as the measure for the MTD determination.

5.5.2 Duration and Extent of Exposure

The study treatment period is defined as the time between the study entry and the last dose of study combination (T-DM1 + non-pegylated liposomal doxorubicin) therapy. T-DM1 administration may continue as a single agent until disease progression or development of intolerable toxicity, whichever occurs first.

For T-DM1 and non-pegylated liposomal doxorubicin the following parameters will be calculated:

- b: "Actual Cycle Duration" is the treatment duration for a cycle per CRF. It is the length of time (days) between actual and next cycle start date dose. At the last cycle is the difference between start and stop date dose.
- c: "Actual Cycle Dose Days" is the number of days with dose administration in the cycle, considering the interruptions.
- d: "Actual Total Dose per Cycle" is the total dose a patient took in a cycle, considering interruptions and reductions.
- e: "Intended Daily Dose per Cycle".
- f: "Intended Cycle Duration".
- g: "Intended Cycle Dose Days".
- A: "Total number of cycles".
- B: "Treatment Duration" = Sum over all cycles of (b).
- C: "Days on drug" = Sum over all cycles of (c).
- D: "Total Actual Total Dose" = Sum over all cycles of (d).
- E: "Mean Intended Daily Dose" = Mean over all cycles of (e).
- F: "Total Intended Duration" = Sum over all cycles of (f).
- G: "Total Intended Dose Days" = Sum over all cycles of (g).

- H: "Intended Total Dose" = G*E
- I: "Actual Average Daily Dose on Dose Days" = D/C
- J: "Ratio for Dose Interruption" = C/G
- K: "Ratio for Cycle Duration" = F/B
- L: "Actual Average Daily Dose Intensity" = I*J*K
- M: "Relative Dose Intensity (RDI)" = L/E*100

The treatment duration (days), days on Drug and Treatment compliance (%) will be summarized in terms of the number of observations, mean, standard deviation (STD), median, minimum and maximum, to each treatment cohort.

Extent of exposure measured as RDI by cohort will be described with median, interquartile range (IQR) and range. The RDI will be dichotomized in different cutoffs (≥50%, ≥70%, ≥80%, ≥90%, ≥100%) and described with frequencies and percentages.

5.5.3 Adverse Events

All AEs will be recorded on the eCRF "Adverse Events" page and will be coded using the current version of MedDRA® to give a system organ class (SOC) and preferred term (PT) for each event. All adverse event safety data will be updated to the version of MedDRA that is current at the time of the database lock and statistical analyses. Adverse events will be coded with grades defined according to CTCAE V4.0 criteria.

Treatment-emergent AEs (i.e. those events occur after the first study medication administration and were not present at baseline or worsened in severity following the start of treatment) will be tabulated. The TEAE will be tabulated according to intensity and causality. If intensity of an AE or causality of an AE to the study medication is missing, a worst-case scenario will prevail (severe in intensity or probably related will be assumed). In the summary tables the number of subjects with events and the number of events will be presented.

The onset date of an AE will be compared to the date of first dose of study drug to determine whether or not the AE is treatment-emergent. Adverse events with an onset date on or after the date of first dose of study drug will be classified as treatment-emergent.

All deaths and SAEs, regardless of cause, from treatment start until 28 days after final dose of treatment. Non-fatal AEs occurring after treatment start regardless of cause, up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first. Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment emergent adverse events with cause possibly, probably or definitely related to treatment as judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

The following summaries will be provided:

- An overview of adverse events (number of subjects with at least one AEs, number of subjects with at least one TEAE, number of subjects with grade 3 and 4 TEAE, number of subjects with related study drug TEAE, number of subjects with serious TEAE, number of subjects with non-serious TEAE, number of subjects with AESI, number of deaths, number of subjects with TEAE leading to discontinuation of study treatment, number of subjects dropped out due to AE).
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by SOC, and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event related to study drug by SOC, and PT.
- A summary of the number and percentage of subjects reporting a grade 3 and 4 treatment-emergent adverse event by SOC, and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by maximum intensity, SOC and PT.

- A summary of the number and percentage of subjects reporting a serious treatment-emergent adverse event, by SOC and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event resulting in death during the study, by SOC and PT.
- A summary of the number and percentage of subjects with adverse events leading to discontinuation of study drug, by SOC and PT.

For adverse events, we will report intensity, casualty, relation, body system, action taken, and outcome.

Serious adverse events, deaths and study discontinuations will be described and examined in each study group.

5.5.4 Cardiac Safety

- Number and proportion (95% Pearson-Clopper confidence interval) of patients with left ventricular dysfunction IV NYHA, defined as LVEF decline >10 percentual points or LVEF <50%.
- Number and proportion (95% Pearson-Clopper confidence interval) of patients who discontinue any of the study drugs due to cardiac function or die due to cardiac cause.
- Number and proportion (95% Pearson-Clopper confidence interval) of patients with cardiac troponin I elevation, according to CTCAE v4.0 criteria.
- Number and proportion (95% Pearson-Clopper confidence interval) of patients with BNP elevation, according to CTCAE v4.0 criteria.
- Association between HER2 Ile655Val single nucleotide polymorphism and LVEF changes will be analyzed by Spearman's rank correlation.
- Association between HER2 Ile655Val single nucleotide polymorphism and prevalence of a cardiac toxicity (binary outcome) will be analyzed by U Mann-Whitney Test.

5.5.5 Concomitant Medications

The number and percent of unique patients taking concomitant medications will be summarized by therapeutic classification, coded term and cohort group. Elective surgeries/procedures performed during the study will be presented in a listing.

The following are conventions that will be used to classify individual medications as prior and/or concomitant:

- Medications with stop dates prior to screening visit date will be considered prior.
- Medications with missing stop dates or stop dates the day of or after screening visit date will be considered concomitant, regardless of start date. Additionally, if the start date is prior to screening visit date or missing, the medication will also be considered prior.

Frequencies and by-subject listing of all prior and concomitant medications will be provided, containing variables listed on Prior/Concomitant Assessment eCRF, their corresponding categories (Prior or Concomitant), and WHO Anatomical Therapeutic Chemical (ATC) level 2 and ATC Name.

5.5.6 Clinical Laboratory Parameters

All hematology and biochemistry parameters will be presented by descriptive statistics in a tabulated summary by time point of assessment per treatment group together with the respective changes from baseline. In addition, a frequency table for clinically significant values will be presented by time point of assessment.

A by-subject listing for hematology and clinical chemistry will be provided. These listings will be presented by treatment group and time point and will include: center, subject identifier, laboratory parameter, parameter values (in SI units), SI unit, normal range and a flag with respect to normal range (below, within and above normal range).

5.5.7 Vital Signs

Weight, systolic and diastolic blood pressure, heart rate and respiratory rate will be presented by descriptive statistics in a tabulated summary by time point of assessment per treatment group together with the respective changes from baseline. In addition, frequency tables for the number of patients with increases or decreases from baseline in systolic/diastolic blood pressure of >20 mmHg and pulse rate of >15 bpm will be provided by time point of assessment and overall. A by-subject listing for all vital signs per treatment group and time point will be provided.

5.5.8 Physical Examination

A frequency table per treatment group, time point, and body system will be provided for assessment results of normal, abnormal and not done.

A by-subject listing for all body systems per treatment group and time point will be provided. Only subjects with at least one abnormal finding will be included in this listing.

5.6 Pharmacokinetic

The Pharmacokinetic Analyses will be performed by PPD.

5.7 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

6 APPENDICES

6.1 List of Tables, Listings, Figures

A complete list of tables, listings and figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output.

All statistical output will identify the underlying analysis populations and indicate the number of patients/events in this population (N) and the number of patient/events actual contributing to the output (n). All statistical output will be presented per treatment (if applicable).

All patient listings will contain additionally to the patient identification the analysis population and the treatment.